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Double Asymmetric Synthesis and a New Strategy for Stereochemical Control in Organic Synthesis

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Dedicated to Professor Raymond U. Lemieux on the occasion of his 65th birthday

This account examines double asymmetric induction from theoretical and practical viewpoints. In the context of four major organic reactions—the aldol, Diels-Alder, catalytic hydrogenation, and epoxidation—it is shown that a double asymmetric induction can be analyzed in terms of the single asymmetric reactions of each of the two chiral reactants. A rule which qualitatively relates the results of these single asymmetric reactions with the outcome of the double asymmetric reaction is proposed. A powerful new strategy based on this rule for the predictable creation of new chiral centers is discussed and the use of this strategy for the synthesis of sugars and macrolides is presented.

1. Introduction

Organic chemists are well acquainted with the notion of (single) asymmetric synthesis, which, as originally defined by *Marckwald*[1], is the process of forming an optically active compound through the reaction of an *achiral* substrate with a *(homo)chiral* reagent[2][**]. It should be stressed at the outset that this process should be distinguished, in an important way, from *double* asymmetric synthesis, which concerns the interaction of *two homochiral* reactants, a substrate and a reagent[3,4][**]. The stereochemical analysis of this *double asymmetric synthesis* will lead to a new hypothesis from which one can design a strategy that is potentially capable of constructing any new *chiral* center or centers on a *chiral* substrate in a *predictable and controlled* manner[**]. Thus, the objective of double asymmetric synthesis is not simply to prepare optically active compounds but to achieve a high diastereoselection as well. Obviously, this process is critically important and frequently encountered in natural products synthesis. As will be elaborated upon below, this strategy demands the development of homochiral reagents that must meet a new set of criteria. Such reagents have been prepared recently to effect four major organic reactions with excellent stereochemical control: the aldol reaction, the Diels-Alder reaction, catalytic hydrogenation, and epoxidation. This account will describe this newly introduced synthetic strategy and then illustrate the use of these reagents in the total synthesis of several natural products of medium complexity which serves to demonstrate the degree of stereochemical control that has now been achieved.

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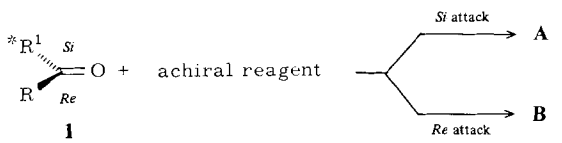
[**] "Homochiral" is synonymous with "enantiomerically pure", a term conventionally used. For the accurate definition of several other terms pertinent to stereochemistry, see reference [2].—The substrate, as opposed to reagent, is defined herein as a reactant whose main structural unit is maintained throughout a sequence of reactions leading to the formation of a target molecule.—"Control" is used throughout this Account in the sense that a new center or centers of *either* chirality can be created with excellent stereoselection.

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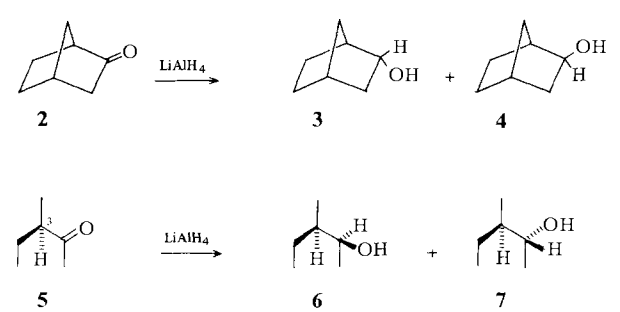
2. Stereochemical Analysis of Double Asymmetric Induction

2.1. Diastereofacial Selectivity

Consider first a general case where a *chiral substrate* **1** having an sp^2 carbon (e.g., a ketone) reacts with an *achiral reagent* to give products **A** and **B** (Scheme 1). Since **1** is chiral, one of the two diastereomeric transition states (*Si*-attack or *Re*-attack) will be lower in energy than the other. This results in one product being produced to a greater extent, and thus the product ratio **A/B** is not unity. This ratio will be referred to throughout this Account as the diastereofacial selectivity (D.S.) of **1**, and this definition is applied to any chiral substrate or reagent[5]. For instance, reduction of norcamphor **2** with lithium aluminum hydride provides a mixture of *endo*- and *exo*-norborneols (**3** and **4**), the D.S. of **2** being 8.1 : 1 in favor of the *endo* isomer[6]. This example, although very simple, illustrates a well-established principle that has guided synthetic organic chemists in (cleverly) *designing the structure of a substrate* in order to incorporate proper stereochemistry in the reaction product. *Note that the chirality of the substrate dictates the stereochemical outcome of the reaction forming the new chiral center,* and that the reagent plays a minor role in this sense. A variety of complex natural products possessing many chiral centers have almost invariably been synthesized in this way[**].



A/**B**(diastereofacial selectivity of **1**) ≠ 1



Scheme 1[*].

In contrast to the cyclic system exemplified above by **2**, a high diastereofacial selectivity is normally more difficult to attain with acyclic systems. For instance, hydride reduction of 3-methyl-2-pentanone **5** will, in all likelihood, proceed non-stereoselectively. The acyclic ketone **5** is conformationally flexible and the differences in both the steric and stereoelectronic effects exerted by the methyl and ethyl groups attached to the C3 carbon of **5** are insignificant. Thus, the two products, **6** and **7**, will be formed in nearly equal quantities. One is led to ask: Are there new means available for achieving high stereoselection in this last case, and further, can we even reverse the "normal" stereochemical course of the reduction of **2** (to secure **4** rather than **3**) without recourse to a classical, perhaps costly structural modification of the substrate?[***] These are fundamental problems and indeed we addressed ourselves to them when our macrolide project was launched a few years ago.

2.2. Interaction of Two Chiral Reactants and the Concept of Matched and Mismatched Pairs

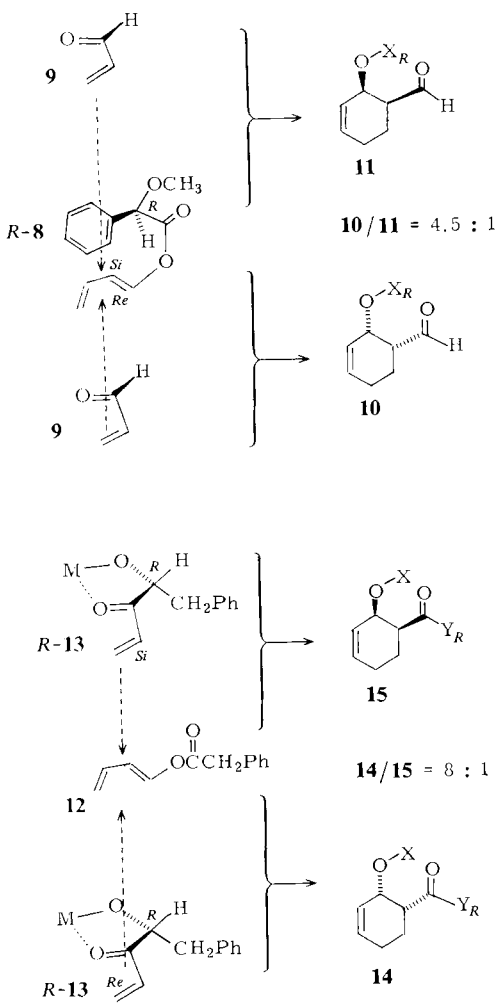
The interaction of two chiral reactants is evaluated in terms of the diastereofacial selectivities of two chiral reactants, and the following two sets of model experiments, the Diels-Alder reaction[7] and the aldol reaction[8] appear to best serve as illustrations. Thus, the pericyclic reaction of *Trost*'s chiral diene *R*-**8**[9] with achiral acrolein **9** in the presence of $BF_3 \cdot OEt_2$ provides a 4.5 : 1 mixture of diastereoisomers **10** and **11** (Scheme 2). This diastereofacial selectivity (D.S.) of *R*-**8** can be rationalized on the basis of the proposed transition state conformation in which the phenyl group of **8** covers one face of the butadiene π-system, i.e., the *Si* face of the diene moiety is more "shielded" to the attack of **9** than the *Re* face (see Section 5). In a similar manner butadienyl phenylacetate **12**, an achiral diene chosen as a model for **8**, is predicted to approach the chiral dienophile *R*-**13** from the latter's *Re* face inasmuch as the coordination of the catalyst $BF_3 \cdot OEt_2$ with the α-hydroxyketone moiety of *R*-**13** brings about a five-membered chelate. The two faces of the chelate ring are differentiated by the (small) hydrogen and (large) benzyl groups attached to the chiral center of *R*-**13**. Indeed, the D.S. of *R*-**13** is 8 : 1, favoring the formation of **14** over **15**[7].

Now that the D.S.'s of the diene *R*-**8** and the dienophile *R*-**13** have been determined, one can evaluate the interaction of the two chiral reactants (Scheme 3). Compare the interaction between the *Re*-face of *R*-**8** and the *Re*-face of *R*-**13** (arrow a) with that between the *Si*-face of *R*-**8** and the *Si*-face of *R*-**13** (arrow b) which should lead to the formation of the products **16** and **17**, respectively. Since the two phenyl groups of *R*-**8** and *R*-**13** both impede the formation of **17** as shown in Scheme 3, the D.S.'s of both reactants are acting in concert. The ratio of **16** and **17** is 40 : 1 (larger than the D.S. of either reactant) and this combination of *R*-**8** and *R*-**13** is referred to as a "matched pair." In contrast, the reaction of *R*-**8** and *S*-**13** brings about a different stereochemical outcome. (Note that the chirality of the dienophile is now reversed from *R* to *S*.) In

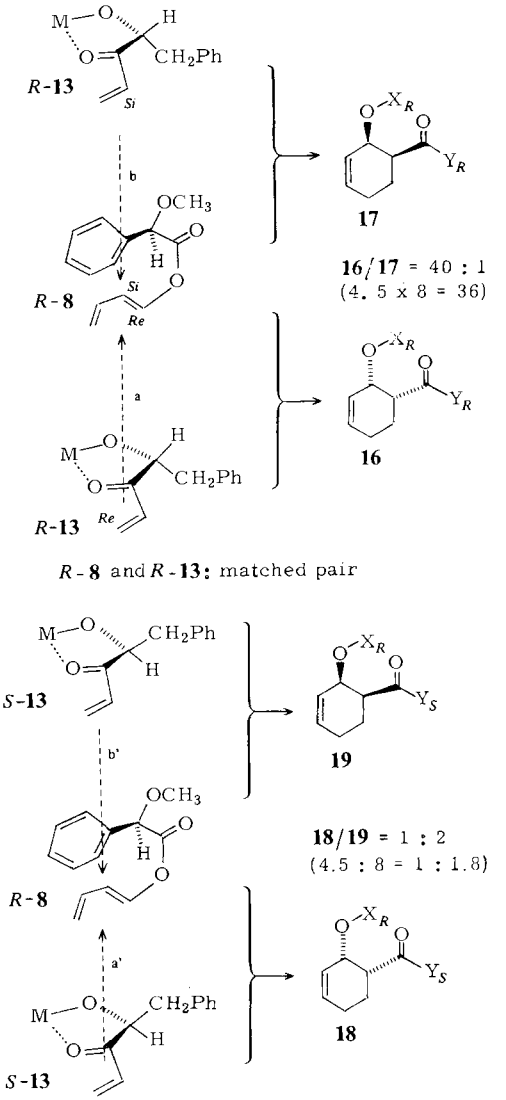
[*] R^1 is chiral. Assuming that the Cahn-Ingold-Prelog priority of R^1 is higher than that of R, the *Si* and *Re* faces of **1** are those shown in Scheme 1.

[**] This statement is valid for virtually all the syntheses of racemic compounds recorded in the literature.

[***] The "art" of organic synthesis exhibited in many multi-step syntheses (much more complicated than the problem of **2**) is attributed, at least in part, to the skills of synthetic chemists in solving these stereochemical problems in this conventional, indirect manner. Readers will find it interesting to devise a pathway leading to **4** stereoselectively and to evaluate it in light of the discussions that will unfold in this Account.



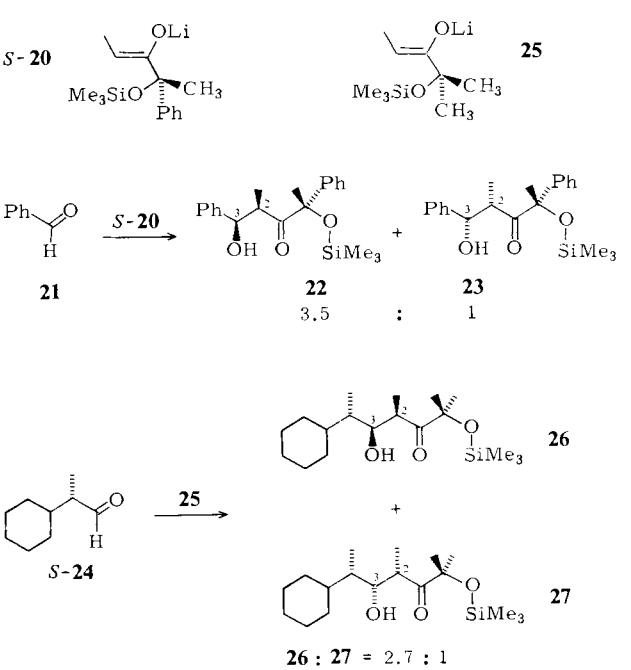
Scheme 2.



Scheme 3.

each of the two face interactions discussed above, designated as paths a′ and b′ in Scheme 3, there intervenes one phenyl group, either that of *R*-**8** or *S*-**13**, between the two reacting π-systems. Therefore, the two diastereofacial selectivities of *R*-**8** and *S*-**13** are counteracting each other. Thus, *R*-**8** and *S*-**13** are called a "mismatched pair," and the expected products **18** and **19** result in a 1 : 2 ratio, a ratio smaller than either of the two D.S.'s[*].

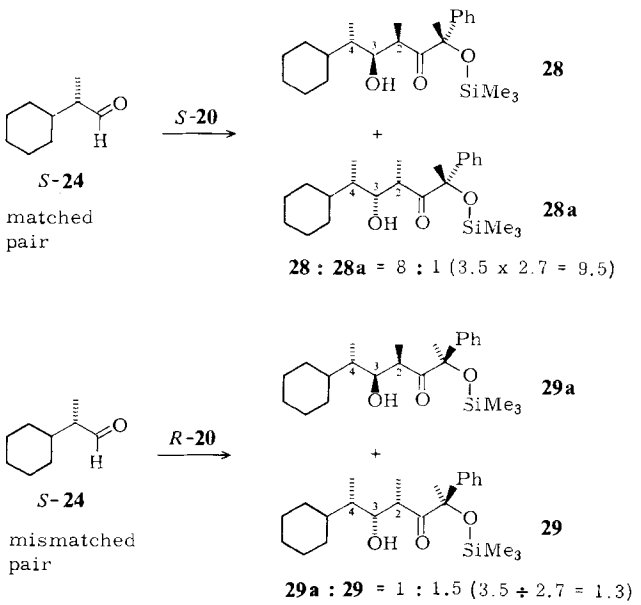
A set of aldol reactions also demonstrates a similar trend (Scheme 4)[8]. The chiral lithium enolate *S*-**20** reacts with (achiral) benzaldehyde **21** to provide the diastereomeric aldol products **22** and **23** in a 3.5 : 1 ratio which represents the D.S. of **20**. The two substituents at the C2 and C3 positions are *syn*-related[8] in both **22** and **23** but their absolute configurations are different; both β in **22** and both α in **23**. As will be elaborated on in Section 4, the absolute configurations are directly related to the face selection exercised by the chiral reagent *S*-**20**. Likewise, using the achiral lithium enolate **25**[10] the D.S. of the aldehyde *S*-**24** is determined to be 2.7 : 1, the ratio of the two products **26** and **27**.



Scheme 4.

[*] In general, this ratio is predicted to be smaller than the larger of the two D.S.'s.

Inspection of the absolute configurations of the C3 hydroxyl groups in **22** and **26** (Scheme 4), both of which are the predominant products of the above two reactions, immediately suggests that *S*-**20** and *S*-**24** constitute a matched pair (Scheme 5). In fact, the reaction of this pair leads to the enhancement of stereoselection (8 : 1), providing the major product **28** which incorporates the C3 hydroxy group in a β configuration and with an *anti*-relationship to the 4-methyl group. The corresponding mismatched pair of *S*-**24** and *R*-**20** reacts with inferior stereoselection (1 : 1.5) as predicted. A slight excess of **29** over its diastereoisomer **29a** is noteworthy in that the larger D.S. of *R*-**20** (reagent) compared with that of *S*-**24** (substrate) determines the stereochemical outcome of this reaction.



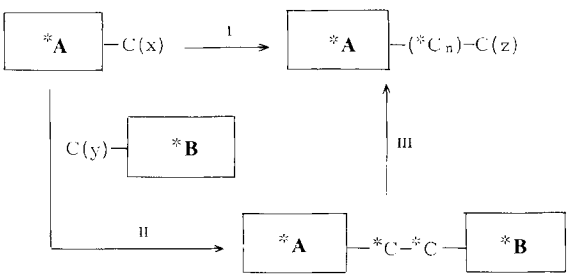
Scheme 5.

With the above results in hand, one cannot resist hypothesizing the multiplicativity of two diastereofacial selectivities in double asymmetric synthesis. The *degree of asymmetric induction is approximated to be (a × b) for a matched pair and (a ÷ b) for a mismatched pair* where a and b are the D.S.'s of a substrate and a reagent, respectively[*]. Fully admitting that several fortuitous events have brought about the above sets of product ratios that support the hypothesis, it is clear even at this preliminary stage that the multiplicativity will be valid only in a qualitative sense. Organic reactions are far too complex to be treated in the simplistic manner presented above, and many secondary interactions which occur in the regions remote from the reaction site are entirely ignored. Moreover, the diastereofacial selectivity is not a fixed number but has a range depending on the choice of an achiral model. A more critical analysis of the reaction course will be presented in Section 9, after having examined many examples of double asymmetric induction in Sections 4—7. For the time being, however, let us accept the validity of this multiplicativity of diastereofacial selectivities and see how it can be utilized for organic synthesis in terms of stereocontrol[3][**].

[*] The values of D.S.'s are selected in such a way as to be greater than 1. Obviously the two terms, a × b and a ÷ b, concern the relative directionality of the two diastereofacial selectivities.

3. A New Strategy for Stereochemical Control

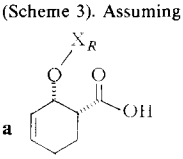
In natural products synthesis we frequently encounter the need to build a new chiral center or centers on a chiral substrate. Process I in Scheme 6 formulates this transformation: chiral substrate *A–C(x) is converted into



Scheme 6. Strategy for generation of new chiral centers on a chiral substrate. **A** and **B** must be homochiral. *A–C(x): chiral substrate; *B–C(y): chiral reagent; I: desired transformation; II: double asymmetric induction; III: removal of the chiral auxiliary.

A–(C_n)–C(z), where both C(x) and C(z) denote appropriate functional groups for the chemical operation. In order to achieve this task a chiral reagent *B–C(y) is allowed to react with *A–C(x) to provide a mixture of stereoisomers expressed by *A–*C–*C–*B (Process II). The reagent *B–C(y) is chosen so that a high stereoselection (at *C) is achieved in this process. Having served its purpose, the chiral auxiliary *B is removed in such a fashion so as to leave a functional group C(z) for further transformation (Process III). During this process the stereochemical integrity of the new chiral centers must be preserved. From the analysis detailed in the preceding section, it follows that: (1) When the desired *A–*C–*C–*B is the major product in the matched pair reaction, the resulting stereoselection should be higher than the diastereofacial selectivity of *A–C(x) (being augmented by that of the reagent), and (2) if the desired product *A–*C–*C–*B happens to be the minor product of the above reaction, then the reagent of

[**] Readers can easily recognize that this hypothesis of multiplicativity of D.S.'s is valid only for a pair of *homochiral* reactants, but not valid with racemates. Consider, for instance, that *R*-**8** (2 equiv.) reacts with a racemate consisting of *R*-**13** (1 equiv.) and *S*-**13** (1 equiv.) in the above Diels-Alder reaction (Scheme 3). Assuming that *R*-**8** couples with both



R-**13** and *S*-**13** at the same rate (no kinetic resolution), a simple calculation predicts that after removal of the chiral auxiliaries Y_R and Y_S (in **16**—**19**) with $NaIO_4$, the resulting product consists of **a** and **b** in a 1.9 : 1 ratio. Compare this ratio with those (40 : 1 and 1 : 2) obtained in the matched and mismatched reactions shown in Scheme 3. When equimolar *rac*-**8** and *rac*-**13** are used in the same reaction, then a mixture of *rac*-**a** and *rac*-**b** (X_R's in both **a** and **b** are X_R and X_S) in the same ratio will result.

the opposite chirality should be used. This latter case represents a mismatched pair reaction, and the diastereofacial selectivity of the reagent must be large enough to outweigh that of *A–C(x) in order to create the desired *C–*C stereochemistry with high selection. Such reagents of either chirality (at *B) can be, and have been, prepared. The same arguments are also applicable to highly enantioselective catalysts[*] which make the direct transformation of Scheme 6 (Process I) possible.

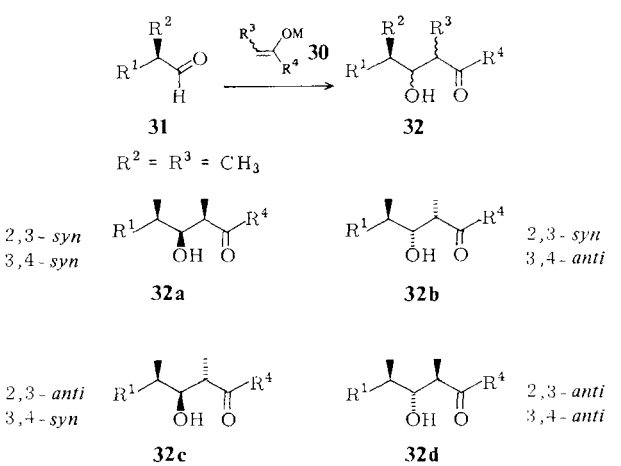
A short time ago, the preparation of a reagent or catalyst with a 20:1 stereoselection [90.4% diastereomeric excess (*de*) or enantiomeric excess (*ee*)] for the reaction with achiral substrates was regarded as a worthy accomplishment. *Chiral* acyclic systems which we *normally* encounter in synthesis exhibit a small diastereofacial selectivity ranging from 1 to 5. Therefore, in order to achieve the same degree of stereoselection (20:1) in the mismatched pair reaction with a *chiral* acyclic substrate possessing a 5:1 D.S., the above analysis of double asymmetric induction demands that to a first approximation the reagent be capable of a D.S. of at least 100:1. With such reagents a >100:1 stereoselection is expected for a matched pair while even a mismatched pair brings about a minimal isomeric ratio of 1:20, roughly the limit of stereoselection which is of practical significance in organic syntheses. Both the D.S. of the substrate and the extent of stereoselection desired in the double asymmetric synthesis determine the D.S. demanded of the reagent. Readers are urged to appreciate the greater demand placed on reagents in double asymmetric reactions.

As elaborated upon above, the stereochemistry of organic reactions may be controlled by the chirality of reagents (and substrates) rather than substrates alone as it has been in most cases to date, and as a result a stereoselection of one order of magnitude higher than that previously attained may accrue through this double asymmetric methodology. As frequently happens in science, the first unequivocal demonstrations (to our best knowledge) of such *stereochemical control* (in the sense defined in Section 1) were documented in 1980 by more than one group engaged in widely diverse branches of chemistry, the aldol reaction[8] and catalytic hydrogenation[11][**]. Let us see how successfully this new strategy has since been applied in the stereocontrol of major organic reactions to achieve 20:1 or better stereoselection, the standard that is set for this Account[***].

4. Aldol Reaction

This venerable reaction formulated in Scheme 7 involves an enolate (**30**) and an aldehyde (**31**) which react to form a new carbon-carbon bond. Recent intense and extensive studies on the reaction have covered a wide variety of reaction conditions and structural modifications[3, 12], and have disclosed that only a few sets of reaction parameters bring about the high stereoselection that meets the standards set above (Section 3). In this regard, the use of chiral boron enolate reagents is notably successful and is discussed below.

In general, the aldol reaction creates two new chiral centers producing four possible stereoisomers **32a–d**, as exemplified for the reaction of a chiral aldehyde (R^2 = Me in **31**) and the enolate (R^3 = Me in **30**) derived from an ethyl ketone (Scheme 7). Two elements of control are necessary to achieve a high stereoselectivity for this process. Assume that the boron-mediated aldol reaction proceeds via the chair-type cyclic transition state (Zimmerman-Traxler model)[13] such as **33** shown for a *Z*-enolate attacking an aldehyde from the *Re* face of the latter (Scheme 8). Then, under kinetic control, there are four possible reaction courses: (1) *Z*-Enolate attacking the *Re*-face of the aldehyde **31** (**33** → **32a**), (2) *Z* attacking *Si* (**34** → **32b**), (3) *E* attacking *Re* (not shown) and (4) *E* attacking *Si* (not shown), thereby forming the isomers **32a–d**[14, 15]. From this analysis, tabulated in Scheme 8, it can be seen that (a) the enolate geometry should be translated into control of the 2,3-stereochemistry of the products (**32**), and (b) the direction of the enolate approach should determine the absolute configuration of the 3-hydroxy group of **32**, thereby providing control of the relative stereochemistry at the 3,4-positions. Two sets of experiments involving *achiral Z*- and *E*-boron enolates with *achiral* aldehydes provide the corresponding racemic 2,3-*syn*- and 2,3-*anti*-aldol products, respectively[16][**]. Thus, these results lend strong support to the proposed model and further justify the pursuit of 3,4-stereochemical control which, obviously from the discussions of the preceding Section, concerns the diastereofacial selectivities of both reactants. The following examples best illustrate this crucial issue.



Scheme 7 [*].

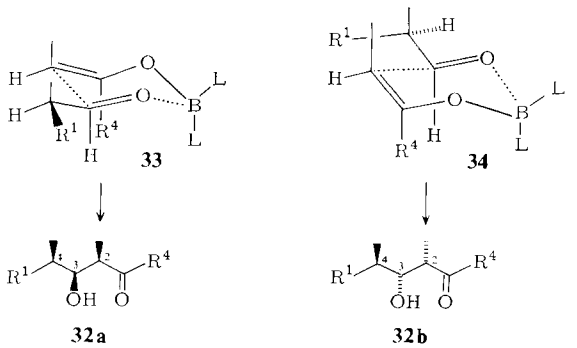
[*] The reaction of an achiral substrate with a chiral catalyst or stoichiometric addend provides the corresponding enantiomers rather than diastereoisomers in unequal quantities. However, since the reaction proceeds through diastereomeric transition states, the term diastereofacial selectivity is also retained for the chiral catalyst and addend.

[**] For the decade preceding these demonstrations, several examples of double asymmetric induction without control appeared sporadically. These will be summarized in Section 9.

[***] We advise that those who are not interested in numerous examples of double asymmetric reactions proceed from here to Section 8.

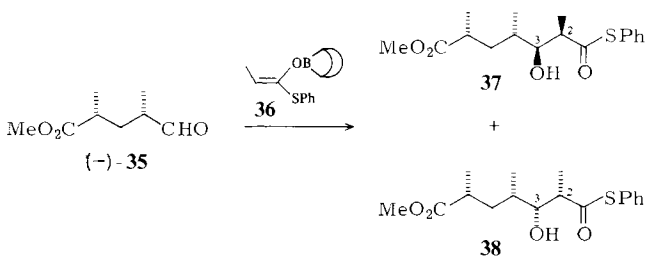
[*] The "*syn,anti*" nomenclature proposed in references [8] and [14] appears to have now been accepted for general use, as it has been used in recent representative review articles (references [12c] and [15]).

[**] For instance, reaction of isobutyraldehyde with the enolate derived from ethyl cyclohexyl ketone (R^1 = Me, R^4 = cyclohexyl in **33** and **34** in Scheme 8) provides **32a** and **32b**, a 1:1 mixture of which is a racemic aldol.



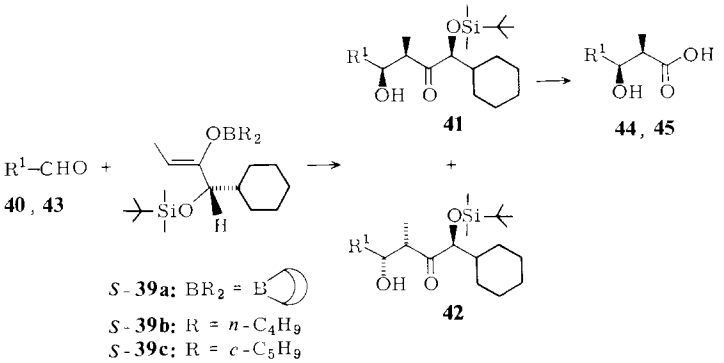
Scheme 8. Routes to **32a—d**.
Re-attack:
Z-**30** + **31** ⟶ **33** ⟶ **32a**, 2,3-*syn*, 3,4-*syn*
E-**30** + **31** ⟶ **32c**, 2,3-*anti*, 3,4-*syn*
Si attack:
Z-**30** + **31** ⟶ **34** ⟶ **32b**, 2,3-*syn*, 3,4-*anti*
E-**30** + **31** ⟶ **32d**, 2,3-*anti*, 3,4-*anti*

As shown in Scheme 9 the reaction of (−)-dimethylglutaric hemialdehyde **35** with an *achiral* *Z*(*O*)-enolate[*], e.g. **36**, provides an approximately 3:2 mixture of **37** and **38** which correspond to **A** and **B** in Scheme 1. Note that (1) the two substituents at the 2,3-position of the products are *syn*-oriented in both **37** and **38** but are opposite in terms of the absolute configuration and (2) the 3:2 ratio is the diastereofacial selectivity for aldehyde **35**. This ratio represents roughly the degree of diastereoselection that one can attain in the aldol reaction of **35** without recourse to double asymmetric induction.



Scheme 9. **36** is a 9-borabicyclo[3.3.1]non-9-yl derivative.

Now the task is to develop chiral enolate reagents which have high diastereofacial selectivities (≥100:1) in single asymmetric reactions. Of the many chiral *Z*(*O*)-enolates that have been prepared and examined, those (**39**) shown in Scheme 10, prepared from optically pure (*S*)- or (*R*)-mandelic acid, meet the criteria set for the chiral reagents[17]. Thus, *achiral* aldehyde **40** undergoes aldol reaction with *S*-**39c**, the most stereoselective (but least reactive) boron enolate of the three (**39a**—**39c**), to provide a 100:1 mixture of diastereoisomers **41** and **42**. With isobutyraldehyde **43**, an α-branched aldehyde, the selectivity of the reaction is very high (>100:1 of **41** to **42**; Table 1) even with the least selective (but most reactive) boron enolate *S*-**39a**. Successive treatment of a mixture of **41** and **42** with hydrogen fluoride (or fluoride anion) followed by sodium metaperiodate provides the corresponding 2,3-*syn*-3-hydroxy-2-methylcarboxylic acids (**44** and **45**) with an enantiomeric excess higher than 98%. This removal of the chiral auxiliary corresponds to Process III of Scheme 6. Thus, the diastereofacial selectivity of **39** exceeds 100:1 with the proper selection of a ligand attached to the boron atom.



Scheme 10. *S*-**39a** is a 9-borabicyclo[3.3.1]non-9-yl derivative.

Table 1. Reaction of aldehydes with boron enolates **39** (see Scheme 10).

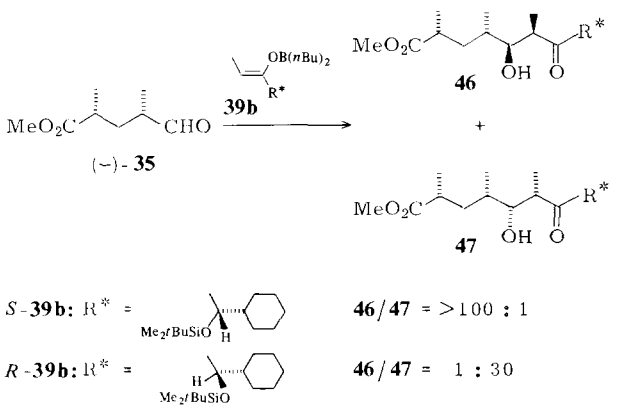
Aldehyde	R^1	Boron enolate	**41**:**42**	Acid [a]
40	$PhCH_2OCH_2CH_2$	*S*-**39a**	16:1	**44**
		S-**39b**	28:1	
		S-**39c**	100:1	
43	$(CH_3)_2CH$	*S*-**39a**	>100:1	**45**
		S-**39b**	>100:1	
		S-**39c**	no reaction	

[a] Main product.

One can now examine the interaction of the *chiral* aldehyde (−)-**35** with the *chiral* enolate *S*-**39b**[18]. This aldol reaction provides two diastereoisomers **46** and **47** in a ratio of >100:1 (Scheme 11). A change in the chirality of the enolate reagent brings about a reversal of the result: The combination of (−)-**35** and *R*-**39b** leads to the formation of **46** and **47** in a ratio of 1:30 favoring the latter (**47**). The significance of these two reactions is threefold: (1) Both ratios are far superior to the ratio of 3:2 obtained with an achiral enolate, (2) the chirality of R* in **39b** is directly correlated to the stereochemistry at the 3,4-positions of the reaction products, and thus either the 2,3-*syn*-3,4-*anti* or 2,3-*syn*-3,4-*syn* system can be constructed in a preselected manner, and (3) the multiplicativity of the two diastereofacial selectivities (3:2 and 100:1) is *roughly* realized; the two reactions, (−)-**35** + *S*-**39** and (−)-**35** + *R*-**39**, representing matched and mismatched pairs, respectively. The stereochemical course of the aldol reaction is now fully under control and the power of double asymmetric induction is clearly demonstrated.

It is appropriate to insert here a brief account of our recent synthesis of the macrolide 6-deoxyerythronolide B **48**[19]. It was during the course of this synthesis that the new strategy emerged as a means of solving the stereochemical problems associated with the target molecule. The achievement was the first successful demonstration of double asymmetric synthesis applied to the construction of molecules of this stereochemical complexity. The macrol-

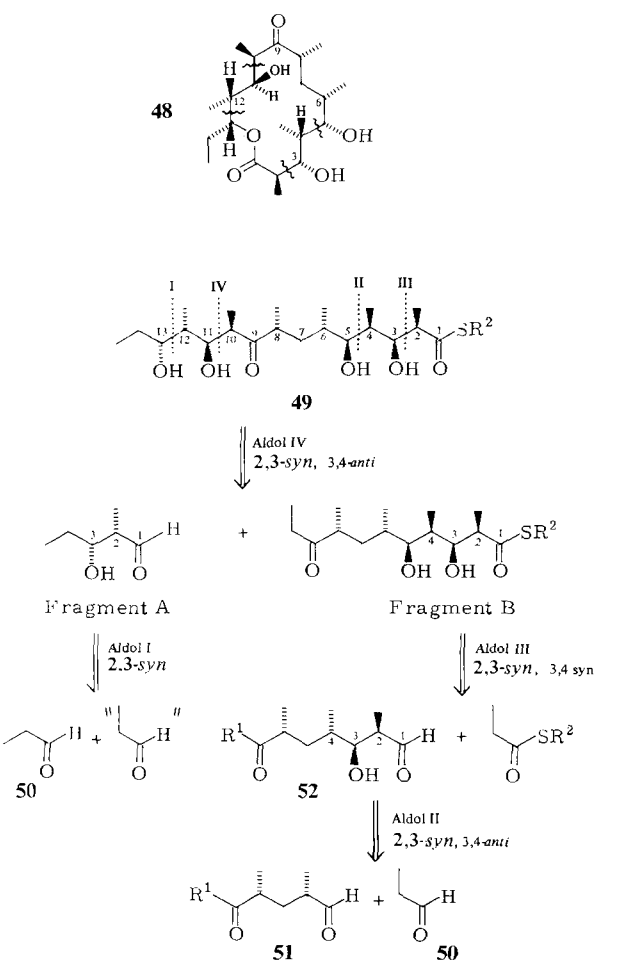
[*] Here, *Z*(*O*) signifies that the element oxygen has arbitrarily been given the highest priority (see reference [14]).



Scheme 11. (−)-**35** + *S*-**39b**: matched pair; (−)-**35** + *R*-**39b**: mismatched pair.

ide **48** is the lactone derived from the 13-hydroxypentadecanoic acid **49** which consists of seven propionate building blocks[*] (Scheme 12).

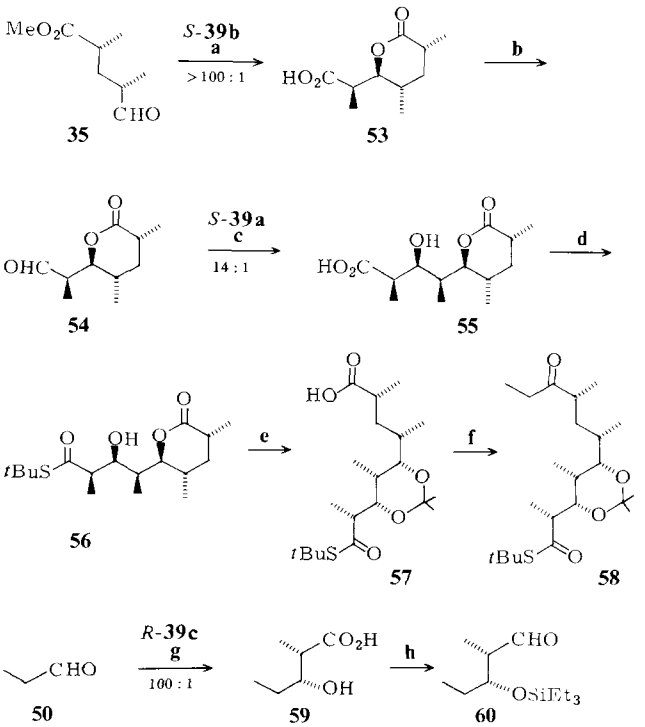
Splitting this seco-acid **49**, drawn in zigzag fashion, into fragments A and B immediately suggests the order of the aldol reactions to be used in the synthesis. Aldol reaction I (involving propanal **50** and its enolate equivalent) produces fragment A, while aldol reactions II (**50** and **51**) and III (**52** and an equivalent of **50**) complete a synthesis of fragment B. Finally, both fragments are combined via aldol reaction IV. Note that aldol reactions I, II, and III all concern the creation of 2,3-*syn* stereochemistry, a task that can be readily achieved with the *Z*-enolates **39a**—**c**.



Scheme 12. Retrosynthetic analysis of 6-deoxyerythronolide B **48**.

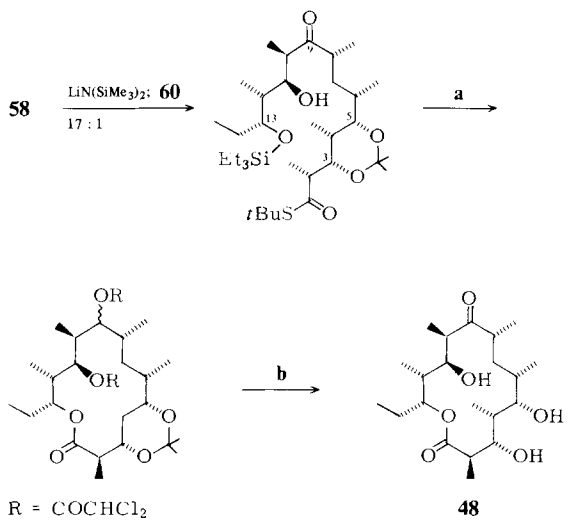
[*] More accurately, these are one propionyl CoA and six methylmalonyl CoA's.

The first step of the seco-acid synthesis has already been discussed (Scheme 11). The reaction of (−)-**35** with *S*-**39b** provides the desired product with > 100 : 1 stereoselection and the resulting aldol product **46**, after removal of the chiral auxiliary (HF and then $NaIO_4$: Process III of Scheme 6), is converted into the Prelog-Djerassi lactonic acid **53** in optically pure form (> 98% *ee*) (Scheme 13). Addition of the C1—C2 fragment (see **49**) to the aldehyde **54** derived from acid **53** uses the *S*-chiral reagent **39a** (aldol reaction III, Scheme 12). Thus, reaction of **54** provides the desired aldol product (14 : 1 stereoselection) which, upon standard treatment, is transformed to the carboxylic acid **55** and then to its thiol ester **56**. After modification of the functional groups of **56** through a series of routine reactions the resulting carboxylic acid **57** is further converted to the corresponding ethyl ketone **58**, which is an equivalent of fragment B. The enantioselective synthesis (selectivity > 100 : 1) of the hydroxy acid **59** corresponding to fragment A is readily achieved using propanal (**50**) and *R*-chiral reagent **39c** (aldol reaction I). A sequence of standard operations converts **59** into aldehyde **60**. Thus, eight chiral centers out of the ten embedded in the target molecule **48** have been created with remarkable efficiency and stereo-



Scheme 13. Synthesis of **58** and **60** (equivalents of fragments B and A, respectively, *in* Scheme 12). **a**: 1) nBu_4NF, 2) $NaIO_4$, 85% yield; **b**: 1) $(COCl)_2$, 2) H_2, 5% $Pd/BaSO_4$, $(Me_2N)_2C{=}S$, 95% yield; **c**: 1) HF, 2) $NaIO_4$, 71% yield; **d**: $ClCO_2Et$, $TlStBu$; **e**: 1) KOH, 2) $tBuPh_2SiCl$, 3) $CH_2{=}C(OMe)Me$, trifluoroacetic acid, 4) nBu_4NF, 46% yield from **55**; **f**: 1) $(COCl)_2$, 2) $LiCuEt_2$, 84% yield; **g**: 1) HF, 2) $NaIO_4$, 85% yield from **50**; **h**: 1) CH_2N_2, 2) Et_3SiCl, 3) diisobutylaluminum hydride, 4) $CrO_3(py)_2$, 75% yield.—The stereoselection is shown under the arrows.

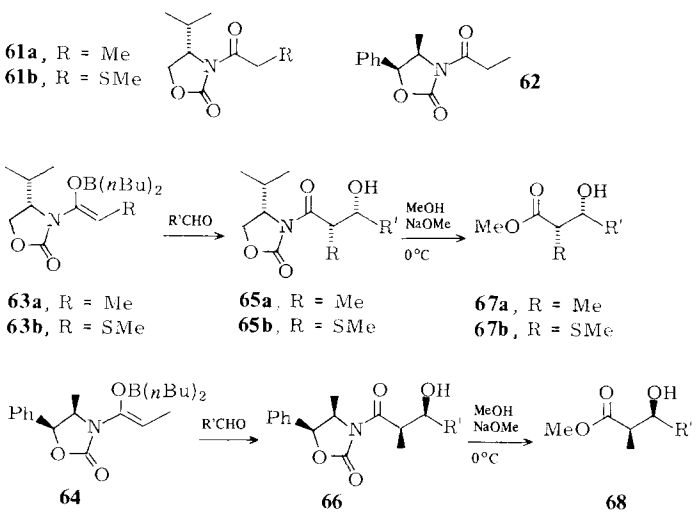
selection (Scheme 13). At this stage the overall yield is 30% and overall stereoselectivity is approximately 90%. The remaining tasks consist of the final aldol coupling (aldol reaction IV in Scheme 12) of fragment A with B and the macro-lactonization of the resulting derivative of the seco-acid **49**, both of which have been successfully executed, as outlined in Scheme 14.



Scheme 14. Synthesis of a derivative of the seco-acid **49** and ring closure to 6-deoxyerythronolide B **48**. The yield in the first step is 88%. **a**: 1) $NaBH_4$, 2) $(Cl_2CHCO)_2O$, 3) AcOH, 4) $CuOSO_2CF_3$; $Et(iPr)_2N$, 34% yield; **b**: 1) KOH, 2) pyridinium chlorochromate, NaOAc, 3) trifluoroacetic acid (quantitative).—The stereoselection is given under the first arrow.

The macro-lactonization has already been adequately reviewed[20], and the stereochemical control in the aldol reaction IV is methodologically different from that which has been discussed above[21][*]. Therefore, both transformations in the final stages of the 6-deoxyerythronolide B synthesis are omitted from the discussion in this Section.

Chiral enolate reagents that exhibit a $>100:1$ diastereofacial selectivity in the aldol reaction are rare at present, and documented examples of double asymmetric induction using such reagents are even more scarce. In this connection, the boron enolate chemistry developed in *Evans'* laboratories along a line similar to that outlined above deserves special mention (Scheme 15). Thus, a pair of chiral *N*-acyl-2-oxazolidinones **61a** and **62** (derived from (*S*)-valine and (1*R*,2*S*)-norephedrine, respectively) are converted under the standard conditions ($nBu_2BOSO_2CF_3$ and iPr_2NEt) into the corresponding *Z*-boron enolates (**63a** and **64**) each of which is allowed to react with a set of achiral aldehydes[22]. The 2,3-*syn* diastereoisomers **65a** and **66** are virtually the sole products of these reactions with **63a** and **64**, respectively, showing that both the enolate formation and the aldol reaction proceed with (near) perfect stereoselection (ca. 500 : 1). Treatment of **65a** and **66** with sodium methoxide (molar ratio 1 : 1) in methanol provides the corresponding 2,3-*syn*-3-hydroxy-2-methylcarboxylates **67a** and **68** of >99% optical purity, and these products **67a** and **68** are opposite in chirality. Similarly the boron enolate **63b** derived from **61b** (R = SMe) reacts with aldehydes to provide the products **65b**. The diastereofacial selectivity of the enolate **63b** ranges from 9 : 1 to 50 : 1 in these cases.



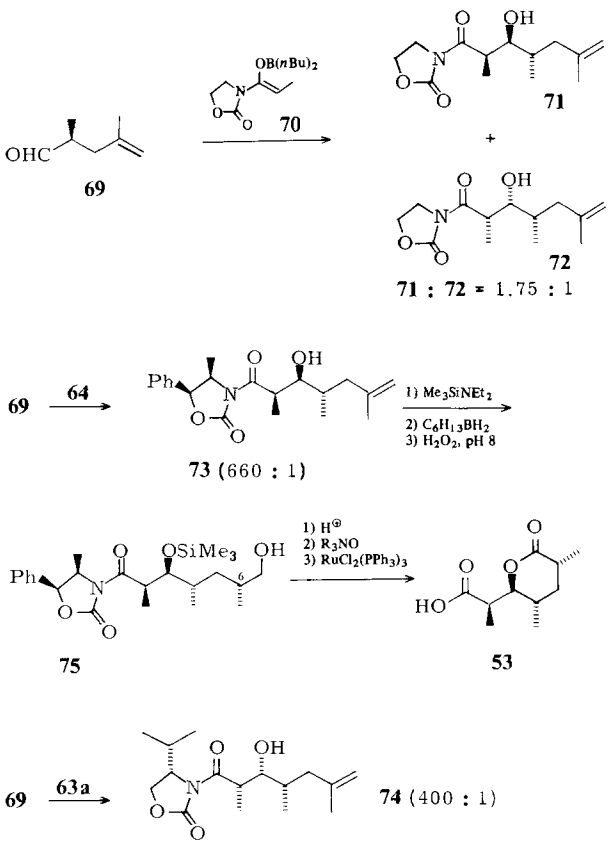
Scheme 15.

A typical demonstration of double asymmetric induction analogous to that shown in Scheme 11 is now available for the pair of reagents **64** and **63a**[23]. The chiral aldehyde selected is **69** which has a diastereofacial selectivity of 1.75 : 1, as determined by the ratio of two aldol products **71** and **72** obtained from the reaction of **69** with the achiral boron enolate **70**, structurally similar to **64** and **63a**. The reaction of **69** with **64** and **63a** provides exclusively **73** and **74** (with stereoselections of 660 : 1 and 400 : 1), respectively. Thus the chirality of the reagents, but not of the substrate, clearly dictates the stereochemical course of the reactions. The concept of matched and mismatched pairs can also be recognized in this example. The product **73** is further converted through a sequence of reactions: (1) trimethylsilylation, (2) hydroboration with thexylborane (*single* asymmetric induction with 5.7 : 1 in favor of the diastereoisomer **75**, see C6) followed by oxidative workup, (3) acid hydrolysis to remove the trimethylsilyl group of **75**, (4) ruthenium-catalyzed oxidation of the primary hydroxy group, and finally (5) hydrolytic removal of the chiral auxiliary. The resulting product is the (+)-Prelog-Djerassi lactonic acid **53** discussed earlier in Scheme 13. More elaborate incorporation of double asymmetric induction in the synthesis of several complex natural products is underway in *Evans'* laboratories[24] and will be formally documented in the near future.

Other qualified chiral reagents include the zirconium enolates **76** and **77**, which are obtainable from the corresponding lithium enolates via metal exchange with Cp_2ZrCl_2[25].

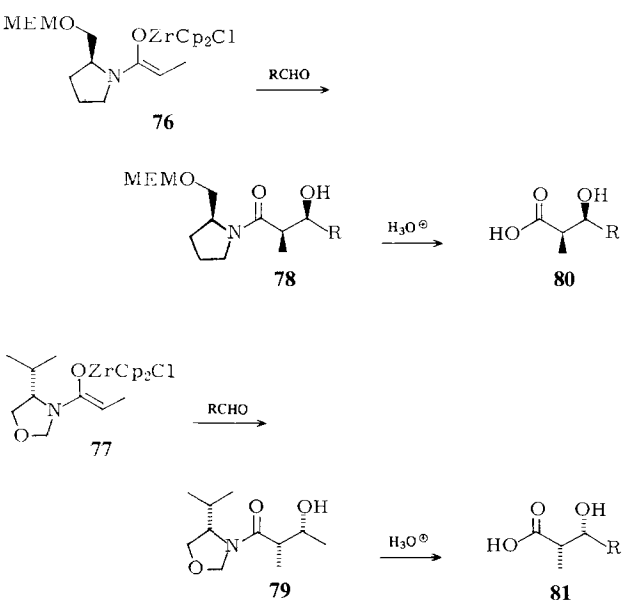
Reactions of both **76** and **77** with representative achiral aldehydes (Scheme 17) proceed with excellent 2,3-*syn*/*anti*

[*] Aldol reaction IV, which is also a double asymmetric reaction, is distinguished from aldol reactions I—III in that it (IV) involves the coupling of two structurally *prefixed* components. Another important aspect of this reaction is that the coordination of $Li^{\oplus}$ with the β-ethereal oxygen atom of the aldehyde **60** is mainly responsible for the attainment of a 17 : 1 stereoselectivity (reference [21]). This chelation effect will be discussed in Sections 8 and 9.



Scheme 16.

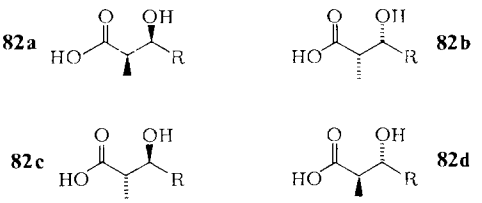
selection (96—98%) and also with a diastereofacial selection ranging from 50:1 to 200:1. Therefore, both **76** and **77** should, and indeed do exert their power in controlling the stereochemistry of aldol reactions with a chiral aldehyde as well. The recorded example uses 3-benzyloxy-2-methylpropanal and the results conform to the concept of matched and mismatched pairs. Removal of the chiral auxiliaries from **78** and **79** to obtain the corresponding carboxylic acids **80** and **81** (Process III of Scheme 6) requires



Scheme 17. MEM = methoxyethoxymethyl, Cp = cyclopentadienyl.

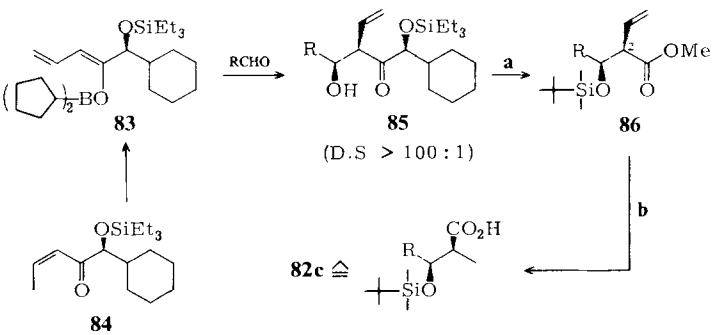
acid-treatment (5% HCl, 10 equiv. $H^{\oplus}$, 100°C, 2 h) which may cause some problems with acid-sensitive aldol products that might be encountered in the synthesis of complex natural products.

The foregoing discussions have been confined to the preparation of 2,3-*syn*-substituted units **82a** and **82b**, using a chiral *Z*-enolate. Because many attempts at devising *qualified* chiral *E*-enolates have met thus far with only partial success, the 2,3-*anti* units **82c** and **82d** (Scheme 18)



Scheme 18.

cannot be constructed through the *direct* aldol methodology at present. An indirect and somewhat circuitous approach (which provides a temporary solution to this problem) is outlined in Scheme 19[14,26]. The dicyclopentylboron *Z*-enolate **83** prepared from *Z*-enone **84** adds to an aldehyde in the expected manner (diastereoselection >100:1) to provide **85** which is converted into **86** in the

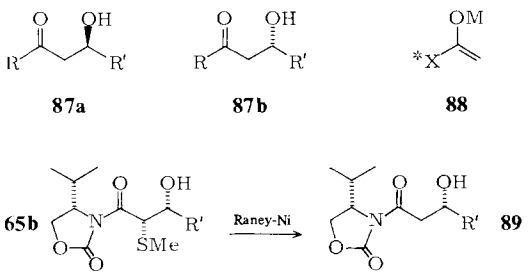


Scheme 19. Synthesis of an **82c**-equivalent. **a**: 1) HF, 2) $NaIO_4$, 3) CH_2N_2, 4) tBuMe$_2$SiOSO$_2$CF$_3$; **b**: 1) diisobutylaluminum hydride, 2) *p*-toluenesulfonyl chloride, 3) NaI, 4) $NaBH_3CN$, 5) O_3.

usual manner. This ester has two different functional groups, an olefin and an ester, both of which can be modified in a straightforward manner to reach **82c**. It is apparent that the right-hand end of the main chain and the 2-substituents of **86** are interchanged in **82c**. Thus, using one of the "tricks" synthetic organic chemists have often employed, a chiral *Z*-enolate eventually leads to the formation of 2,3-*anti* aldol products.

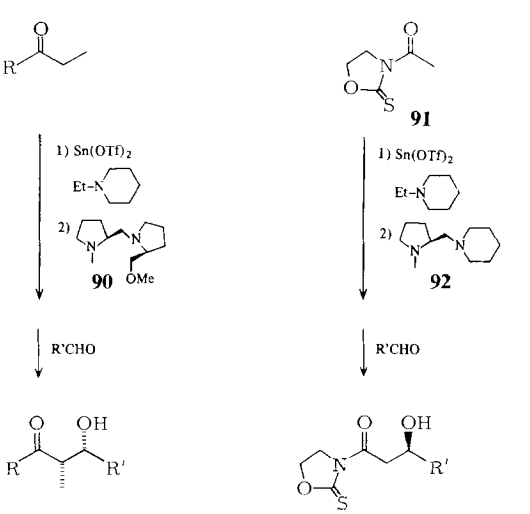
In the biosynthesis of important polyketide natural products another important structural unit (**87a**, **b**) emerges from the incorporation of an acetate building block (rather than a propionate as in the cases of **82a—d**). For several reasons now becoming clearer, all of the chiral enolates **88** (*X = chiral auxiliary) prepared in a manner analogous to that for **39**, **61**, and **76** exhibit an insignificant diastereofacial selectivity. Hence, the enolates **88** are at present incapable of constructing either **87a** or **87b** with high stereoselection. (However, see ref. [108]) A device to

surmount this problem utilizes the aldol product **65b** obtainable in sufficient homogeneity as discussed earlier (Scheme 15). Desulfurization with Raney nickel proceeds to provide, "in good yield," **89** from which the chiral auxiliary can be removed (Scheme 20)[22][*]. Thus, the indirect methods for the construction of **82c, d** and **87a, b** discussed above are viable for the aldol reaction with a variety of chiral aldehydes (double asymmetric inductions).



Scheme 20.

Our criteria set for the chiral enolate reagent are that it exhibits >95% *syn/anti* selection and a ≥100:1 diastereofacial selectivity. The tin(II)-mediated aldol reaction (developed in *Mukaiyama*'s laboratories), although not meeting both criteria, deserves due attention in that the asymmetric induction is brought about not by a chiral auxiliary attached to the enolate, but importantly by a chiral ligand[27]. Thus, each of several representative achiral ethyl ketones is converted with tin(II) bis(trifluoromethanesulfonate) and *N*-ethylpiperidine into its tin enolate, which, after the addition of the diamine **90** derived from (*S*)-prolinol, is allowed to react with a set of achiral aldehydes (Scheme 21). The *syn/anti* selection and the diastereofacial selectivity for the *syn* products range between 3:1 and 20:1 and between 3:1 and 9:1, respectively. The same reaction using 3-acetylthioazolidine-2-thione (**91**) as the enolate precursor and the diamine **92** as the chiral ligand provides a mixture of two enantiomers, the ratio of which ranges from 4.7:1 to 19:1, the diastereofacial selectivity of



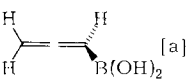
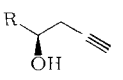
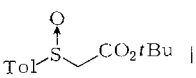
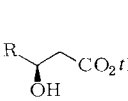
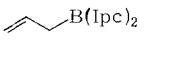
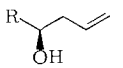
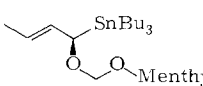
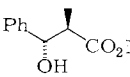
Scheme 21. Tf = CF_3SO_2O.

[*] For comments on this removal, see p. 56 of reference [3a].

the reaction species carrying the diamine. Further improvement of these stereoselectivities is eagerly awaited as the advantage of this aldol reaction which does not require removal of a chiral auxiliary is clear.

In closing this Section, several chiral reagents or catalysts are tabulated which are equivalent to the enolate reagents discussed above in the sense that all these achieve the same task of constructing the 3-hydroxycarbonyl system formulated in **82a–d** and **87a, b**. None of these "equivalents" has been tested in terms of double asymmetric induction, but their diastereofacial selectivities are excellent (Table 2)[28–31]. These reactions are reserved for a future review. They are complementary with the aldol methodology in that the latter is still inefficient in effecting the "acetate" addition. In Section 7 we will address an entirely different approach to the solution of this "3-hydroxycarbonyl" problem.

Table 2. Reactions of some chiral reagents or catalysts with aldehydes. Tol = *p*-tolyl, Ipc = 3-pinanyl ("isopinocampheyl").

Aldehyde	Reagent	Product	D.S.	Ref.
RCHO	 [a]		4:1 to 39:1 (60–95% *ee*)	[28]
RCHO	 [b]		ca. 9:1 (ca. 80% *ee*)	[29]
RCHO			11:1 to 49:1	[30]
PhCHO	 [c]		*anti* products: 99:1	[31]

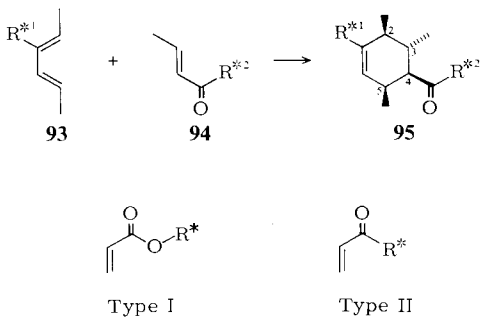
[a] (+)- or (−)-Diethyl tartrate added. [b] Second step: desulfurization with Raney nickel. [c] Second step: O_3, oxidative work-up; third step: CH_2N_2.

5. Diels-Alder Reaction

The Diels-Alder reaction effects one of the most efficient organic transformations in that it can create as many as four chiral centers as exemplified in Scheme 22. The pericyclic reaction of two chiral components, diene **93** and dienophile **94** can hypothetically produce $2^4 = 16$ stereoisomers, isomeric at the C2, C3, C4, and C5 atoms in **95**. The attainment of the potential stereoselection requires the advantageous (and simultaneous) exercise of, at least, four elements which govern the stereochemical course of the reaction. These elements are well known: *cis*-addition, *endo*-addition, and diastereofacial selectivities of both the chiral ene and diene[*]. With regard to the last factors, diastereoselectivities have received renewed interest in recent years. Since many chiral reactants recorded prior to early 1982 are adequately surveyed in several review articles[32],

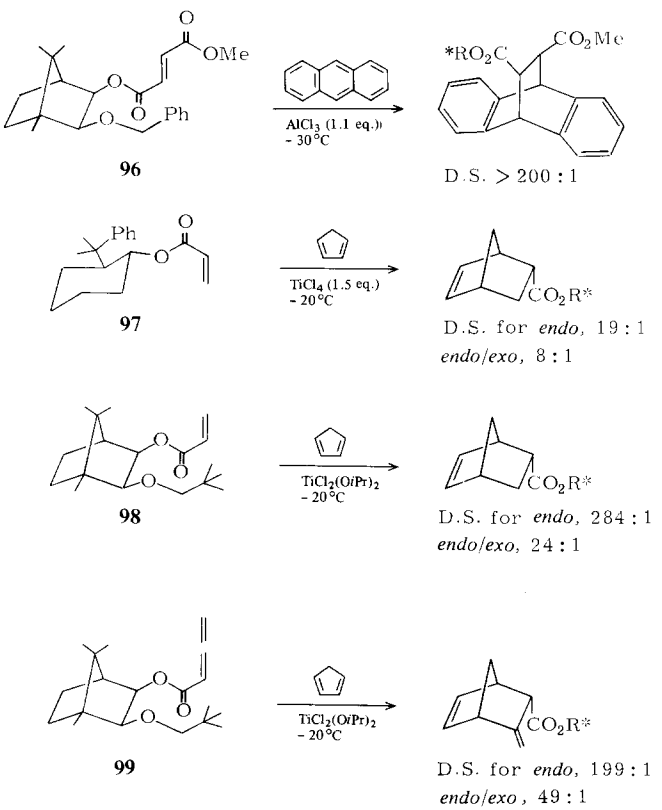
[*] The last factor (the diastereofacial selectivity of the chiral diene) is closely related with the orientation of **93** to **94** in the transition state (regiochemistry of **93**).

this section is mainly concerned with the most recent development of chiral dienophiles, which may be divided into two categories, the Type I and Type II reagents. In the Type II reagents a chiral auxiliary (R*) is attached one atom closer to the three-carbon enone unit than in the Type I[*].



Scheme 22.

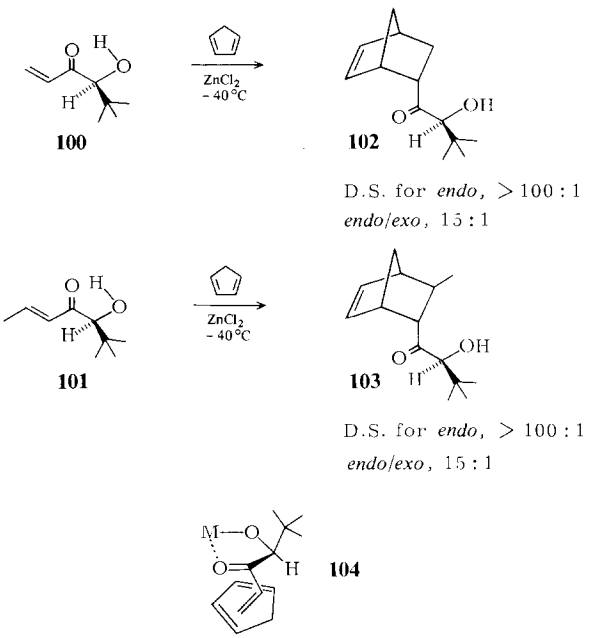
Of the many Type I chiral dienophiles some recent additions, **96**—**99**, clearly stand out as compared with the dienophiles reported earlier. As exemplified in Scheme 23[33-36], **96**—**99** undergo Diels-Alder reactions in the presence of a Lewis acid catalyst with a diastereoselection exceeding 100 : 1. The Type II dienophiles are newcomers to the asymmetric Diels-Alder reaction and were devised with the hope that the chiral group (R*) may act as a highly effective chiral inducer because it is placed so closely to the reaction site. Since the reagents **100** and **101** have been investigated far more thoroughly than the others in terms of diastereofacial selectivity and double asymmetric induction[37], the following discussions mainly concern these dienophiles.



Scheme 23.

[*] After completion of this Account, a further review of asymmetric Diels-Alder reactions appeared in the literature [104].

Coupling of **100** with cyclopentadiene in the presence of $ZnCl_2$ at $-40\,^{\circ}C$ is complete within 1 h and provides almost exclusively one *endo*-adduct (**102**) (diastereoselection for the two *endo*-products, > 100 : 1; *endo/exo*, 15 : 1) (Scheme 24)[*]. Likewise, the reaction of **101**, a homolog of



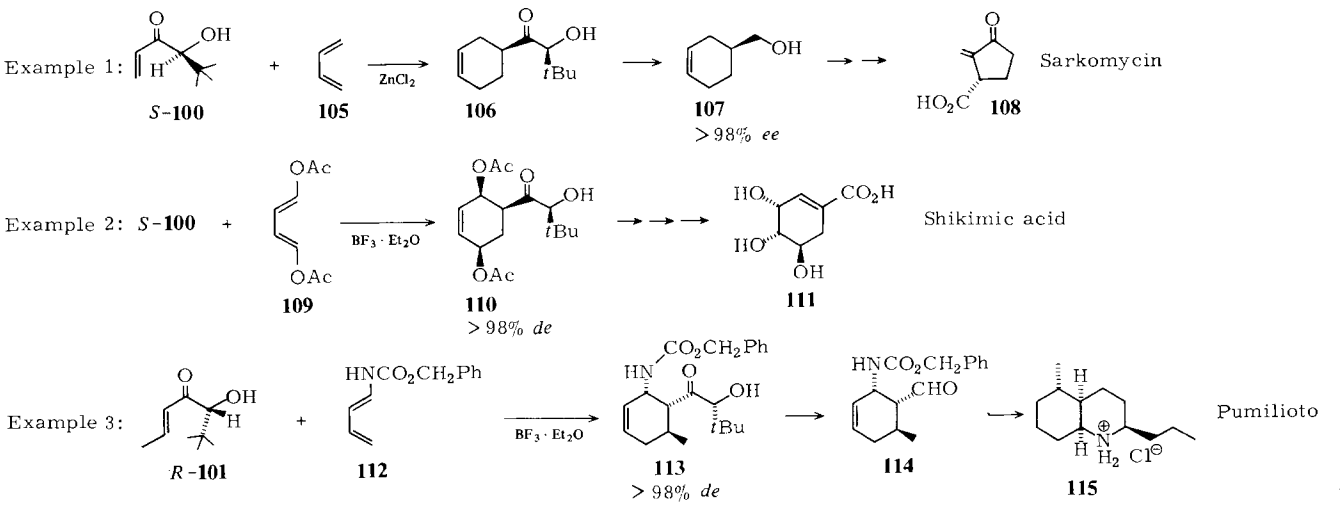
Scheme 24.

100, with cyclopentadiene under identical conditions proceeds smoothly with equally high stereoselection (D.S. for *endo* adducts, > 100 : 1). The results of these and other related experiments disclose at least two important features of the Diels-Alder reaction. First, coordination of the Lewis acid catalyst with the α-hydroxyketone moiety of the dienophile **100** leads to the formation of a rigid five-membered chelate, thus making the two diastereotopic faces of the enone system highly distinguishable (see **104**). Second, from the established absolute configurations of **100** and **101** (and also **102** and **103**), one concludes that within the chelated framework of **104** the Diels-Alder reaction proceeds, at least in these particular instances, with the enone fragment in its cisoid (synplanar) conformation (as opposed to the transoid conformation often postulated earlier for chiral esters of Type I)[**].

A variety of dienes react with **100** and **101**[37]. In the three examples shown in Scheme 25 the cycloaddition reaction provides a single adduct to the detection limits of ^{1}H-NMR spectroscopy (270 MHz). Oxidative removal of the chiral auxiliary group from the adduct (cf. a similar

[*] General problems associated with the *endo/exo* ratio have not been fully resolved. This important issue, however, is excluded from discussion.

[**] These experiments show how the investigation of an asymmetric synthesis can provide rich information about the transition state of a reaction.

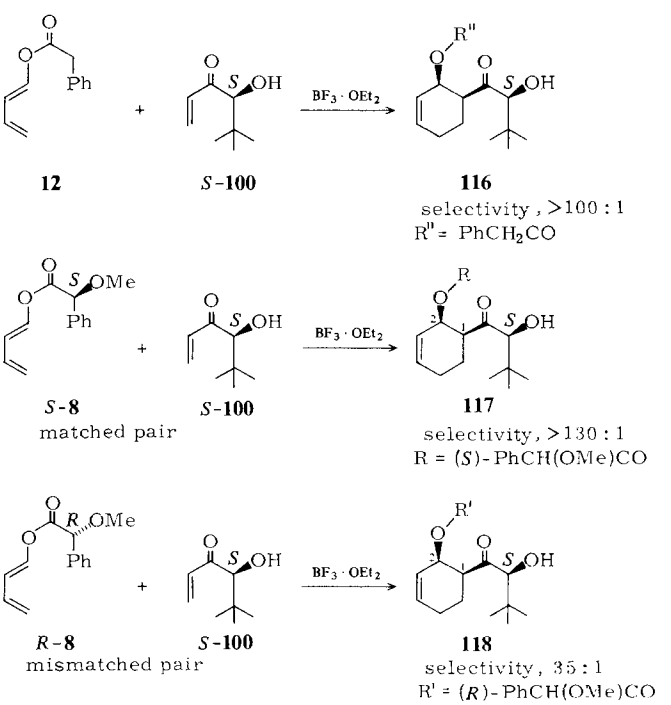


Scheme 25.

transformation of the aldol products discussed in Section 4) leads to a homochiral product (at minimum 98% *ee* or *de*) which serves as an intermediate for the synthesis of a natural product. *Example 1:* Reaction of *S*-**100** with excess butadiene (**105**) in the presence of $ZnCl_2$ gives rise to **106** which is in turn transformed via three steps to alcohol **107** (98% *ee*). Conversion of the enantiomer of **107** into natural sarkomycin **108** has already been documented[38]. *Example 2:* 1,3-Butadienylene diacetate (**109**) and *S*-**100** are coupled with the aid of $BF_3 \cdot OEt_2$ as catalyst. Product **110**, which is the exclusive stereoisomer of this cycloaddition, is then subjected to a series of six transformations analogous to those used earlier to provide optically pure shikimic acid (**111**)[39]. *Example 3:* A mixture of *R*-**101** and $BF_3 \cdot OEt_2$ is allowed to react with excess diene **112** to provide an adduct **113** with >100:1 diastereoselection, which is in turn converted in two steps to aldehyde **114**. Conversion of **114** to the hydrochloride of (+)-pumiliotoxin **115** follows the published procedure[40].

The above examples of single asymmetric induction clearly demonstrate that the chiral dienophilic reagents **100** and **101** are highly diastereoselective (>100:1), and satisfy the prerequisites for successful double asymmetric induction which is the issue central to this Account. In order to examine the validity of the matching and mismatching concept as applied to the Diels-Alder reaction, a set of experiments has been carried out using butadienyl phenylacetate **12** as an achiral diene and (*S*)- and (*R*)-*O*-methyl mandelates (*S*-**8** and *R*-**8**) as chiral dienes. Diene **8** has a moderate diastereoselectivity of 4.5:1 as described earlier in Section 2[*].

The first experiment involving *S*-**100** and **12** (Scheme 26) reconfirms the high diastereofacial selectivity of *S*-**100** as applied to **12**, which is close in structure to chiral diene **8**. As expected, **116** is the major product of the reaction which proceeds with >100:1 stereoselection in the presence of the catalyst $BF_3 \cdot OEt_2$. In the next two experiments, two chiral reactants are coupled under identical conditions. The reaction of diene *S*-**8** with dienophile *S*-**100** provides a >130:1 mixture of **117** and its diastereoisomer, while the ratio of adduct **118** and its stereoisomer



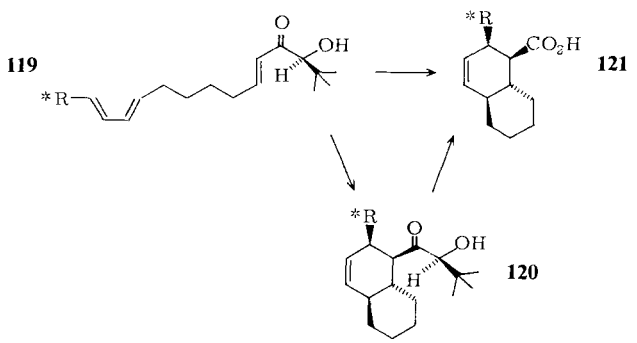
Scheme 26.

obtained from diene *R*-**8** and *S*-**100** is 35:1. Note that in the latter two cycloadditions the absolute configurations of the two major products **117** and **118** are the same at the C1 and C2 centers and are directly correlated with the chirality of **100** (but not with that of **8**). Thus the stereochemistry of these reactions is controlled through the selection of *R*- or *S*-**100**. As demonstrated in the aldol reaction (Sec-

[*] The corresponding hexahydromandelic acid derivative, cyclohexyl replacing phenyl in **8**, is as diastereoselective as **8** with the same directionality (reference [41]). Therefore, these results cast some doubt upon the validity of the proposed "π-stacking" as the origin of diastereoselectivity (see reference [9]).

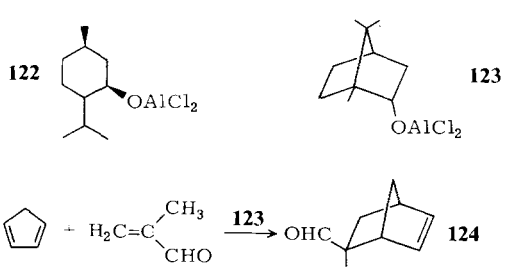
tion 4), this outcome reflects the large diastereofacial selectivity of **100** as compared with that of **8**. The different ratios (130 : 1 and 35 : 1) observed in the above reactions obviously correspond to matched and mismatched pairs, respectively. Thus, both **100** and **101** have been proven to be capable of creating new chiral centers in a predictable manner[*].

Intramolecular versions of the asymmetric Diels-Alder reaction abound in the recent literature and have achieved notable success in many natural product syntheses[32b,42]. The majority of these examples, if not all, use single asymmetric induction in the process of creating new chiral centers and also do not exactly follow Scheme 6 outlined in Section 3. The chirality-inducing moiety is not used as an auxiliary but is incorporated in a substrate as in the case of the aldol reaction discussed in Scheme 14 (also see Section 9). Therefore, the stereochemistry of these Diels-Alder reactions is not "controlled" in the sense used in this account. Those which should be "controlled" are formulated in Scheme 27 and several examples of double asymmetric induction that fall in this category (**119** to **121** via **120**) are currently under investigation[43].



Scheme 27.

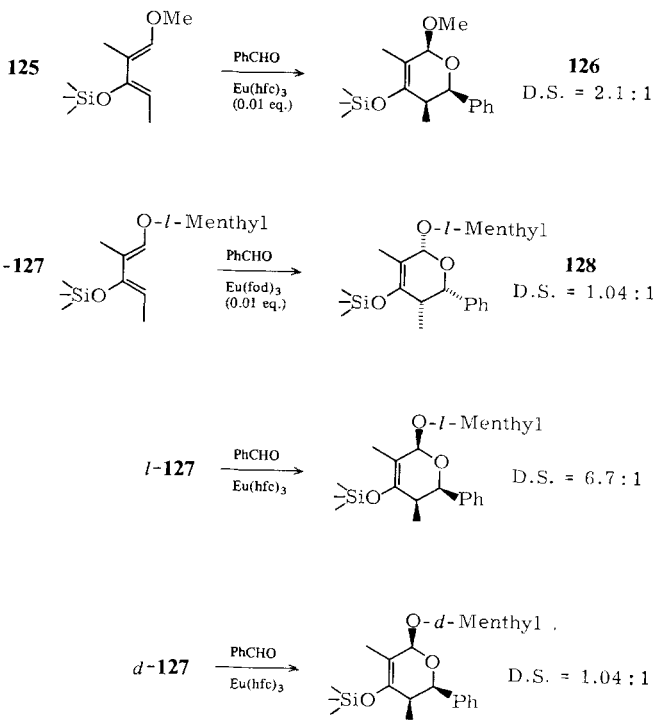
Only a few chiral Lewis acid catalysts such as **122** and **123** have been used in the Diels-Alder reaction[44]. The D.S.'s of these catalysts as determined by the cycloaddition of cyclopentadiene with methyl acrylate and acrolein are low (1 : 1 to 1.7 : 1) but they become rather significant in the reaction with methacrolein (6 : 1) (Scheme 28). Note that the major product **124** is formed via *exo*-addition. The rational design of effective chiral catalysts is indeed difficult because knowledge concerning the exact orientation of the catalysts in the transition state is lacking. In this



Scheme 28.

[*] The application of this double asymmetric synthesis to complicated cases (e.g., natural product syntheses) can be visualized if two major fragments are assembled via a Diels-Alder reaction.

connection, *Danishefsky*'s recent studies on the Lewis-acid catalyzed cycloaddition of benzaldehyde to dienes are of special interest[45], although this reaction involves a hetero-dienophile rather than the homo-dienophile, to which the discussions have been confined thus far.



Scheme 29. *l*- and *d*-Menthyl denote the substituents derived from (−)- and (+)-menthol, respectively.

Like common Lewis acids, the lanthanide NMR shift reagents, present even in trace amounts, catalyze the formal cycloaddition of benzaldehyde with several dienes. The chiral version of the reagents, $Eu(hfc)_3$, exhibits a small but non-negligible D.S. of 2.1 : 1 as exemplified by the reaction of **125** with benzaldehyde leading to **126** (Scheme 29)[46]. The D.S. of the chiral diene *l*-**127** as determined with (achiral) $Eu(fod)_3$ is very small (1.04 : 1) (see **128**). Since the facial selections of $Eu(hfc)_3$ and *l*-**127** (if these small numbers are taken seriously) are opposite, the combinations of *l*-**127** + $Eu(hfc)_3$ and *d*-**127** + $Eu(hfc)_3$ should constitute mismatched and matched pairs, respectively. The experiments that have been carried out show that in the former mismatched combination the selectivity (6.7 : 1) exceeds even that of $Eu(hfc)_3$, while the chirality of the catalyst has no influence on the stereoselectivity of the latter matched pair reaction. A similar trend prevails with three other dienes similar to **127**. Thus, this set of reactions represents an apparent anomaly to the postulated multiplicativity of two diastereofacial selectivities. There have been recorded in the literature other (albeit few) such anomalies which occur when the degree of diastereofacial selectivity to be dealt with is small, as will be seen in Section 6. It would be desirable to use other dienes with a larger D.S. to evaluate the validity of the matched and mismatched concept in this set of experiments. As pointed out in Section 3, our analysis is of first order, ignoring many

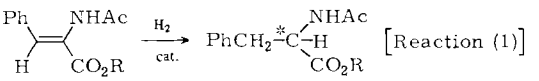
elements of a complex organic reaction which perturb the multiplicativity. This perturbation can become relatively significant in the case where both reactants have small diastereofacial selectivities (see Section 9).

6. Homogeneous Catalytic Hydrogenation

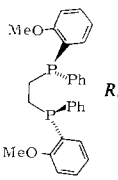
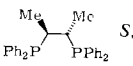
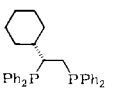
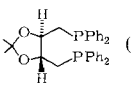
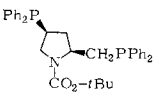
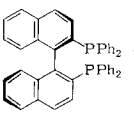
During the mid-1960's, three significant events took place making possible the development of homogeneous catalytic hydrogenation, namely: (1) *Wilkinson* et al. discovered chlorotris(triphenylphosphane)rhodium $[RhCl(PPh_3)_3]$, which exhibited remarkable properties as a soluble hydrogenation catalyst for unhindered olefins[47]. (2) Optically active phosphanes were prepared by two groups led by *Horner* et al. and *Mislow* et al.[48]. (3) *Horner* et al. and *Knowles* et al. independently demonstrated that the replacement of the triphenylphosphane in *Wilkinson*'s catalyst by chiral methyl(phenyl)propylphosphane effected a modest but definite asymmetric induction in catalytic hydrogenation of substituted styrenes[49]. Not surprisingly, therefore, the following decade witnessed a surge of efforts directed towards the preparation of more stereoselective chiral catalysts. Thus, while the range of substrates is limited, notably high optical yields, approaching 100% enantiomeric excess (*ee*), are now attainable in the hydrogenation of *N*-acetylaminocinnamic acid derivatives, such as **129**, to yield the corresponding amino acid derivatives (**130**) [reaction (1)]. The catalyst may be prepared in situ by adding 2 equivalents of chiral ligand (per mole of rhodium) to $[Rh(olefin)_2Cl]_2$ or a preformed complex of the type $[Rh(bis\text{-}ligand)(diene)]^{\oplus}BF_4^{\ominus}$ may be used. Table 3[50–55] lists some representative chiral catalysts (**131** — **136**) that exhibit high stereoselection. The dependence of the rates and stereoselectivities of catalytic hydrogenation on the electronic and structural variations of the catalysts and substrates have been investigated empirically, and elaborate mechanistic studies have been carried out notably by *Halpern* et al.[56] and by *Brown* et al.[57]. Since numerous comprehensive reviews have recently appeared[58], only the salient features of homogeneous hydrogenation will be outlined before the utility of this reaction for double asymmetric induction is discussed.

The seemingly simple net transformation of hydrogenation takes a complex stereochemical course (Scheme 30)[56]. Thus the prochiral olefin **129b** (R = Me in **129**) and the catalyst **132** form a rapidly equilibrating pair of diastereomeric complexes, **137a** (minor) and **137b** (major). The rate of complex formation and equilibration is much faster than that of the overall hydrogenation process. In the next stage oxidative addition of hydrogen to the minor complex **137a** proceeds *much more rapidly* than the addition to the main isomer **137b**, with the outcome that the former complex **137a** is responsible for the formation of the major hydrogenation product **130**. The resulting dihydride **138** rearranges to the organorhodium complex **139** in which hydrogen is transferred to the β-carbon and the metal bonds to the α-position. Reductive elimination to give *R*-**130b** and to regenerate the catalyst **132** completes the catalytic cycle. The stereochemical control occurs at either step **137a** → **138** or **138** → **139**.

Table 3. Hydrogenation with chiral rhodium catalysts and the enantiomeric excess of **130a** (R = H) in reaction (1). The catalysts **131–133** form five-membered rings, the catalysts **134–136** form seven-membered chelates.



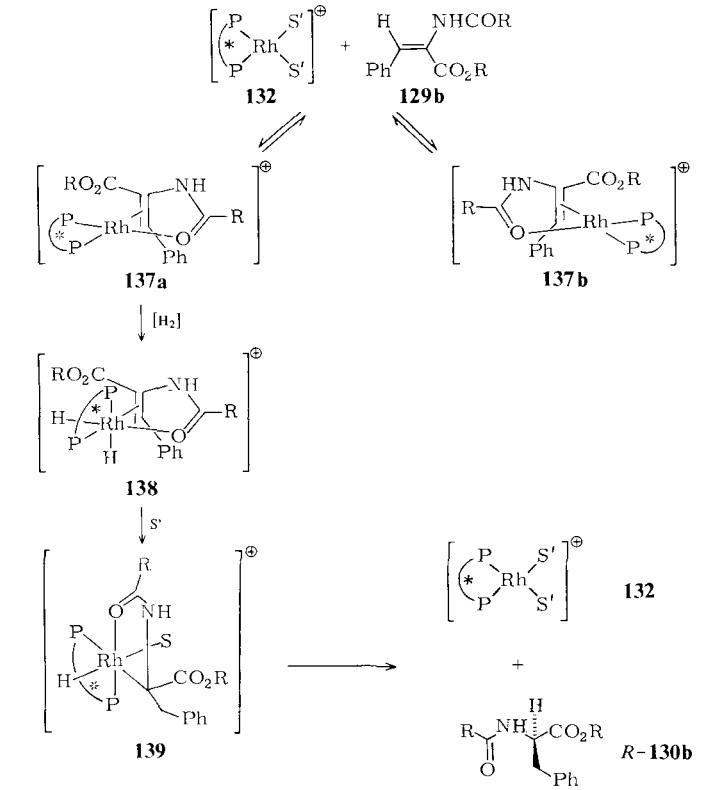
129 **130**

Catalyst [a]	Ligand	**130a** *ee* [%]	Ref.
[Rh(dipamp)]⊕ **131**	 *R,R*-dipamp	95 (*S*)	[50]
[Rh(chiraphos)]⊕ **132**	 *S,S*-chiraphos	>95 (*R*)	[51]
[Rh(cyphos)]⊕ **133**	 *R*-cyphos	91 (*S*)	[52]
[Rh((−)-diop)]⊕ (−)-**134**	 (−)-*R,R*-diop	83 (*R*)	[53]
[Rh((−)-bppm)]⊕ (−)-**135**	 (−)-*S,S*-bppm	91 (*R*)	[54]
[Rh(binap)]⊕ **136**	 *R*-binap	84 (*S*)	[55]

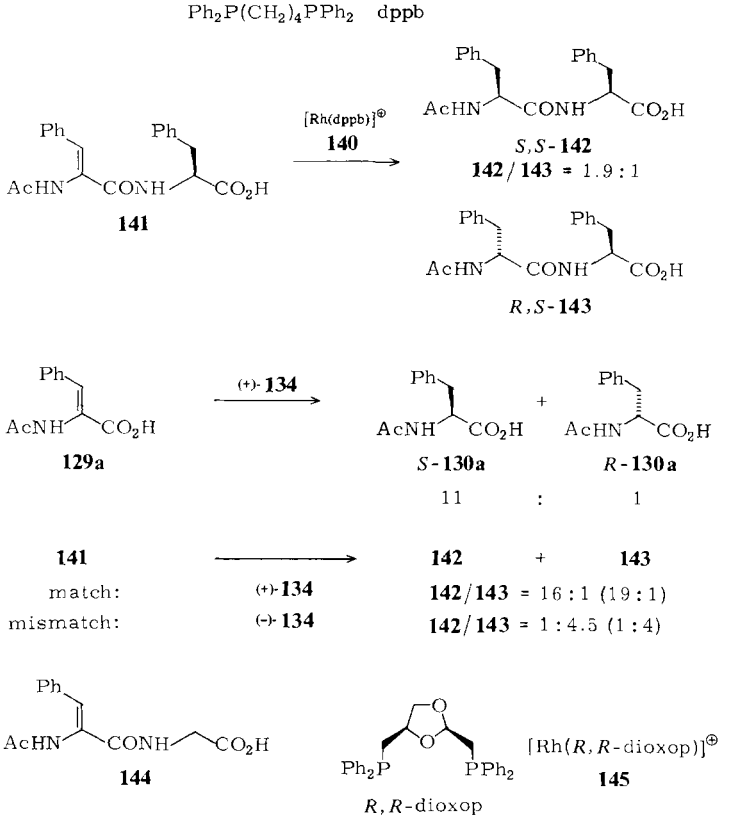
[a] Olefin ligands are omitted.

With highly stereoselective catalysts at hand (see Table 3) the effect of these catalysts on chiral substrates can be examined, and numerous examples of double asymmetric induction have been recorded since 1980. The major contributors have been *Kagan* et al.[59] and *Ojima* et al.[60]. Unfortunately, some data pertinent to the diastereofacial selectivities of both substrate and catalyst used in many of these examples are not available. Therefore only a few *full* sets of experiments for double asymmetric induction can be discussed. One such set is shown in Scheme 31.

Upon hydrogenation with the achiral rhodium catalyst **140**, the dehydrodipeptide **141** provides a 1.9 : 1 mixture of two diastereomers in favor of the *S,S*-combination (**142**). The diastereofacial selectivity of the diop catalyst **134** can be calculated to be 11 : 1 from Table 3, using **129a** as a substrate. The stereoselectivities observed for the pairs **141**/(+)-**134** and **141**/(−)-**134**, 16 : 1 and 1 : 4.5[60] (or 19 : 1 and 1 : 4[59]), respectively, are in excellent (but obviously fortuitous) agreement with those (21 : 1 and 1 : 5.8) predicted from the postulated multiplicativity of D.S.'s. In Ta-



Scheme 30. R = CH_3, S' = Solvent, $\widehat{P*P}$ = Chiraphos.



Scheme 31.

ble 4 the entries 1–4 summarize these results. When the bppm catalyst **135** with a D.S. of 21 : 1 (from Table 3) is used for the same reaction (entries 5 and 6), the product ratios **142/143** obtained with (+)-**135** (matched) and (−)-**135** (mismatched) are remarkable: 161 : 1 and 1 : 25, ratios that are definitely higher than one would expect from the multiplicativity. This may be due, at least in part, to the injudicious choice of achiral models for the determination of the D.S.'s of **141** and **135**[*]. For instance, the protected dehydrophenylalanylglycine **144** would appear to be a better model substance to evaluate the above set of experiments. As repeatedly stated earlier, the multiplicativity should be appreciated in a qualitative sense rather than a quantitative sense. In particular, caution must be taken in the case where small D.S.'s are dealt with. In entries 7 and 8 of Table 4, the [Rh(dioxop)]$^{\oplus}$ catalyst **145** has a small D.S. of 1.2 : 1[61], smaller than that of the substrate **141** (1.9 : 1), yet in the mismatched reaction (entry 8) the stereochemistry of the product formed slightly in excess is correlated with the directionality of the D.S. of the catalyst **145** (rather than **141**) and the ratio in the matched case, 13 : 1, is much higher than predicted.

Table 4 [a]. Catalytic hydrogenation of the dehydrodipeptide *S*-**141** to *S,S*-**142** and *R,S*-**143** (see Scheme 31).

Entry	Substrate	Catalyst	Ligand	**142** : **143** matched	**142** : **143** mismatched	Ref.
1	*S*-**141**	(+)-**134**	(+)-diop	16 : 1		[60]
2		(−)-**134**	(−)-diop		1 : 4.5	[60]
3		(+)-**134**	(+)-diop	19 : 1		[59]
4		(−)-**134**	(−)-diop		1 : 4	[59]
5		(+)-**135**	(+)-bppm	161 : 1		[60]
6		(−)-**135**	(−)-bppm		1 : 25	[60]
7		**145**	*R,R*-dioxop	13 : 1		[61]
8	*R*-**141**	**145**	*R,R*-dioxop		1 : 1.5 [b]	[61]

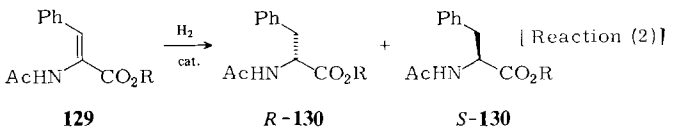
[a] The D.S. of the substrate **141** is 1.9 : 1 (**140**). The D.S.'s of the catalysts **134**, **135**, and **145** are 11 : 1 (**129**), 21 : 1 (**129**), and 1.2 : 1 (**144**). The numbers in parentheses are the compound numbers of models used to determine these values. [b] Ratio *R,R* : *S,R*.

There have been recorded many other examples of double asymmetric hydrogenation in which the chirality of the catalyst is the dominating factor for the stereochemical course of this process. Most of these examples are adequately reviewed in several articles[60,62] which interested readers should consult. What has escaped attention are *Glaser*'s earlier studies on double asymmetric induction[63]. In order to clarify the chronological development of this field and also to further illustrate how the arbitrariness in the model selection for D.S. effects the postulated multiplicativity, his work is summarized below.

Of several achiral acetyldehydrocinnamates examined, the isopropyl ester **129c**[63b] appears to be the most appropriate model for determining the D.S. of the chiral diop catalyst as **129c** is structurally similar to the chiral menthyl **129d** and bornyl **129e** esters (Table 5). Thus, the D.S. of (−)-**134** is taken as 7.3 : 1 (entry 1). The determination of the D.S.'s for **129d** and **129e** is somewhat problematic. As shown in entry 2, **129d** shows two different values with the

[*] *Ojima* invokes the concept of "induced fit", a term that should be used in the same sense as that used in enzyme chemistry (see reference [60]).

Table 5. Hydrogenation with chiral rhodium catalysts according to reaction (2) (cf. Table 3).

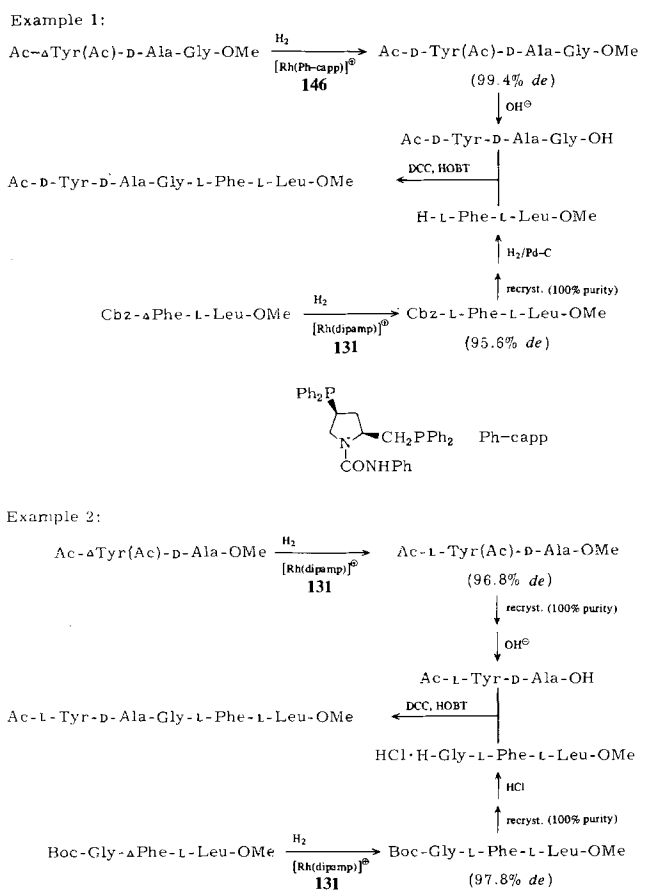


129 *R*-**130** *S*-**130**

Entry	R	Catalyst	*R*-130 : *S*-130
1	**129c** *i*Pr	$[Rh((-)\text{-diop})]^{\oplus}$	(−)-**134** 7.3 : 1
2	**129d** (−)-Menthyl	$[Rh(Ph_2P(CH_2)_3PPh_2)]^{\ominus}$	**140a** 1 : 1.1
	129d (−)-Menthyl	$[Rh(Ph_2P(CH_2)_4PPh_2)]^{\ominus}$	**140b** 1.3 : 1
3	**129d** (−)-Menthyl	$[Rh((-)\text{-diop})]^{\oplus}$	(−)-**134** 3.2 : 1
	129d (−)-Menthyl	$[Rh((+)\text{-diop})]^{\oplus}$	(+)-**134** 1 : 7.6
4	**129e** (−)-Bornyl	$[Rh(Ph_2P(CH_2)_3PPh_2)]^{\ominus}$	**140a** 1 : 1.1
	129e (−)-Bornyl	$[Rh(Ph_2P(CH_2)_4PPh_2)]^{\ominus}$	**140b** 1.2 : 1
5	**129e** (−)-Bornyl	$[Rh((-)\text{-diop})]^{\oplus}$	(−)-**134** 4.6 : 1
	129e (−)-Bornyl	$[Rh((+)\text{-diop})]^{\oplus}$	(+)-**134** 1 : 3.0

achiral catalysts $[Rh(Ph_2P(CH_2)_nPPh_2)]^{\ominus}$ **140** (**a**: n = 3; **b**: n = 4), namely 1 to 1.1 and 1.3 to 1, respectively. Thus, the directionality of asymmetric induction is *opposite* in these two cases of hydrogenation using the achiral catalysts. Inspection of entry 3 shows that the D.S. of the catalyst outweighs that of the substrate, and the two pairs, **129d**/(+)-**134** and **129d**/(−)-**134** appear to correspond to the matched and mismatched pairs, respectively. Therefore the lower D.S. (1 : 1.1) of **129d** obtained by the use of **140a** fits with the data. The dilemma created by this selection emerges in the case of the bornyl ester **129e** (see entries 4 and 5). Now **129e**/(−)-**134** (entry 5) appears to be a matched pair and the D.S. (1.3 : 1) of **129e** secured through **140b** fits the result better. Obviously the "numbers" entertained above are too small to be of practical significance, and as in the case of the hetero-Diels-Alder reactions (discussed towards the end of Section 5), readers should not "play" numbers in the analysis of double asymmetric induction.

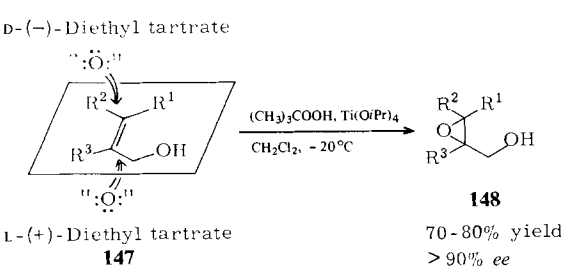
Before this Section is concluded an impressive recent application should be described. The asymmetric hydrogenation of dehydrodipeptides described above has been extended to cover dehydrotripeptides and dehydrotetrapeptides as substrates[64]. The degree of success in attaining high diastereoselectivities is equally superb and in fact all these efforts have now culminated in the synthesis of two leucine-enkephalin analogues (Scheme 32)[65]. Other useful applications of this hydrogenation technology including the regio- and stereoselective incorporation of deuterium and tritium into peptides are evident and have been recorded[64].



Scheme 32. The conventional descriptors D and L are used instead of *R* and *S*. DCC = dicyclohexylcarbodiimide; HOBT = hydroxybenzotriazole; CBz = Benzyloxycarbonyl; Boc = *tert*-butyloxycarbonyl.—Δ before the symbol of an amino acid means dehydro.

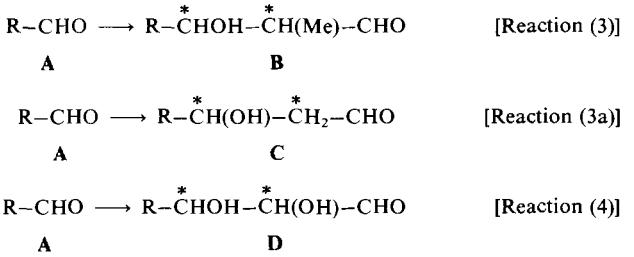
7. Epoxidation of Allylic Alcohols with the Katsuki-Sharpless Reagent

The celebrated Katsuki-Sharpless reagent consists of titanium(IV) tetraisopropoxide, *tert*-butyl hydroperoxide, and (+)- or (−)-diethyl tartrate (Scheme 33)[66]. With (−)-diethyl tartrate the oxidant approaches the allylic alcohol from the topside of the plane shown in **147**, whereas the bottom side is open for the (+)-diethyl tartrate reagent, giving rise to the corresponding optically active epoxy alcohols **148**. This asymmetric epoxidation in all likelihood proceeds through a chiral reagent-substrate complex which exhibits a high face-selection, approaching 100 : 1, as demonstrated in many reactions with achiral allylic alcohols[67]. This important reactive intermediate has been an object of intense study in *Sharpless*' laboratories, and the mechanistic course of this entire process will be documented in definitive terms in the near future[68]. The reagent, when announced in 1980, immediately caught our attention and we have been involved in a joint project with Professor *Sharpless*' group in order to investigate some aspects of the reaction. Thus, the writing of Section 7 reflects this background.



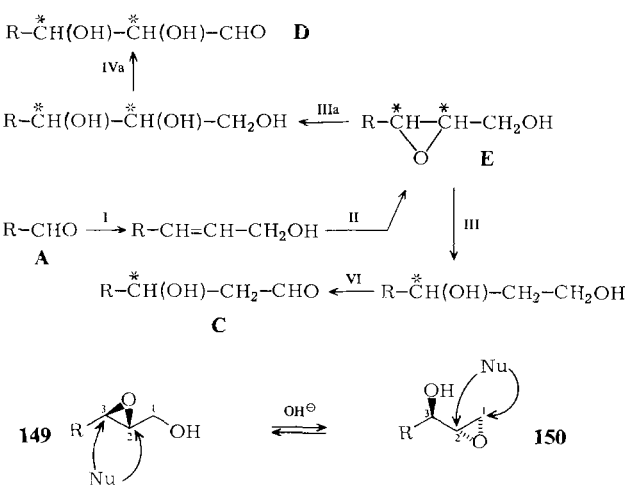
Scheme 33. Epoxidation of an allyl alcohol with the Katsuki-Sharpless reagent. The unnatural D-(−)-diethyl tartrate attacks "from above", the natural L-(+)-enantiomer "from below".

As already described in Section 4 concerning the aldol reaction, the excellent stereoselective addition of a propionate unit to an aldehyde **A** can be used to prepare any of the stereochemically possible 3-hydroxy-2-methylaldehydes **B** [reaction (3) Scheme 34], whereas the aldol reaction for transforming **A** into **C**, formally the addition of an acetate unit [reaction (3a)] proceeds with marginally useful stereoselection. For the latter transformation, a route involving epoxidation and reductive ring opening was considered promising. All that was needed for this transformation was an epoxidizing reagent with high diastereofacial selectivity, a property that seemed to be ideally satisfied by the Katsuki-Sharpless reagent. It soon became apparent that this intentionally general route, with some modification, would bring about another important transformation, **A** to **D** [reaction sequence (4)], thus creating two consecutive chiral hydroxymethylene (−*CHOH−) centers in one sequence.



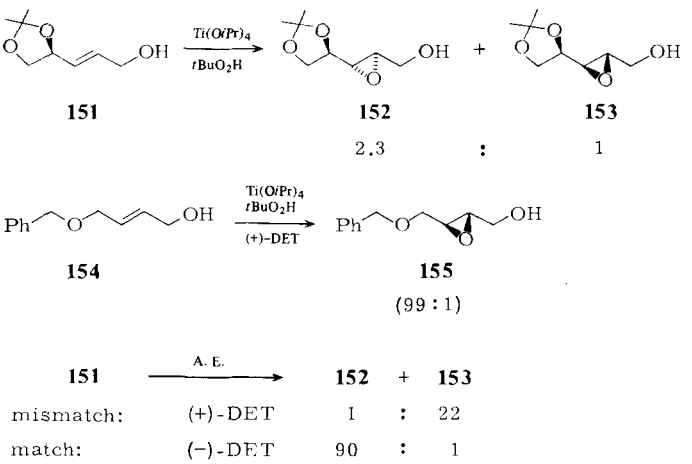
Scheme 34.

Reaction sequences (3a) and (4) are formulated as follows (Scheme 35): The first step I consists of the construction of an *E*- or *Z*-allylic alcohol (or a precursor) via a Wittig reaction. In the next step II the asymmetric epoxidation plays a key role. Together, these two steps could provide the necessary elements of stereochemical control. For the overall conversion of **A** into **C** and **A** into **D**, the subsequent steps, III and IIIa, involve little known transformations of the epoxy alcohol **E**. For example, **149** can be rearranged to the isomeric alcohol **150** with base (Payne rearrangement)[69]. Thus, all of the C1, C2, and C3 positions of **E** can be sites for appropriate nucleophilic attack as shown in **149** and **150**.



Scheme 35. Step II is an asymmetric epoxidation with the Katsuki-Sharpless reagent [Ti(O*i*Pr)$_4$, *t*BuO$_2$H, and (+)- or (−)-diethyl tartrate].

Our prime concern was then the question of whether the multiplicativity of D.S.'s in double asymmetric induction would also be applicable to the asymmetric epoxidation as we had observed for the aldol reaction (Section 4). To answer this question the epoxidation of allylic alcohol **151** derived from D-glyceraldehyde was studied (Scheme 36). Treatment of **151** with titanium(IV) tetraisopropoxide and *tert*-butyl hydroperoxide (Katsuki-Sharpless reagent *without* (+)- or (−)-diethyl tartrate) provides a 2.3 : 1 mixture of epoxy alcohols **152** and **153**. This ratio (2.3 : 1) which represents the D.S. of **151** is much smaller than that of the chiral epoxidizing agent, as reconfirmed with the asymmetric epoxidation of the allyl alcohol **154**, which provides **155** with 99 : 1 stereoselection. All the conditions necessary to achieve the stereochemical control of epoxidation in a double asymmetric reaction appear to have been met. The asymmetric epoxidation of **151** with (+)- or (−)-diethyl tartrate proceeds smoothly to provide epoxy alcohols **152** and **153** in ratios of 1 : 22 and 90 : 1, respectively. As predicted and verified by these results, **151** with the (+)-ester and **151** with the (−)-ester constitute mismatched and matched pairs, respectively.

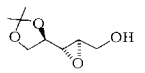
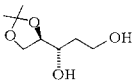
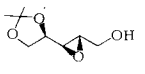
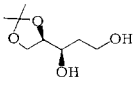


Scheme 36. DET = diethyl tartrate. A.E. = asymmetric epoxidation.

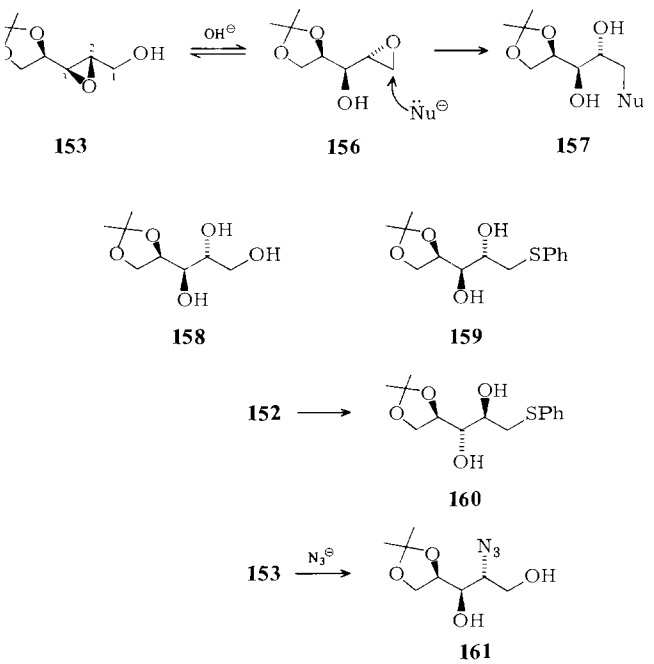
A brief comment may be appropriate at this point on the ring opening of epoxy alcohols which have been proven to be extremely versatile synthetic intermediates. Of many transformations now fully documented in several review articles[67], the following reactions are rather illustrative. The C1 position of compound **153** (Scheme 37), for instance, is by far the most reactive electrophilic site for a range of nucleophiles under basic conditions. Thus, the attack at C1 of **156** leads to **157**, as exemplified by the predominant formation of **158** (with hydroxide) and **159** (with benzene thiolate as nucleophile)[70]. In a similar manner **152** gives **160**. Thus, equilibration of 2,3- and 1,2-epoxy alcohols (i.e., **149** and **150**) has been exploited to draw out a subtle mode of reactivity. Under proper conditions it is also possible to direct nucleophiles selectively to either C2 or C3. For example, reaction of **153** with the azide ion provides compound **161** as the major product[67b]. A most interesting example is reduction at C2 with metal hydrides, in particular sodium bis(methoxy-

ethoxy)aluminum hydride (Red-Al®). The regiospecificity of this reduction plays a major role in developing the reaction sequence (3a) which can achieve the stereospecific addition of an acetate unit to aldehydes (see Section 4). Table

Table 6. Two examples of the reduction of epoxides with $Na[Al(CH_3OCH_2CH_2O)_2H_2]$ (Red-Al) at 0 °C.

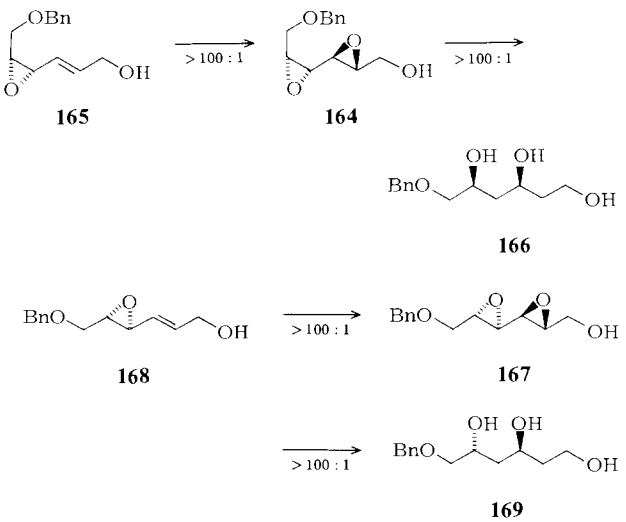
Epoxy alcohol	1,3-diol : 1,2-diol	Yield [%]	Major product
152 	> 100 : 1	78	**162** 
153 	> 100 : 1	82	**163** 

6 lists two examples of many in which Red-Al reduction of epoxy alcohols proceeds smoothly under normal conditions to provide a single product, a 1,3-diol[71]. The regioselectivity is uniformly high and in many cases no traces of the corresponding 1,2-diols are found.

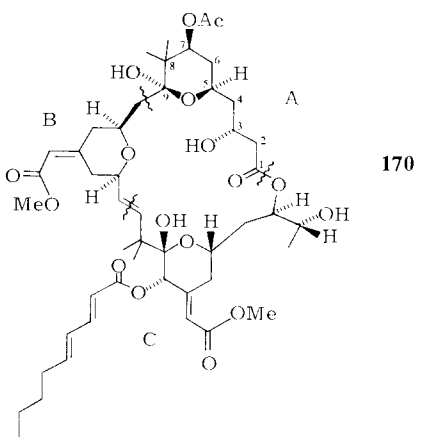


Scheme 37. **153** is allowed to react with azide in 2-methoxyethanol/water under reflux.

A more impressive demonstration of this selectivity includes the reduction of 2,3 : 4,5-diepoxy alcohols with the same reductant. Compound **164** (prepared from **165** by asymmetric epoxidation) undergoes clean double ring-opening to provide only one product, 1,3,5-triol **166** with the indicated stereochemistry (Scheme 38). Similarly, Red-Al reduction of **167** (obtained from **168**) provides **169** exclusively. These findings, in particular the simultaneous creation of two new hydroxylated chiral centers of 1,3-relationship, are important and have been utilized in the construction of the C1–C9 fragment of bryostatin 1 (**170**)[72].



Scheme 38. Bn = benzyl.



Reaction sequence (4) (see Scheme 34) is aimed at the stereoselective, systematic synthesis of monosaccharides and their analogues. An efficient, practical execution of this bishomologation has been developed by *Kishi* et al.[73] and by us[74] for the synthesis of the pentoses. Scheme 39 outlines our version. Thus, the epoxy alcohol **152** undergoes ring opening to provide **160**, which is converted to the acetonide **172** through kinetically controlled acetonation followed by oxidation and acetylation. Reaction of **172** with diisobutylaluminum hydride provides, virtually without epimerization, a product **173** which has been proven to have the ribose configuration. Compound **172** can also be converted to the C2 epimer of **173**. Thus, treatment of **172** with potassium carbonate in methanol causes hydrolysis of the acetoxythioacetal group and epimerization at the C2 center to give a mixture of **174** and **173** in a 98 : 2 ratio. Compound **174** has the arabinose configuration. The acetonides (**175** and **176**) of xylose and lyxose are prepared from **177** in exactly the same manner. In this way a highly efficient route from the single intermediate **151**[*] to either the *erythro-* or *threo*-2,3-dihydroxyalde-

[*] Epoxidation of the corresponding *Z*-allylic alcohol with either (+)- or (−)-diethyl tartrate is too slow to be practical (reference [70]). Thus, readers notice that one element of control, the olefin geometry, which was originally planned, could not be fully employed and the two pentoses **174** and **175** are obtained via the epimerization reaction.

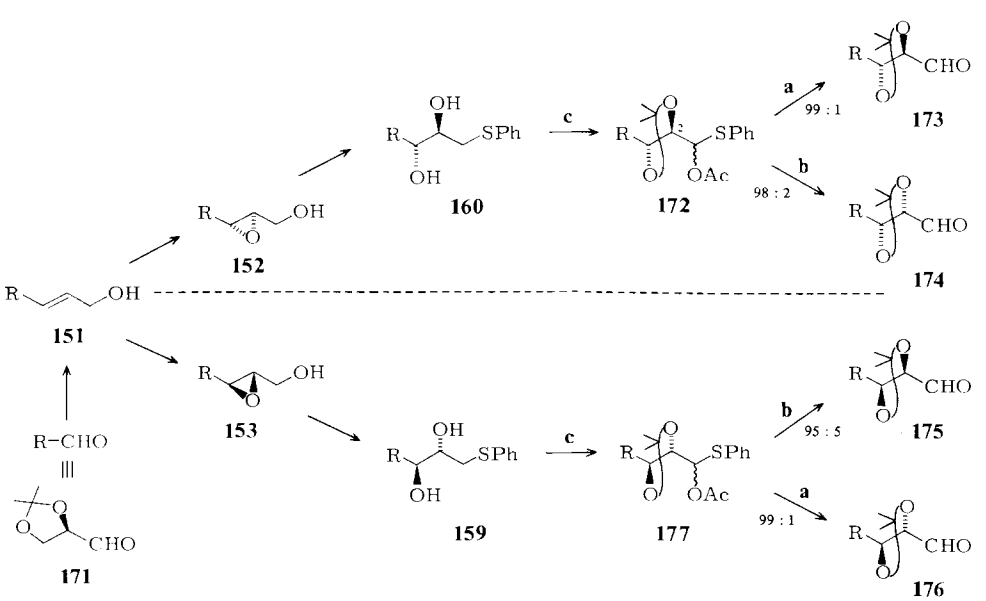
hydes has been established. It is obvious that the success of this scheme depends heavily upon both the high double asymmetric induction realized by the titanium-catalyzed epoxidation with (+)- or (−)-tartrates and the conventional, but highly critical epimerization technique. These constitute two elements of control, the conditions necessary and sufficient for the stereoselective creation of any two new chiral centers. Note that through this sequence a single chiral aldehyde has been converted into the four stereochemically possible bishomologated aldehydes, each of which is ready for a second two-carbon extension. Indeed, the synthesis of all the possible hexoses via a double application of the sequence has been completed as shown in Scheme 40[75]. The top row of the scheme represents the first cycle of the hexose synthesis, which begins with a single building block, 4-benzhydryloxy-(*E*)-2-buten-1-ol **178**, readily prepared from (*Z*)-2-butene-1,4-diol. Step I of the extension cycle is therefore eliminated in this initial case. Conversion of **178** into **181** and **182** completes the first cycle, and the conversion of **181** and **182** into **193**—**200** constitutes the entire set of the second cycle. The yield and selectivity are described for each step. All steps in this scheme except for the conversions **179** → **180** and **186** → **190** proceed with remarkable regio- and stereoselection. Since the mirror image of every compound can be prepared by simple exchange of the chiral ligand (tartrate ester) in the asymmetric epoxidation, the formal synthesis of the D-hexoses has also been achieved. This achievement adequately proves that the concept of matching and mismatching is valid for asymmetric epoxidation as well.

Finally, mention should be made of recent monumental achievements by *Kishi* et al. which have led them to propose the entire stereochemistry of palytoxin **201**[76]. This marine product, having 64 asymmetric centers, was degraded into numerous fragments through the elaborate work of *Hirata* et al.[77] and *Moore* et al.[78]. Altogether these fragments incorporate all of the chiral carbon atoms embedded in the carbon framework of **201** and the connectivity among them has been established. *Kishi* et al. have synthesized each of these fragments using reactions which are supposed to proceed with predictable stereochemical outcomes whenever the creation of a new chiral center or centers is involved. *Kishi* has developed reaction sequences conceptually similar to those in Scheme 39 as mentioned above and repeatedly used them in this work. It is evident that his work could not have been accomplished without recourse to such a strategy. Thus, the approximate multiplicativity of D.S. is taken implicitly as an *established rule which is apparently valid in all asymmetric epoxidations of E-allylic alcohols they have examined.*

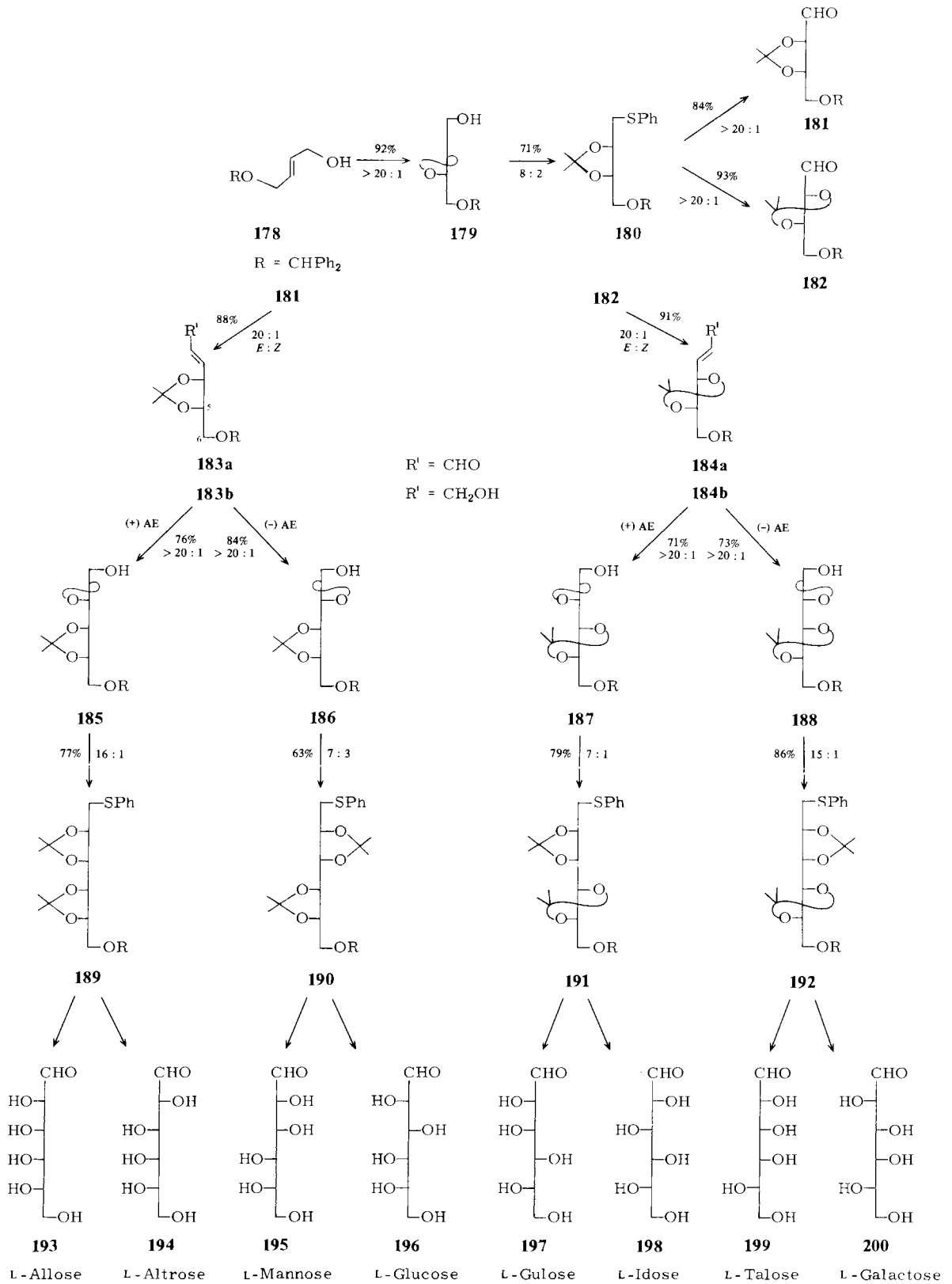
8. Merits of the New Synthetic Strategy as Applied to Natural Products Synthesis

Numerous reactions documented in the preceding Sections have established the multiplicativity of diastereofacial selectivities as a valid rule within defined limitations. At least four major organic transformations[79][*] can be executed with high diastereoselection using chiral reagents or catalysts. This Section will emphasize two distinct features of natural product synthesis based on the new synthetic strategy: 1) The target molecules are necessarily synthesized in optically pure form since any substrates to be used in double asymmetric synthesis are homochiral, and—*much more importantly*—2) the process of retrosynthetic analysis for many stereochemically complex molecules and the execution of the synthetic plan are substantially simplified. In some cases retrosynthesis becomes straightforward and provides a relatively short and efficient synthetic scheme (see the example of 6-deoxyerythronolide B **48** in Section 4). Even for those natural products such as bryostatin 1 **170** and palytoxin **201**, which are much more

[*] Single asymmetric alkylation has already been reviewed adequately by *Evans* [79b], *Meyers* et al. [79c], and *Enders* [79d]. Since examples of double asymmetric alkylation are scarce, this subject is not presented in this article.



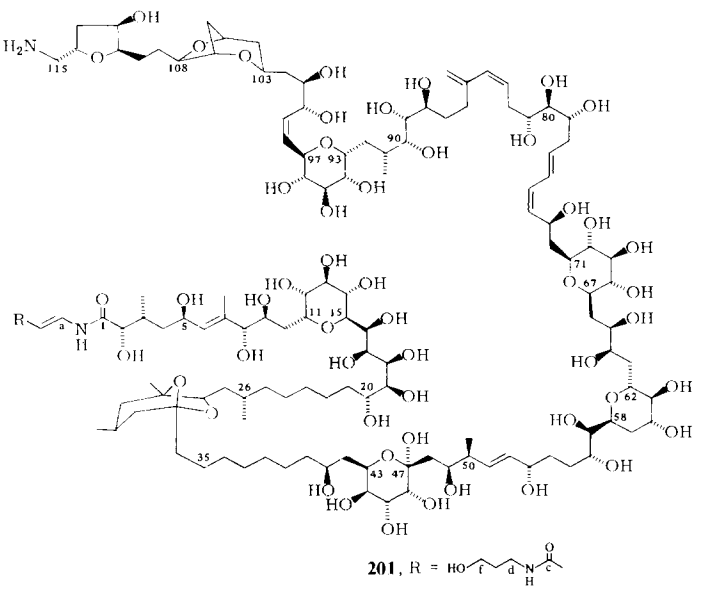
Scheme 39. **a**: diisobutylaluminum hydride; **b**: K_2CO_3, MeOH; **c**: 2-methoxypropene, *m*-chloroperbenzoic acid, Ac_2O.



Scheme 40. (+)AE and (−)AE signify asymmetric epoxidation in the presence of (+)- and (−)-diethyl tartrate, respectively.

complicated than the celebrated erythromycins[80][*], workable schemes can now be drawn with *relative* ease. Natural products, in particular those of polyketide origin, very

[*] The late Professor *Woodward* made the following often quoted remark in 1956; "Erythromycin, with all our advantages, looks at present quite hopelessly complex, particularly in view of its plethora of asymmetric centers. ..." [80].



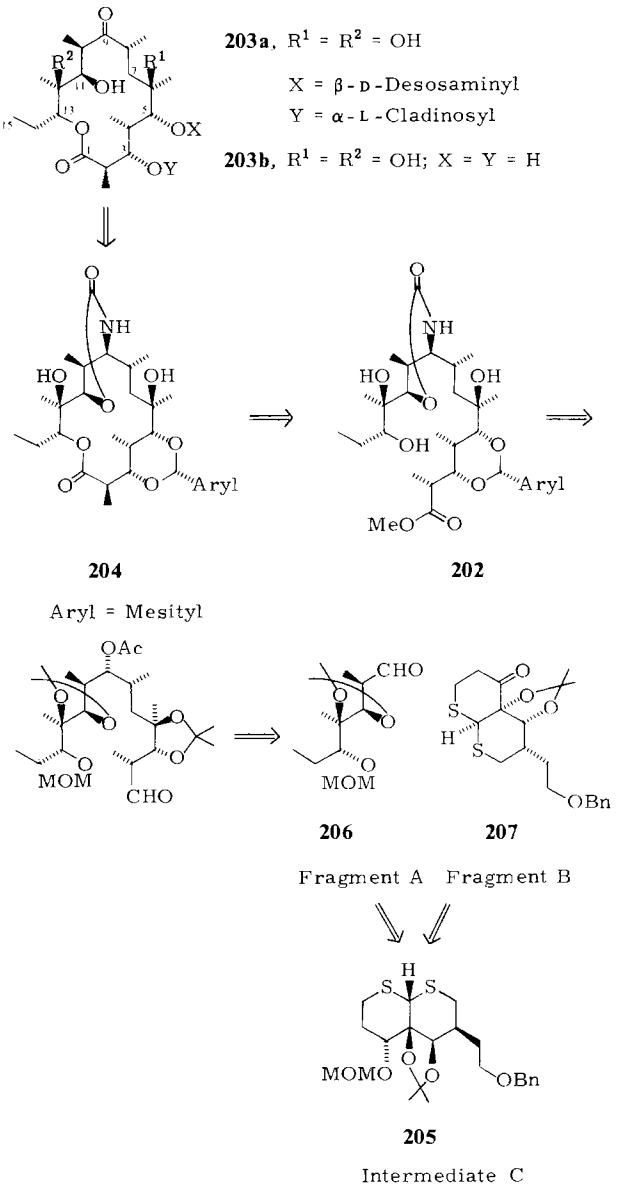
201, R = HO(f)(d)N(H)(c)=O

often consist of a limited number of basic units. Therefore, judicious reiteration of several reaction sequences as discussed in Sections 4—7 leads to a final target molecule.

We will now critically evaluate the new strategy which uses homochiral reagents for stereochemical control (reagent-control) in comparison with the traditional strategy which uses chiral substrates for the same purpose (substrate-control). This evaluation will be made using several recent examples of macrolide synthesis in which both strategies have been applied to the synthesis of the same or closely-related macrolide antibiotics[3c].

One of the three major synthetic challenges posed by this class of antibiotics is the construction of the seco-acid esters (e.g., **202**) having a "hopelessly complex"[80] array of chiral centers. This challenge has been met by several groups[3c]. For instance, *Woodward* et al. recorded in mid-1981 the synthesis of the antibiotic erythromycin A **203a** which had been brilliantly executed in the traditional Woodward style (substrate-control)[81]. As has already been described, acyclic substances normally have synthetically insignificant diastereofacial selectivities (Section 3). Without recourse to powerful chiral reagents, the required stereochemical control must take full advantage of cyclic systems which can be designed in such a way as to have a large D.S. Once substituents are introduced on a cyclic system with clearly defined *cis* or *trans* relationships, ring cleavage transfers this stereochemistry to the resulting acyclic system. This "cyclic approach" in general demands ingenious design and unique solutions to each new stereochemical problem, and indeed *Woodward*'s group spent many years for the construction of the erythronolide framework by adopting this approach. A brief summary of their accomplishment to the stage of the synthesis of an erythronolide A[*] derivative (**204**) is given below in order to illustrate merits of each of the traditional and new approaches, although this description may digress somewhat from the main theme of this Account.

[*] Erythronolide A **203b** is the aglycone of erythromycin A.

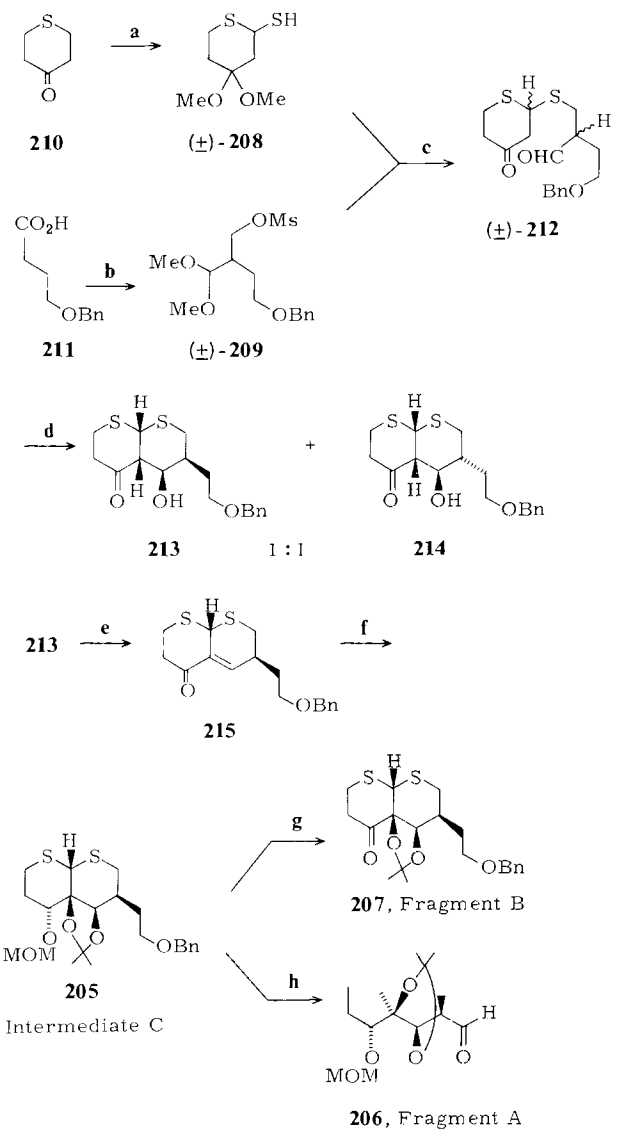


Scheme 41.

Woodward's synthesis recognized "hidden symmetry"[20a] in the aglycone **203b** (cf. the stereochemistry of the fragment C4—C6 with that of C10—C12) and thus uses the common intermediate C **205** for the construction of the two segments, A **206** and B **207**, of the aglycone (Scheme 41). The majority of the erythronolide stereochemistry is built on the rigid dithiadecalin ring system and then the sulfur atoms are extruded.

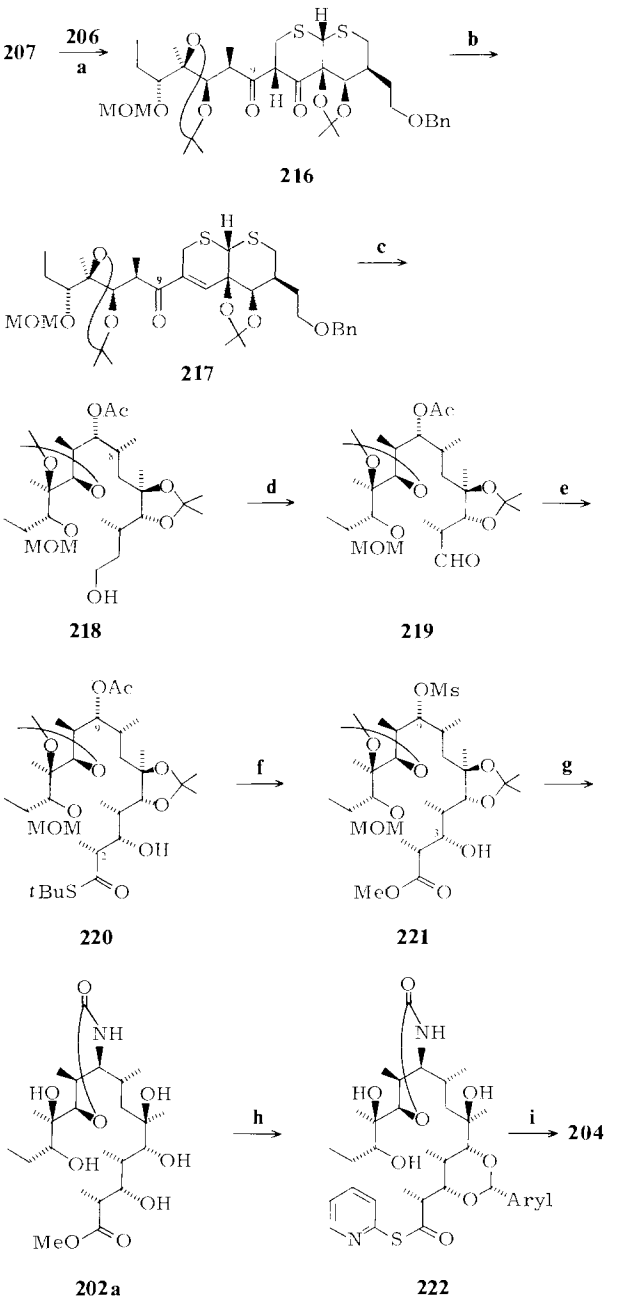
The synthesis of the common intermediate C **205** is described in Scheme 42. Racemic compounds **208** and **209** are prepared from **210** and **211**, respectively, through a sequence of routine transformations. Coupling of **208** and **209** leads to **212**, which is a mixture of two diastereomers, each diastereomer being a racemic mixture. Intramolecular aldol reaction of **212** catalyzed by D-proline leads to a 1 : 1 mixture of diastereomers **213** and **214**, each diastereomer being enriched in the enantiomer drawn by 36% ee. Ketone **213** is separated from the diastereomer **214** and is dehydrated to give enone **215**, which is resolved by recrystallization. Thus, optically pure **215** is obtained in 10—12%

yield from racemic starting materials **208** and **209**. Reduction of the keto functionality of **215**, protection of the resulting hydroxyl group, osmylation, and finally acetonide formation convert **215** into **205** (Intermediate C). Note that the stereochemistry of this osmylation is fully governed by the rigid conformation of the dithiadecalin system.



Scheme 42. Synthesis of the intermediate product C **205** and of the Fragments A **206** and B **207**. **a**: 1) $(CH_2OH)_2$, $H^{\oplus}$, 2) *N*-chlorosuccinimide, 3) thiourea, 4) NaOH, 5) HCl, 6) $(MeO)_3CH$, toluenesulfonic acid, MeOH, 65% yield; **b**: 1) esterification, 2) $LiN(iPr)_2$; HCO_2Me, 3) $(MeO)_3CH$, H_2SO_4, MeOH, 4) $LiAlH_4$, 5) methanesulfonyl chloride, pyridine, 60% yield; **c**: 1) NaH, 2) AcOH; **d**: catalyst D-proline; **e**: 1) methanesulfonyl chloride, pyridine, 2) Al_2O_3, 3) recrystallization; yield of optically pure (+)-**215** 10 to 12% from (±)-**208** and (±)-**209**; **f**: 1) $NaBH_4$, 2) $MeOCH_2I$, KH, 3) OsO_4, 4) $Me_2C(OMe)_2$, toluenesulfonic acid, 74% yield; **g**: 1) trifluoroacetic acid, 2) $(CF_3CO)_2O$, dimethyl sulfoxide, $Et(iPr)_2N$, 85% yield; **h**: 1) H_2, Raney nickel W-2, 2) o-$O_2NC_6H_4SeCN$, PBu_3, 3) H_2O_2, 4) O_3; Me_2S, $NaHCO_3$, 80% yield.—Ms = mesyl, MOM = $-CH_2OMe$.

Intermediate C **205** is converted into both Fragment A **206** and Fragment B **207**. Hydrolysis of the methoxymethyl group of **205** followed by oxidation gives **207**. Reductive desulfurization and debenzylation of **205** give an alcohol which is converted into the aldehyde **206** (Fragment A) via the corresponding selenide, selenoxide, and olefin.



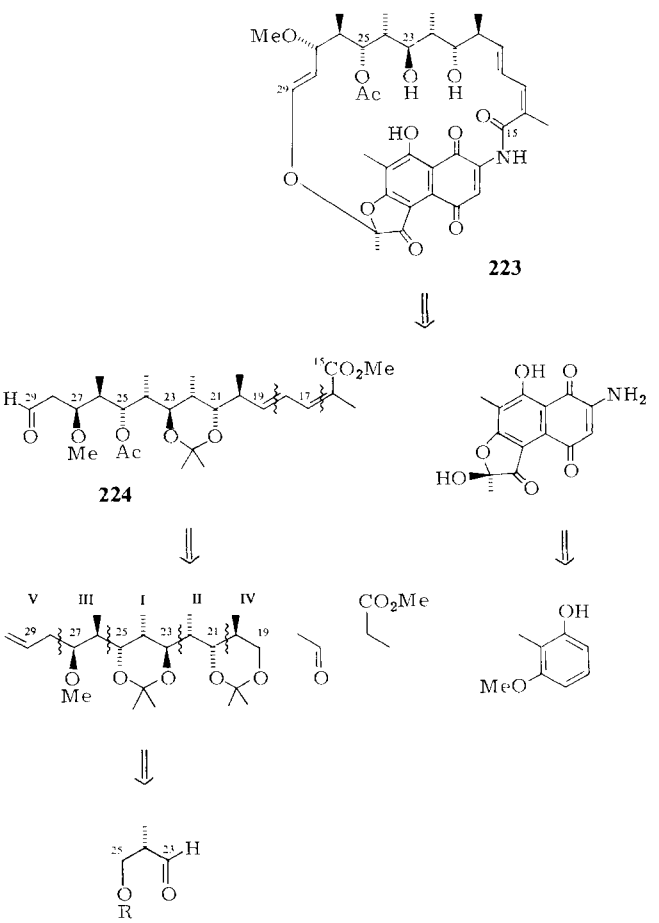
Scheme 43. Synthesis of the erythronolide A derivative **204**; **a**: 1) mesityllithium, 2) $(CF_3CO)_2O$, dimethyl sulfoxide, $Et(iPr)_2N$, 76% yield; **b**: 1) KH, 2) AcCl, 3) $NaBH_4$, 4) methanesulfonyl chloride, 5) 4-dimethylaminopyridine, pyridine, MeOH; **c**: 1) $PhCH_2SLi$, 2) $LiAlH_4$, 3) Ac_2O, 4) H_2, Raney nickel W-2; **d**: 1) o-$O_2NC_6H_4SeCN$, PBu_3, 2) H_2O_2, 3) O_3; Me_2S, 50% yield from **216**; **e**: 1) EtCOS*t*Bu, $LiN(iPr)_2$, 2) *t*BuLi, tetramethylethylenediamine, 3) AcOH, 77% yield, 11 : 1 at C2; **f**: 1) Na_2CO_3, MeOH, 2) $(PhOCH_2CO)_2O$, 4-dimethylaminopyridine, pyridine, 3) methanesulfonyl chloride, pyridine, 4) LiOH, H_2O_2; 75% yield; **g**: 1) LiN_3, 2) H_2, PtO_2, 3) p-$O_2NC_6H_4OCOCl$, 4) $NH_2OH \cdot HCl$, KH_2PO_4, 5) Et_3N; 53% yield; **h**: 1) mesitylaldehyde dimethyl acetal, trifluoroacetic acid, 85% yield, 2) EtSLi, hexamethylphosphoric triamide, 3) 2-pyridyl-S-COCl, Et_3N; **i**: toluene, reflux, 70% yield.—Aryl = mesityl.

The coupling of Fragments A **206** and B **207** and cyclization of an erythronolide seco-acid derivative (**202a**) is outlined in Scheme 43. Aldol reaction between the lithium enolate of **207** and aldehyde **206** followed by oxidation gives **216**, which is converted into enone **217** via the C9

enol acetate. Conjugate addition of phenylmethanethiolate to **217** gives a single ketone product which, after hydride reduction, protection of the hydroxy group, and hydrogenation with Raney nickel, provides **218**. The stereochemistry at the C8 position in **218** arises from kinetically controlled protonation on the convex face of the dithiadecalin ring system in the conjugate addition. The following hydride reduction of the C9 keto functionality proceeds through chelation with the C11 ethereal oxygen to yield a single hydroxy group. Through the same sequence of reactions used earlier (i.e., **205** to **206**) **218** is converted into the aldehyde with one less carbon **219**. Aldol reaction of **219** with the lithium enolate derived from *tert*-butyl thiopropionate followed by kinetically controlled protonation of the presumed trianion[*] of the aldol product gives the thiol ester with the desired C2 stereochemistry shown in **220**[82][**].

With all the chiral centers of erythronolide A in place, modification of the protecting groups present in **220** was necessary for efficient macrocyclization[***]. After considerable investigation, the following selection was found to be satisfactory. Thiol ester **220** is converted to ester **221** through a sequence of reactions: 1) hydrolysis of the C9 acetate with concomitant conversion of the thiol ester into the corresponding methyl ester; 2) selective acylation at the C3 hydroxyl group; 3) mesylation of the C9 hydroxy group; and finally 4) deprotection at the C3 hydroxy group. Displacement of the mesylate in **221** with lithium azide followed by reduction gives the inverted C9 amino group that is converted into the carbamate. The subsequent removal of the acetonide groups with concomitant cleavage of the methoxymethyl protecting group and then cyclization lead to the formation of the cyclic carbamate **202a**. Selective acetal protection of the C3, C5 dihydroxy group and conversion to an activated ester (**222**) sets the stage for macrocyclization, which proceeds in very high yield to provide **204** (see Scheme 41). A series of deprotections and glycosidations converts **204** into erythromycin A. This final conversion alone, though not discussed here, is a remarkable achievement.

Readers have now seen the elaborate design and experimentation that the cyclic, "substrate-controlled" approach demands in order to properly introduce the ten chiral centers[****] onto the long-chain seco-acid **222**. This monumental achievement represents an ultimate demonstration of organic chemists' imagination, but at the same time demonstrates the limitations of this popular traditional approach. Imagine an analog of erythronolide A that had several more chiral centers somewhere in the ring system or that was stereoisomeric at several chiral centers. The synthesis of this hypothetical molecule would very likely constitute an entirely new project which would be just as demanding as that described above. It is the recognition of these limitations that spurred the conceptual development of the new synthetic strategy based on double asymmetric induction. 6-Deoxyerythronolide B **48**, whose synthesis was recorded in early 1981[19], has the same number (10) of chiral centers as that of erythronolide A, but is missing the hydroxy groups at the C6 and C12 positions that exist in the latter. Therefore, it is not entirely justified to compare the synthesis of 6-deoxyerythronolide B with that of erythronolide A[83][*]. However, a striking difference is noted when reexamining our retrosynthetic analysis of **48** and its synthesis (Schemes 12, 13, and 14). The two major fragments A and B are basically constructed through one and two aldol reactions, respectively, using the enolate reagent **39** with the chirality of the reagent being appropriate for each reaction. Assembly of the two fragments, again via the aldol methodology followed by macro-lactonization, completes the synthesis. The comparative evaluation of the two syntheses of **48** and **204** in terms of the overall selectivity, the overall yield, and the number of steps involved in the synthesis is tabulated in Table 7. The power of the new



Scheme 44. Retrosynthetic analysis of rifamycin S **223**. Chain extension by two carbon atoms in each step takes place in the sequence I→V.

[*] The three protons located at C2–H, C3–OH, and C9–$OCOCH_3$ are probably removed under these conditions.

[**] The dianion derived from a β-hydroxy ester exists in a cyclic conformation. Kinetic protonation from the least hindered face of this ring would probably have brought about the desired C2 stereochemistry (see reference [82]).

[***] The efficiency of macrolactonization depends highly on the seco-acid conformation (reference [20a]). The many erythronolide seco-acid derivatives examined in this work serve as an excellent demonstration of this effect.

[****] The 9-amino group in **202** or **222** is oxidized to the keto-group at a later stage of the synthesis.

[*] Readers will find it interesting to design a scheme leading to erythronolide A using methods outlined in Sections 4–7 and some additional information now available in the literature. (For instance, see reference [83] for the construction of a tertiary hydroxy group.) Several concise and likely workable schemes can be drawn.

Table 7. Comparison of some total syntheses of natural products [a].

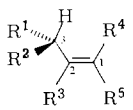
Target Molecule	Approach (control)	Number of new chiral centers created	Overall Stereo-selectivity [%]	Overall yield [%]	Number of steps	Starting Material	Ref.
48, 6-Deoxyerythronolide B	acyclic (reagent)	8	85	5.7	23	**35**	[19]
204, Erythronolide A derivative	cyclic (substrate)	10	46	0.3	49	**210**	[81]
(±)-**236**, Ansa chain of rifamycin S	acyclic (substrate)	7	50	0.2	49	(±)-**226**	[84]
236	acyclic (reagent)	7	75	2.1	46	(−)-**226**	[85]
236	acyclic [b]	8	78	13.8	24	**40**	[87]

[a] For a convergent synthesis, the values are those of the longest reaction sequence connecting the indicated starting material and final product and are calculated from the schemes shown in this Account. When both yield and selectivity are stated for a series of transformations in the schemes, that yield represents the combined yield of the desired and undesired products. Yields presented here do not account for recycling. [b] The control is not clearly defined.

strategy is clear: retro-synthesis is straightforward, the resulting schemes are efficient, and the stereochemical outcome of each reaction is capable of creating virtually any stereoisomer (also see the hexose synthesis in Section 7).

In the preceding discussions, the *cyclic, substrate-control* approach has been compared with the *acyclic, reagent-control* approach. This latter approach can also be compared with the *acyclic, substrate-control* approach which is illustrated below by the first synthesis of rifamycin S **223**[84], one of *Kishi*'s many landmark synthetic achievements. This antibiotic is a representative ansamycin, characterized by a distinct structural feature: A long aliphatic "ansa" (Latin for handle) chain **224** that is joined to an aromatic nucleus (such as a benzene or naphthalene derivative) at two non-adjacent positions to form a macrolactam. Our discussions in this section are limited to the construction of the ansa chain which is rich in chirality (Scheme 44).

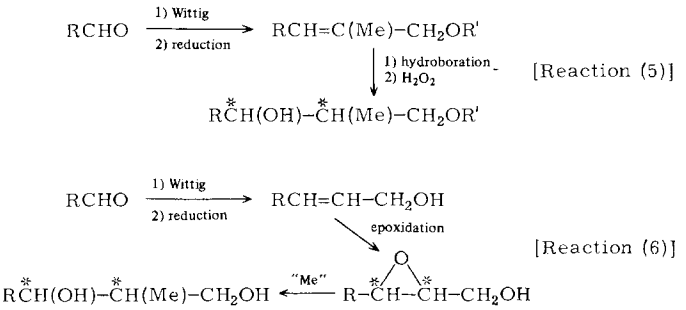
The acyclic, substrate-control approach must necessarily utilize the properties of some acyclic systems which exhibit a significant D.S., a feature that is rarely seen in these systems as repeatedly mentioned above. Thus, *Kishi* recognized that a certain type of *Z*-olefin (R^1, R^2, $R^4 \neq H$) **225** prefers to take the unique conformation in which the C1,



225

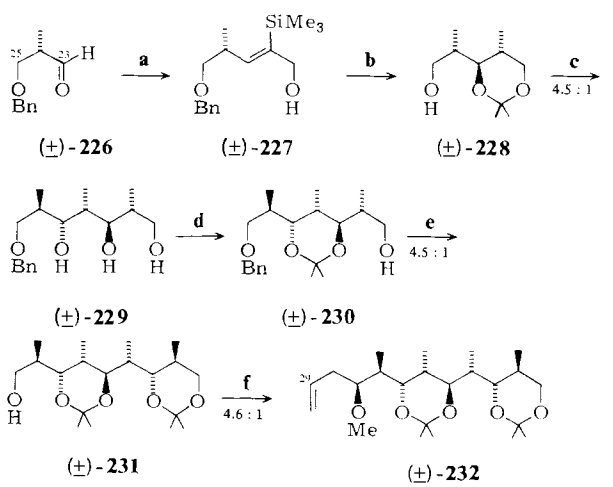
C2, C3, and H3 are (nearly) coplanar due to allylic strains as shown. This conformation in all likelihood is retained in the transition states of many reactions, and thus the two sides (faces) of the plane are differentiated. In this way, hydroboration in reaction sequence (5) (Wittig followed by hydroboration) and epoxidation in reaction sequence (6) (Wittig, epoxidation, and epoxide opening by a methyl anion or vinyl anion equivalent) can be executed with moderate diastereoselection (Scheme 45).

Both sequences, similar to those discussed in Section 7, constitute two basic methods for the two-carbon extension to be utilized in the synthesis of **224**. (±)-3-Benzyloxy-2-methylpropionaldehyde **226** is the starting material and the two-carbon extension methods are repetitiously applied in the order indicated in Scheme 44.



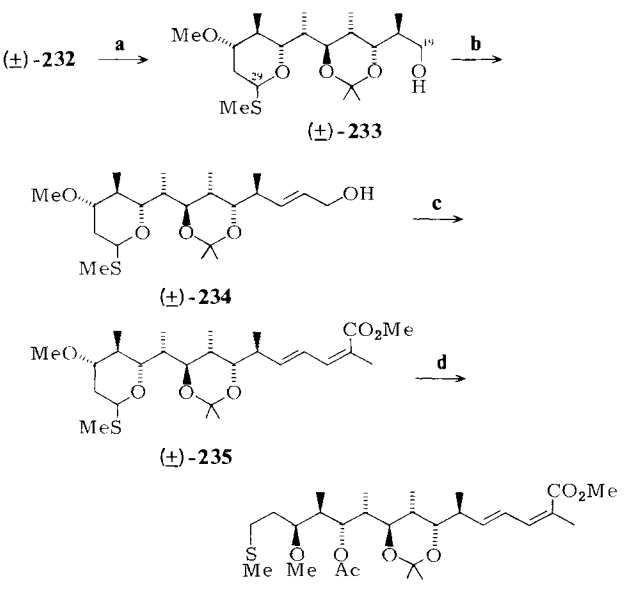
Scheme 45.

The aldehyde (±)-**226** constitutes the C23–C25 fragment (rifamycin numbering) in the synthesis of the racemic antibiotic (Scheme 46). Conversion of **226** into a silylacetylene ($Me_3SiC{\equiv}C-$) followed by hydroalumination and iodination give a vinyl iodide that is transformed into the allylic alcohol **227** (cf. **225**). Epoxidation of **227** proceeds



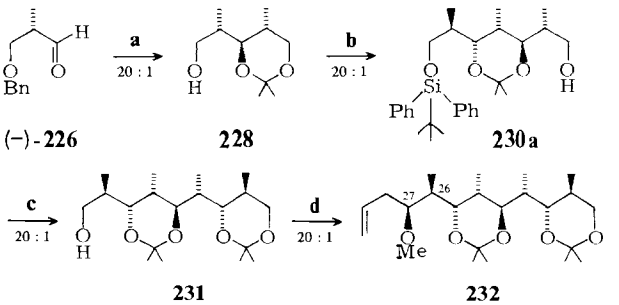
Scheme 46. Synthesis of the precursor (±)-**232** for *rac.* rifamycin S (±)-**223**. **a**: 1) CBr_4, PPh_3, 2) *n*BuLi; Me_3SiCl, 3) diisobutylaluminum hydride; I_2; 4) *n*BuLi, $ClCO_2Me$, 5) diisobutylaluminum hydride, 45% yield; **b**: 1) *m*-chloroperbenzoic acid, 2) nBu_4NF, 3) $LiCuMe_2$, 4) Me_2CO, camphorsulfonic acid, 5) Li, liq.NH_3, 70% yield; **c**: dimethyl sulfoxide, $(COCl)_2$; Et_3N, 2) $Ph_3P{=}C(Me)CO_2Et$, 3) $LiAlH_4$, 4) $PhCH_2Br$, KH, 5) HCl, 6) B_2H_6, H_2O_2, NaOH, 36% yield; **d**: 1) *t*BuCOCl, pyridine, 2) Me_2CO, camphorsulfonic acid, 3) $LiAlH_4$, 90% yield; **e**: steps 1)—3) as in **c**, 4) HCl, 5) B_2H_6, H_2O_2, NaOH, 6) $Me_2C(OMe)_2$, camphorsulfonic acid, 7) Li, liq.NH_3, 34% yield; **f**: 1) dimethyl sulfoxide, $(COCl)_2$; Et_3N, 2) diallylzinc, 3) MeI, KH, 66% yield.—The stereoselection is given under the arrows.

stereoselectively to yield a single epoxide which, after a series of reactions (desilylation, cuprate opening, protection of the diol, and liberation of the C25 hydroxy group) [corresponding to Sequence (6)] affords **228**. A Wittig reaction on the aldehyde derived from **228**, followed by reduction, leads to the formation of an allylic alcohol that, after protection of the hydroxy group and removal of the acetonide group, undergoes stereoselective hydroboration to provide **229** (4.5 : 1 selection). Repetition of nearly the same sequence converts **230** to **231** which, after oxidation to the corresponding aldehyde, is allowed to react with diallylzinc to provide **232** (4.6 : 1 selection), a key intermediate that contains all eight chiral centers present in the ansa chain. Further transformation of **232** to the full ansa chain involves the addition of the *E,Z*-diene moiety which is another challenging task. However, since this transformation does not involve the creation of any new chiral centers, the sequence of reactions leading to the ansa chain derivative **236** through **234** and **235** is simply summarized in Scheme 47. The compound **236** is properly functionalized for coupling with the aromatic portion of rifamycin. Several difficult problems involved in this coupling have been solved in an elegant manner to complete the synthesis of the antibiotic.



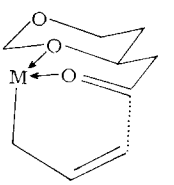
Scheme 47. Synthesis of the precursor (±)-**236** for *rac.* rifamycin S(±)-**223**. **a**: 1) HCl, 2) *t*BuCOCl, pyridine, 3) OsO_4, KIO_4, 4) MeSH, $BF_3 \cdot Et_2O$, 5) $Me_2C(OMe)_2$, camphorsulfonic acid, 6) $LiAlH_4$, 56% yield; **b**: 1) pyridinium dichromate, 2) $Ph_3P{=}CHCO_2Et$, 3) diisobutylaluminum hydride; **c**: 1) pyridinium dichromate, 2) $(MeO)_2P(O)CH(Me)CN$, KO*t*Bu, 3) diisobutylaluminum hydride, 4) NaCN, MnO_2, MeOH, 45% yield from (±)-**223**; **d**: 1) $HgCl_2$, $CaCO_3$, 2) $NaBH_4$, 3) *t*$BuPh_2SiCl$, 4) Ac_2O, pyridine, 5) *n*Bu_4NF, 6) methanesulfonyl chloride, Et_3N, 7) MeSNa, 69% yield.—The stereoselection is given under the arrows.

This synthesis of the racemic ansa chain can be compared with an enantioselective version which *Kishi* et al. documented a year later[85][*]. This version (acyclic, reagent-control approach) incorporated the concept of double



Scheme 48. Synthesis of the precursor **232** for natural rifamycin S **223**. **a**: 1) $(iPrO)_2P(O)CH_2CO_2Et$, KO*t*Bu, 2) diisobutylaluminum hydride, 3) (+)-diethyl tartrate, $Ti(OiPr)_4$, *t*BuO_2H, 4) $LiCuMe_2$, 5) Me_2CO, camphorsulfonic acid, 6) Li, liq. NH_3, 57% yield; **b**: 1) dimethyl sulfoxide, $(COCl)_2$; Et_3N, steps 2)—5) as in **a**, steps 1)—4), 6) *t*$BuPh_2SiCl$, 7) AcOH, 8) *t*BuCOCl, pyridine, 9) $Me_2C(OMe)_2$, camphorsulfonic acid, 10) $LiAlH_4$, 63% yield; **c**: steps 1)—5) as in **b**, but with (−)-diethyl tartrate, 6) $Me_2C(OMe)_2$ camphorsulfonic acid, 7) *n*Bu_4NF, 68% yield; **d**: 1) dimethyl sulfoxide, $(COCl)_2$; Et_3N, 2) $CH_2{=}CHCH_2I$, $SnCl_2$, 3) MeI, KH, 65% yield.—The stereoselection is given under the arrows.

asymmetric induction earlier demonstrated in the synthesis of 6-deoxyerythronolide B. The entire scheme shows significant improvements in terms of overall stereoselectivity owing mainly to the incorporation of Katsuki-Sharpless asymmetric epoxidation (Section 7) in the synthetic routes. Thus, the synthesis which begins with enantiomerically pure aldehyde **226**[86][*] uses this asymmetric epoxidation three times (Scheme 48). The construction of tri-substituted *Z*-olefins of the type **225** to effect substrate-controlled reactions is no longer necessary (see above). Reaction of (−)-**226** with a stabilized Wittig (Horner-Wadsworth-Emmons) reagent, followed by reduction gives an allylic alcohol, which is subjected to asymmetric epoxidation and regioselective cuprate opening of the resulting epoxide to establish the desired stereochemistry. Standard protecting group manipulations lead to **228**. The overall stereoselectivity of this entire process is 20 : 1. The ensuing steps, conversions of both **228** to **230a** and **230a** to **231** are, in essence, repetition of the above sequence. The last chiral center to be created is at C27. Addition of allyltin to the aldehyde derived from **231** proceeds with high stereoselection to provide the chiral aliphatic segment **232**. In order to explain this stereoselection, the *trans*-decalin-type transition state **237** was proposed. At this stage, the synthetic route takes the same path as the synthesis in the racemic series (Scheme 47).



237

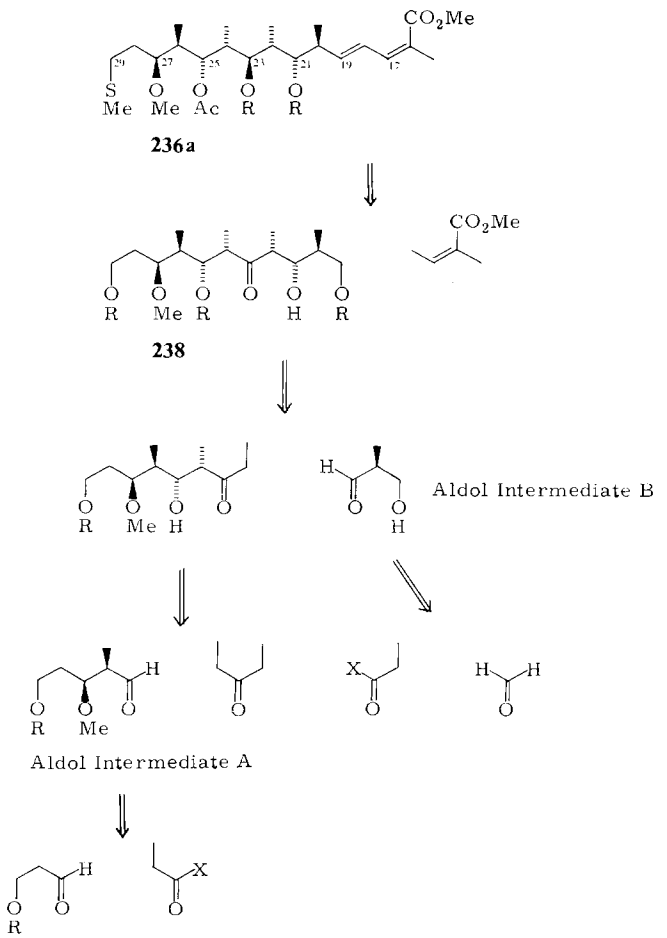
The merits of the acyclic, reagent-controlled approach (exemplified by *Kishi*'s enantioselective synthesis of **236**) as compared with the acyclic, substrate-controlled approach (see *Kishi*'s first synthesis of (±)-**236**) are clear. Interestingly, the reaction sequences for the two-carbon extension can be replaced by a single aldol reaction which

[*] Another enantioselective version has also been documented [85] by *Kishi* but will not be discussed here fore the sake of brevity.

[*] Prepared in six steps from (*S*)-3-hydroxy-3-methylpropionic acid; see reference [86].

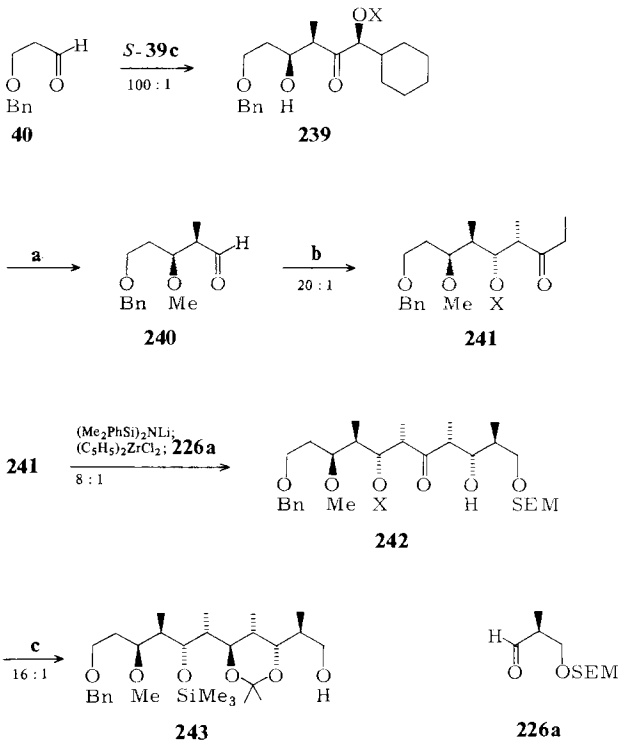
achieves the overall transformations even more efficiently. The aldol reaction (Section 4) establishes two chiral centers in one step, and this approach has also been applied to the synthesis of the ansa chain **236** (cf. Scheme 51)[87].

Our retrosynthetic analysis demonstrates that seven chiral centers out of the eight present in the chain **236a** can be constructed through a convergent series of four asymmetric cross-aldol reactions (Scheme 49). The two aldol intermediates A and B were prepared earlier in connection with the development of the chiral boron reagents shown in Scheme 11. The remaining chiral center, C23, is created by stereoselective reduction of the corresponding ketone **238**. Finally, the construction of the *E,Z*-dienoate moiety [C15–C19] leads to **236a**. Scheme 50 shows the synthesis.



Scheme 49. Retrosynthetic analysis of **236a**.

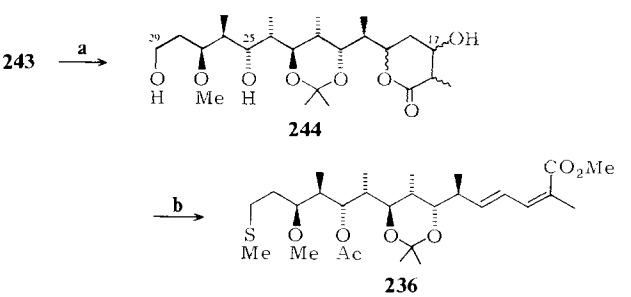
Reaction of the aldehyde **40** with the boron-enolate reagent *S*-**39c** almost exclusively provides the aldol product **239** which is converted to aldehyde **240** through removal of the chiral auxiliary, protection, and adjustment of oxidation state (Section 4)[17]. Aldehyde **240** is allowed to react with the *Z*-enolate of 3-pentanone, selectively generated with lithium 1,1,3,3-tetra-methyl-1,3-diphenyldisilazide[21], and the resulting product is silylated to provide **241**. Note that the cation used in this aldol reaction is lithium and that the methoxy group at the β-position of **240** plays an important role in this stereochemical outcome.



Scheme 50. Synthesis of **243**, a precursor of **236**. The first step proceeds in 75% yield, the fourth step in 70% yield. **a**: 1) HF, CH_3CN, 2) $NaIO_4$, 3) CH_2N_2, HBF_4, 4) $LiAlH_4$, 5) pyridinium chlorochromate, 75% yield; **b**: 1) Et_2CO, $(Me_2PhSi)_2NLi$, 2) *t*$BuMe_2SiOSO_2CF_3$, 90% yield; **c**: 1) diisobutylaluminum hydride, 2) $Me_2C(OMe)_2$, H_2SO_4, 3) *n*Bu_4NF, 4) Me_3SiCl, aqueous work-up, 85% yield.—X = *t*$BuMe_2Si$, SEM = $CH_2OCH_2CH_2SiMe_3$.—The stereoselection is given under the arrows.

The coupling of **241** and **226a** is achieved through a zirconium-mediated aldol reaction (Section 4) with the *Z*-enolate of **241** to provide the ketone **242** which, after stereoselective reduction and subsequent protecting group manipulations, is converted to the alcohol **243**. The addition of the [C15–C19] *Z,E*-dienoate moiety to **243** has been carried out efficiently to yield through **244** the same ansa chain derivative **236** as that used in *Kishi*'s synthesis (Scheme 51). A detailed discussion of this last transformation is deleted for the reason mentioned above.

Readers may wonder if the above aldol-based synthesis of **236** is "reagent-controlled". Not exactly. Two aldol reactions (**40** → **239** and formaldehyde → **226a**) use the chiral reagents solely for single asymmetric induction, and the

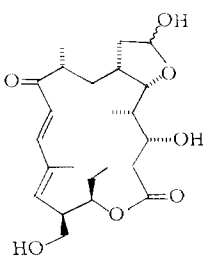


Scheme 51. Conversion of **243** into **236**. 1) $CrO_3(py)_2$, 2) benzyl-2-methylacetoacetate, 2) $LiN(iPr)_2$, 3) $NaBH_4$, 4) H_2, Pd/C, 5) toluene, reflux, 85% yield; b: 1) $(CF_3CO)_2O$, Et_3N, 2) hydrolysis, 3) toluenesulfonyl chloride, pyridine, 4) MeSNa, 5) CH_2N_2, 6) Ac_2O, pyridine, 68% yield.—The stereoselection is given under the arrows.

other two (**240** → **241** and **241** → **242**) take advantage of metal-chelation in order to obtain the desired stereoisomers. Even the last reaction (**241** → **242**), although it is a double asymmetric reaction, is not stereochemically *controlled* in the sense defined earlier. However, we have included the aldol-based synthesis in this Section, because, like the two examples described earlier (**58** + **60** and the aldehyde derived from **231** + diallyltin), the formation of a metal-chelated ring intermediate leads to the highly selective synthesis of a diastereoisomer whose stereochemistry can be predicted. This metal chelation methodology which effectively enhances the D.S. of a reactant to the extent of a synthetically acceptable level has received renewed interest in recent years and its importance justifies its inclusion above.

Having discussed several total syntheses, it is worth tabulating 1) the overall stereoselectivity, 2) the overall yield, and 3) the number of steps associated with each of the syntheses. Since the last two criteria are subject to the arbitrary choice of starting material, the starting materials used to calculate these figures are listed in Table 7. It is evident that the reagent-controlled syntheses are clearly more advantageous than those which are substrate-controlled in virtually all the criteria used to evaluate the efficiency of the multi-step synthesis.

There have been recorded only a few natural product syntheses in which the majority of the chiral centers are constructed through reagent-controlled reactions. The synthesis of 6-deoxyerythronolide B **48** served as a prototype and has been followed by those of tylonolide **245** (aglycone of the antibiotic tylosin[5, 88]) and the pentoses and



245

hexoses[*]. The other three examples are the synthesis of enkephalin S (Section 6) by *Ojima* et al. and the syntheses of the pentoses and rifamycin S by *Kishi*. Now that the distinct advantages of this approach are delineated, the new strategy will receive more attention from synthetic organic chemists.

Finally, mention should be made of the availability of homochiral substrates used in double asymmetric reactions as starting materials or synthetic intermediates[**]. Such substances are prepared from appropriate achiral compounds through either single asymmetric synthesis (as shown above on a number of occasions) or conversion of abundantly available homochiral natural products such as glucose, malic acid, tartaric acid, and several terpenes. Conversion of a natural product into another compound of a vastly different structural type has been used quite often in the past, as exemplified notably and perhaps most elegantly by the transformation of (+)- and (−)-camphor into fragments of vitamin B_{12}[89]. Many examples in the field of macrolide synthesis also demonstrate the rather efficient conversion of these natural products into small fragments which have several chiral centers. Readers should consult recent reviews for this development[3c, 90]. It is our belief that the adoption of the new strategy coupled with the judicious selection of a homochiral substrate will become a standard method for designing the synthesis of many natural products of polyketide origin.

9. Concluding Remarks

The term "synthèses asymétriques par double induction" was first used by *Horeau, Kagan* and *Vigneron* in 1968[4a]. Since then the experimental outcome of this process has been recorded sporadically, e.g., *Glaser*'s experiments in catalytic hydrogenation (1976, Section 6), *Ojima*'s hydrosilylation[91] and *Aratani*'s cyclopropanation[92] (1977), *Heathcock*'s aldol reaction[93] and *Noyori*'s aluminum hydride reduction[94] (1979), and *Hoffmann*'s carbonyl addition of crotylboronic acid esters (1980)[95]. All these have conceptually contributed to the first demonstrations of "reagent-controlled" organic reactions that appeared in 1980[8, 11]. In Sections 1—3, several new terms have been coined which may be used to explain some processes closely related to double asymmetric induction. For example, kinetic resolution can be understood on the basis of a rate difference between "matched" and "mismatched" reactions. The discussion of this important process, however, is deliberately excluded from this Account to simplify the presentation of this new strategy.

What changes may organic synthesis undergo? It is evident from Section 3 that the validity of multiplicativity of two diastereofacial selectivities is not limited to either the acyclic systems used to illustrate the rule, or the four major organic reactions discussed in Sections 4—7. Thus, additional highly diastereoselective reagents and catalysts are expected to emerge. Catalytic processes are obviously more advantageous than those using chiral reagents and therefore stronger emphasis will probably be placed on the design of chiral catalysts. These anticipated developments are reserved for a future review. With appropriate chiral reagents and catalysts at hand, the synthetic design of many natural (and unnatural) products will become straightforward, and as a result some of the aesthetic elements of traditional organic synthesis, as exemplified by the synthesis of erythronolide A in Section 7, may well be lost. *Woodward*'s 1956 remark, "There is excitement, adventure, and challenge, and there can be great art, in organic synthesis"[80], will still pertain to the many synthetic problems not amenable to iterative solutions. However, the power of the new strategy has already made possible what appeared to be almost impossible even a few years ago. In this sense a new era which is characterized by the evolu-

[*] Our synthesis of the ansa chain of rifamycin S **223** is excluded from this listing.

[**] Somewhat ironically, many syntheses in racemic form now turn out to be more difficult to design and execute with equal efficiency than the corresponding enantioselective syntheses. See also the footnote on p. 4.

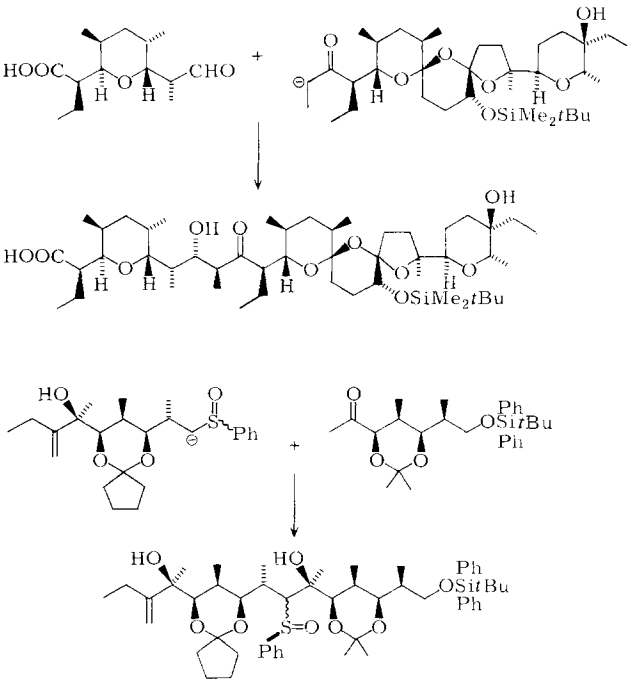
tion from substrate-controlled to reagent-controlled organic synthesis is definitely emerging[*].

In order to further understand the interaction of two chiral reactants, some comments are in order on two aspects of diastereofacial selectivities: 1) their multiplicativity and 2) their extent and directionality. The multiplicativity is dependent on the validity of the assumption that the single and double asymmetric reactions used as a set to evaluate the rule proceed through very similar transition states. Using energy terms, this statement may be illustrated more conveniently. Thus, $\Delta\Delta G_1^{\ddagger}$ and $\Delta\Delta G_2^{\ddagger}$, which correspond to the D.S.'s of two reactants, represent the energy difference in the two diastereomeric transition states of the reaction used to determined the D.S. of each reactant in a specific reaction. Expressing the stereoselectivity observed in the double asymmetric reaction by $\Delta G^{\ddagger}$, the D.S. multiplicativity rule is now shown by the following equations for the matched and mismatched pair reactions.

$$\Delta G^{\ddagger}(\text{matched}) = \Delta\Delta G_1^{\ddagger} + \Delta\Delta G_2^{\ddagger} + \Delta G_{12}^{\ddagger}$$
$$\Delta G^{\ddagger}(\text{mismatched}) = \Delta\Delta G_1^{\ddagger} - \Delta\Delta G_2^{\ddagger} + \Delta G'^{\ddagger}_{12}$$

Both $\Delta G_{12}^{\ddagger}$ and $\Delta G'^{\ddagger}_{12}$ are perturbation terms closely related, in most cases, to the (normally small) conformational change brought in the transition state of the double asymmetric reaction relative to the transition states of the model single asymmetric reactions (for the D.S. measurements). The magnitude of these terms is difficult to estimate a priori and constitutes a limitation of the rule. Many examples in this Account show that they are small as compared with $\Delta\Delta G_1^{\ddagger}$ and $\Delta\Delta G_2^{\ddagger}$, provided that the selection of achiral model compounds is appropriate.

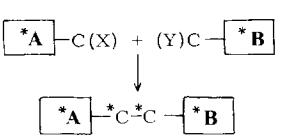
The extent and directionality of the D.S. of an acyclic compound is, by definition, the same as the Cram : *anti*-Cram ratio often used in the recent literature. Which stereoisomer results as the predominant product from the reaction of an acyclic compound with an achiral reagent (the directionality of the D.S.) is supposedly predictable on the basis of *Cram*'s *acyclic* model[96] or its later version, *Felkin*'s model[97]. Unfortunately, many predictions have proven to be incorrect. Readers may note that the aldol reactions of **24**, **35**, and **69** all provide the respective *anti*-Cram products predominantly[**]. Moreover, the Cram : *anti*-Cram ratio (or its reciprocal) normally does not exceed 5 : 1 (or 1 : 5) (Section 3), a stereoselectivity that does not quite satisfy today's standards and should either be enhanced or effectively overridden. In contrast to the *acyclic* model, *Cram*'s *cyclic* metal-chelate model[98] is extremely useful for predicting the stereochemical outcome of many reactions. The proper design of either reactant or both reactants brings about a rigidly chelated framework which creates two highly distinguishable diastereotopic faces, resulting in a stereoselectivity of the reaction being as high as 100 : 1 in some cases[99]. Thus, the metal-chelation methodology effectively enhances the normally small D.S. of an acyclic reactant with predictable directionality. Examples quoted in this account are: the two aldol reactions **57** + **60** in Scheme 14, and **241** + **226a** in Scheme 50. Two notable others chosen from many examples in the literature are shown in Scheme 52[100,101].



Scheme 52. *Kishi*'s narasin synthesis [100] proceeds with exclusive stereoselection; in *Stork*'s erythronolide A seco-acid synthesis the selectivity is 5 : 1.

These four examples are deliberately selected because they illustrate an important synthetic process: Two prefixed homochiral segments [*A–C(X), *B–C(Y)] are joined together with the concurrent creation of a new chiral center or centers (Scheme 53). This process must be clearly distinguished from the major theme of this review formulated in Scheme 6. Note that neither *A–C(X) nor *B–C(Y) serves as a chiral reagent. Therefore, these successful connections have not been executed *with control* in the sense defined in the account. Therefore at the time of retrosynthesis one must be confident that the assembly of two segments of this type, which normally appears in the late stages of the synthesis, will proceed in the desired manner. Can we control this stereochemistry? The answer is no; at least not at present. A *general* solution to this extremely challenging, fundamental problem appears to demand a third chiral component in the form of a catalyst.

In concluding this lengthy Account we would like to express briefly our personal feelings about the entire problem of asymmetric synthesis. When we agonized over the



Scheme 53. Neither A nor B is a reagent.

[*] By "evolution" the authors do not imply a "revolution" in which the traditional order is destroyed. There is much that the new supplements and complements the old.

[**] In formulating his rule, *Cram* often used phenyl-substituted substrates. This substituent exerts a strong electronic effect which can override other effects. Therefore, the rule does not necessarily apply to aliphatic substrates.

stereochemical complexity of 6-deoxyerythronolide B, our thoughts turned to enzymatic processes just as they had when we secured the hint of using a thiol ester to effect macrolactonization of the methynolide seco-acid[102]. How does an enzyme create chiral centers? Since a substrate binds tightly to an enzyme which is rich in chirality, only one face of the reacting prochiral group of the substrate is effectively exposed to external attack. We have succeeded in creating a small chiral environment near the reaction site which mimics the active site of the enzyme. Although lacking the catalytic nature of an enzyme or its substrate-specificity, our reagent holds one decisive advantage over the enzyme in that both matched and mismatched reactions can be utilized to our benefit. An enzyme is generally limited to the matched pair reaction. Once again we have learned from Nature only to wonder what we might be taught next[*].

With great pleasure we thank many collaborators whose names appear in the references. They have contributed experimentally as well as conceptually to the development of the new strategy presented in this Account. It is also a memorable and gratifying experience for us to have collaborated with Professor Sharpless in the exploitation of his reagent which has culminated in the synthesis of the hexoses. This Account has evolved from the senior author's preliminary documentations[3a–c], one of which is coauthored by Peter McCarthy. His careful and concise review on the ever-growing field of macrolide synthesis has greatly aided us in completing Section 8. We would like to acknowledge the helpful criticisms of various Sections provided by Rick Danheiser, Samuel Danishefsky, Iwao Ojima, Bill Roush, and Barry Sharpless. Many of the improvements are a direct result of their efforts but errors remain ours. We would also emphasize that Professor Kagan has brought our attention to the early work on double asymmetric syntheses. The work and this writing have been supported by grants from the National Institutes of Health and National Science Foundation (USA) as well as from the Kao Corporation (Japan). J.S.P. is a National Cancer Institute Trainee (NCI-5-T-32-CA-09112) of the Public Health Service, USA.

[*] After the final version of this review was completed, several additional publications pertinent to what has been expounded here have appeared in the literature. For instance, see [103]–[108].

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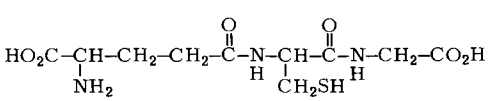
Chemical Basis of the Action of Glyoxalase I, an Anticancer Target Enzyme

By Kenneth T. Douglas* and Seiji Shinkai

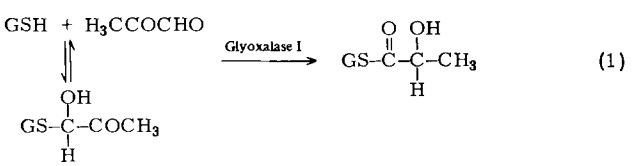
Although glyoxalase I was discovered in 1913 the physiological role of this ubiquitous enzyme is still far from clear. It catalyzes the reaction of α-ketoaldehydes and glutathione to produce *S*-D-lactoylglutathione, from which D-lactate and glutathione are produced by glyoxalase II. Argument raged for many decades about the nature of the natural substrate. Was it methylglyoxal? Was methylglyoxal ever formed metabolically or was it purely artifactual? Some of these questions have been resolved in that a number of metabolic processes which produce α-ketoaldehydes have now been recognized. Equally unsuccessful have been attempts to ascribe a physiological role to glyoxalase. This is clearly an important question since glyoxalase I occurs in cells at all levels of evolution. Time and time again glyoxalase I has been claimed to be linked to cancer, and a number of research groups worldwide are using it as a model for designing potential anticancer drugs. In this review article the mechanism of action of the enzyme is discussed, knowledge of which enables stronger inhibitors to be synthesized. Until roughly ten years ago when powerful NMR techniques were used to study it for the first time, it was assumed that the key step in the mechanism was a hydride ion transfer. Today, the mechanism is envisaged as a proton transfer.

1. Introduction

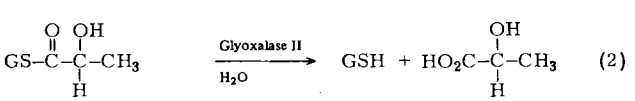
It has long been known that α-keto aldehydes are strongly carcinostatic[1]; however, their direct use as anticancer drugs is prevented by their rapid conversion in vivo into the corresponding inactive[1] α-hydroxy acids by the glyoxalase enzyme system. The glyoxalase system was discovered[2] in 1913 and consists of two enzymes and their cofactor, glutathione (GSH). Glyoxalase I (lactoylglutathione lyase, EC 4.4.1.5) converts the monohemithioacetal formed from GSH and methylglyoxal or other α-oxoaldehydes into *S*-lactoylglutathione[3] as shown in equation (1). This thioester is then hydrolyzed by glyoxalase II (hydroxyacylglutathione hydrolase, EC 3.1.2.6), as shown in equation (2), to produce lactic acid and free glutathione [Eq. (2)].



Glutathione (GSH)

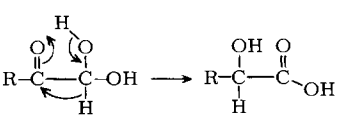


(1)



(2)

Walsh[4] has suggested that direct oxidation of the aldehyde would require removal of two electrons from an already strongly electrophilic site. Prior formation of the glutathione monohemithioacetal allows ready removal of two electrons from a nonelectrophilic center and gives a thioester product, with a high group transfer potential. Undoubtedly, this aids in the hydrolase step catalyzed by glyoxalase II. However, another mechanism which leads directly from the hydrated form of the aldehyde (the vastly predominant species) to lactic acid is also feasible [eq. (3)].



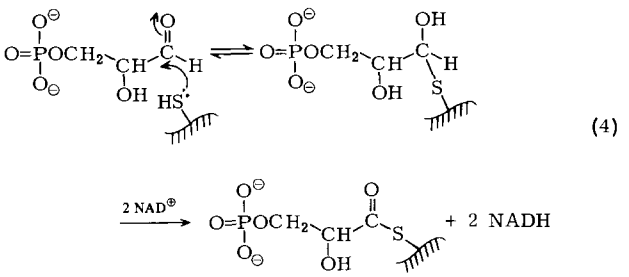
(3)

Presumably, the use of two enzymes and a glutathione coenzyme, with a free thioester intermediate, offers better metabolic and control advantages. The sequence may be sensitive to GSH cellular flux, and to relative rates of synthesis and breakdown of the enzymes, etc. The *S*-lactoylglutathione intermediate itself may possess important biological properties as reported by *Gillespie*[7].

Although it has been known for so long, many features of the glyoxalase reaction are unclear. What is its physiological role? What is its detailed mechanism of action? The nature of the substrate for glyoxalase I is a complex question. The substrate could either be the hemithioacetal of GSH and CH_3COCHO (formed nonenzymically) or free GSH and CH_3COCHO which react in a random or ordered way with the enzyme. The importance of glyoxalase I can be seen as two-fold. 1) It is of interest as a current anticancer target enzyme—a considerable body of data appears to support the view that its inhibitors are frequently cytotoxic and several have in vivo antitumour activity. 2) The enzyme is also of interest from a mechanistic stand-

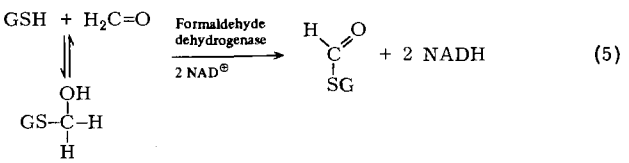
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point. A similar sequence of reactions occurs in the reaction of glyceraldehyde 3-phosphate dehydrogenase[5]. The Cys-149 residue of the enzyme forms a hemithioacetal with glyceraldehyde 3-phosphate, which is then oxidized (using $NAD^{\oplus}$) to an enzyme-bound thioester [eq. (4)].



(4)

The redox process is intramolecular for glyoxalase I (1,2 hydrogen shift) and intermolecular for glyceraldehyde 3-phosphate dehydrogenase (hydride transfer to $NAD^{\oplus}$). Glutathione-dependent formaldehyde dehydrogenase[6] similarly converts formaldehyde into a high energy glutathione thioester of formic acid via an intermolecular ($NAD^{\oplus}$-dependent) redox reaction of the glutathione hemithioacetal [eq. (5)].



(5)

2. Biological Basis

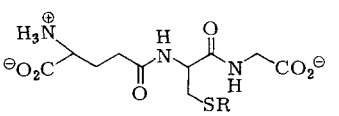
2.1. Hypotheses on Why Glyoxalase I Inhibition Should Be Anticancer Active

Although a number of proposals concerning the natural role of glyoxalase I have been made, little has been firmly established. It has been suggested that it plays a role in the enhancement of anti-(immunoglobulin E)-induced histamine release[7a], in microtubule assembly[7b], in protection against intestinal bacteria[8], in a postulated metabolic cycle for the degradation of glycine and threonine (since methylglyoxal is the deamination product of aminoacetone)[9], and is possibly involved in the heme biosynthetic pathway[10]. These will not be discussed further here.

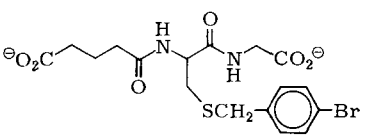
The possibility that glyoxalase I inhibitors might have anticancer activity appears to have been suggested at about the same time by *Vince* and *Wadd*[11] and by *Szent-Györgi*[12]. *Vince* and *Wadd* argued[11] that because glyoxalase I rapidly converts[13-15] the cytotoxic methylglyoxal into nontoxic lactate in the presence of GSH, which is known[16] to be necessary for cell division, inhibitors of glyoxalase I might be used to concentrate methylglyoxal in tumor cells and thus inhibit cellular growth. *Szent-Györgyi* argued[12] that normal cellular growth requires a careful balance between a growth-retarding force (methylglyoxal) and a growth-promoting force (glyoxalase I). Thus, inhibitors of glyoxalase I might be expected on this rather simple basis to be anticancer agents. It is now clear that the situation is much more complicated than either of these suggestions.

2.2. Some Examples of Glyoxalase I Inhibitors with Cytotoxic or Anticancer Activity

Early approaches to anticancer compounds involved the preparation and screening of analogues of glyoxalase I substrates. Thus, a large number of *S*-substituted glutathiones **1** have been synthesized and found to be strong inhibitors of glyoxalase I[11, 17, 18, 19]. Many of these were cytotoxic to L1210 leukaemia and KB cells in tissue culture[20]. In addition, several *S*- and *N*-substituted cysteinylglycines have been evaluated as glyoxalase inhibitors[21]. However, their rapid metabolism rendered them (including **1**) inactive in vivo[21, 22]. One compound which is resistant to γ-glutamyl cleavage by γ-glutamyl transpeptidase is **2**: this appears to have promising biological properties.

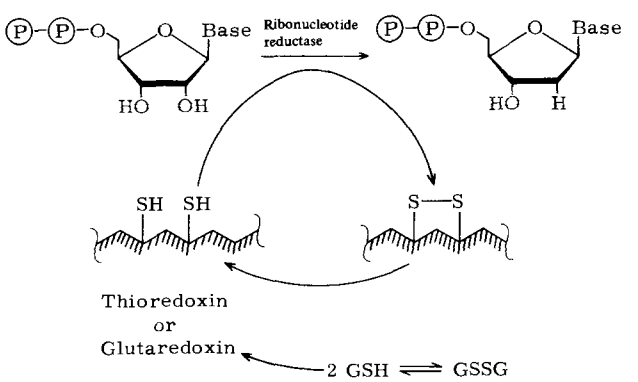


1a, R = $-(CH_2)_nH$
1b, R = $-CH_2Aryl$
1c, R = $-(CH_2)_nCOAryl$



2

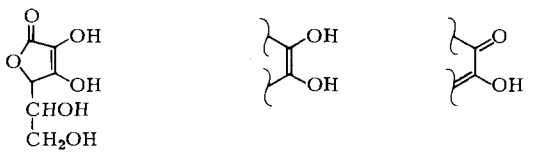
Whilst *S*-(*p*-bromobenzyl)glutathione is a strong glyoxalase I inhibitor (especially of the human erythrocyte enzyme), it is not clear whether its antitumour activities and those of analogous compounds result from this effect. For example, glutathione derivatives inhibit ribonucleotide reductase (Scheme I), an enzyme which catalyzes the reduction of the furanose moiety of ribonucleotides to deoxyribonucleotides, in a complex manner[23, 24]; a process which can be the rate-determining step in DNA replication in many systems. Consequently, inhibition of this vital process can be seen as a prime target for potential anticancer activity and much research has been invested in this area. One of the dithiol donor proteins, glutaredoxin, is recycled via a pathway involving glutathione, and it was surprising to find that glutathione derivatives blocked on sulfur or nitrogen inhibited the donor activity of glutaredoxin or of *E.*



Scheme 1. Mechanism for the conversion of ribonucleotides into deoxyribonucleotides catalyzed by the enzyme system ribonucleotide reductase.

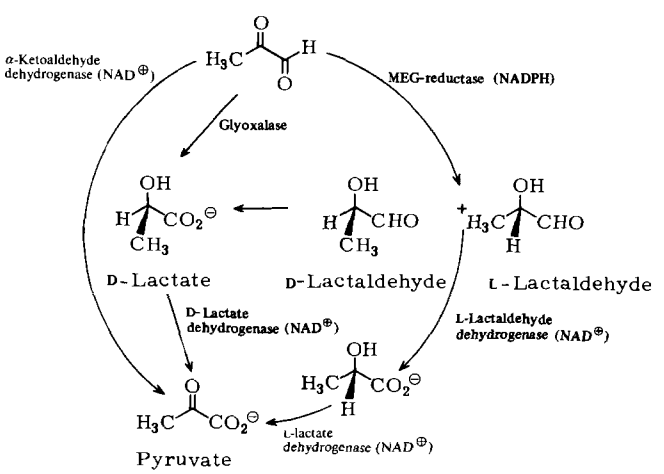
coli ribonucleotide reductase[23]. Even more striking inhibitory effects have been observed with analogues of oxidized glutathione and ribonucleotide reductase from *E. coli*[24].

Reductones (e.g. ascorbic acid **3**) suppress the growth of Sarcoma 180 and are also effective glyoxalase inhibitors, suggested to be because of their structural similarity to methylglyoxal[25]. However, the inhibition of glyoxalase I by **3** and other compounds containing the enediol **4** or *paene*-enediol structure **5**[*] has been rationalized[26] on the basis of their similarity to part of the putative transition state structure for glyoxalase I reactions of this enzyme. Such compounds are powerful chelating agents and some or all of their inhibition of glyoxalase I, a Zn-containing metalloenzyme, may result from this[27].



3 **4** **5**

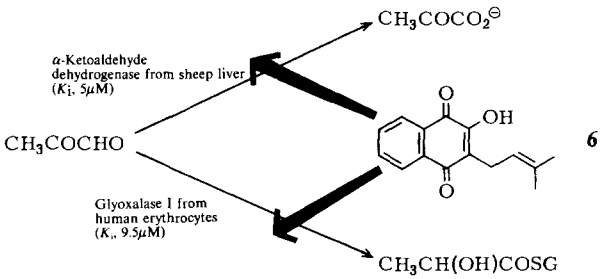
Methylglyoxal is detoxified by a number of other routes, which are summarized in Scheme 2. The direct (NAD-dependent) reduction to pyruvate by α-ketoaldehyde dehydrogenase occurs in mammalian cells[27], including some tumor cells, and in bacteria. The NADPH-branch, via lactaldehyde, has been reported in bacteria[28]. For effective build-up of the concentration of cellular α-ketoaldehyde in mammalian systems, at least both the glyoxalase I and α-ketoaldehyde dehydrogenase detoxification routes must be blocked, a point first emphasized by *Vince* and *Daluge*[20].



Scheme 2. α-Ketoaldehyde catabolism.

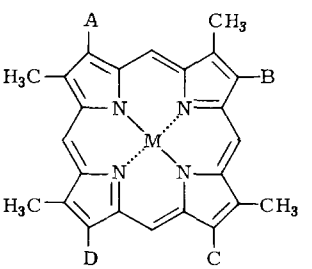
Lapachol **6** and some derivatives are effective against several tumor types. We have recently shown that lapachol not only strongly inhibits human erythrocyte glyoxalase I, but also sheep liver α-ketoaldehyde dehydrogenase[29].

Lapachol is involved in other places in metabolism[29]. As a hydroxyquinone it decouples oxidative phosphorylation, presumably in an analogous manner to 2,4-dinitrophenol. It also inhibits succinate dehydrogenase and 3-α-hydroxysteroid-mediated transhydrogenase. Recently, it has been suggested that its primary antineoplastic activity may involve inhibition of L-dihydroorotate dehydrogenase in pyrimidine biosynthesis.

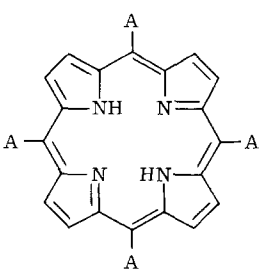


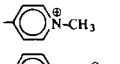
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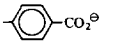
The cytotoxic action of methylglyoxal is potentiated by co-application of an *S*-blocked glutathione as glyoxalase I inhibitor[20]. Further, *Yamamoto*[30,31] has reported that the binding of phytochlorin sodium (a porphyrin) to cancer cells in vitro upon irradiation with visible light is enhanced by methylglyoxal. Methylglyoxal also lowers the tumor-forming ability by almost threefold[30,31]. In view of the synergism between α-ketoaldehyde and porphyrin in cancer cell division, *Yamamoto* suggested involvement of the glyoxalase system in mitosis. We have found that glyoxalase I purified from a number of species (see Fig. 1) is



	A,B	C,D	"M"
Hemin	$CH=CH_2$	$(CH_2)_2CO_2^{\ominus}$	FeCl
Protoporphyrin IX	$CH=CH_2$	$(CH_2)_2CO_2^{\ominus}$	2 H
Hematoporphyrin	$CH(OH)-CH_3$	$(CH_2)_2CO_2^{\ominus}$	2 H
Coproporphyrin III	$(CH_2)_2CO_2^{\ominus}$	$(CH_2)_2CO_2^{\ominus}$	2 H



meso-Tetra(4-*N*-methylpyridyl)porphin(TMPyP), A = 

meso-Tetra(4-carboxyphenyl)porphin(TCCP), A = 

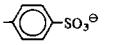
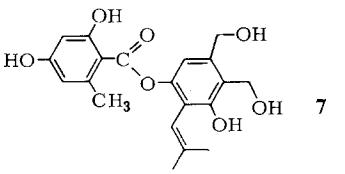
meso-Tetra(4-sulfonatophenyl)porphin($TPPS_4$), A = 

Fig. 1. Porphyrin inhibitors of glyoxalase I.

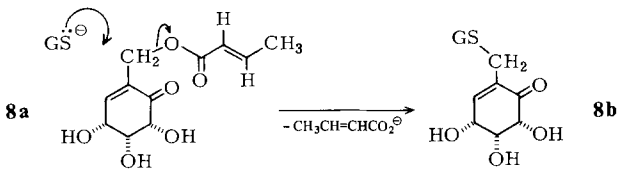
[*] The word "paene" is derived from Latin and means almost or nearly. The prefix was introduced in order to distinguish related but not fully analogous structures [26].

strongly inhibited by a range of porphyrins[32,33], supporting *Yamamoto*'s proposal. The inhibition is stronger at lower pH, and since cancer cells, especially after glucose treatment, have lower pH values than normal tissues[34], inhibition of glyoxalase I by porphyrins may be stronger than in normal cells and contribute to the selective uptake of some porphyrins by cancer cells[32].

Umezawa et al. have found a potent, competitive inhibitor[35] ($K_i = 4.6 \times 10^{-6}$ M) of glyoxalase I in the culture broth[35] of a mushroom. This compound **7** inhibits the growth of Yoshida sarcoma cells but has no in vivo effect, presumably because of the ready cleavage[36] of the ester bond. Recently, **7** has been found to inhibit a number of other enzymes[37]. Another glyoxalase I inhibitor isolated



7



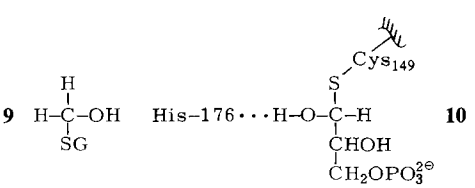
8a **8b**

from actinomycetes[38,39] is the crotonate ester **8a** which reacts rapidly with glutathione to give **8b**, thus inhibiting glyoxalase I. **8** showed no significant antibacterial activity, but did inhibit Yoshida rat sarcoma cells in tissue culture. Growth of both ascitic and solid forms of Ehrlich carcinoma in mice was suppressed by daily intraperitoneal injection of **8**, which also prolonged the survival period in mouse leukaemia L1210[38,39].

3. Chemical Basis of the Action of Glyoxalase I

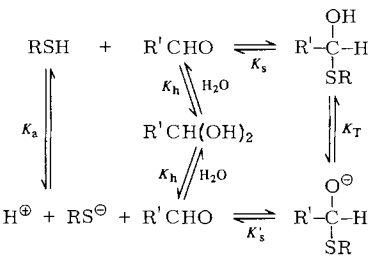
3.1. The Thiol-Aldehyde Reaction

The reaction between thiols and aldehydes has been known for a hundred years[40]. This reaction provides the substrates for glyoxalase I [eq. (1)], and for formaldehyde dehydrogenase (**9**)[41,42] together with intermediates in the glyceraldehyde 3-phosphate dehydrogenase reaction sequence (**10**)[43]. The tight-binding inhibition of some thiol



9 **10**

proteases by aldehydes also involves this reaction. The behavior is complicated by a) hydrates of the aldehyde[44], b) ionization of the thiol[44,48], and c) ionization of the OH group of the monohemithioacetal[41,48]. Equation (6) shows a minimal reaction scheme[44] (K_s = true association constant of RSH and the aldehyde; K_a = acid dissociation constant of the thiol). Since values of pK_T (for the dissociation



(6)

constant of the OH group of the hemithiolacetal) for the aldehyde used were greater than 12, the observed equilibrium constant (K^{obs}) for hemithioacetal formation is given by equation (7).

$$K^{obs} = K_s/(1 + K_a/H^{\oplus})(1 + K_h) \quad (7)$$

Using this relationship the effects on K_s of structural variations in the aldehyde were determined[44] for both glutathione and 4-nitrothiophenol. Steric effects in aldehydes would be expected to be more significant with the bulky glutathione than with water, but both hydration and hemithioacetal equilibria responded in a similar way to steric changes ($\log K_s$ correlated well with $\log K_h$). Aldehydes with ionic substituents (e.g. glyceraldehyde 3-phosphate) fitted the correlation, indicating that ionic interactions between GSH and the aldehyde do not contribute to the hemithioacetal stability[44].

Within experimental error, K_s appears to be independent of thiol, and the sensitivity to σ^* for aliphatic aldehydes also appears to be thiol independent[44]. For the aldehydes (including methylglyoxal) the hemithioacetal adduct with glutathione was found to be 4.3 (± 0.2) kcal mol^{-1} more stable than the corresponding hydrate[44].

The pK_a of the hemithioacetal (pK_T) is rather insensitive to the thiol pK_a [eq. (8)] for acetaldehyde[44,47].

$$pK_T = 0.16\ pK_a + 11.1 \quad (8)$$

A number of experimental equilibrium constants (K^{obs}) for hemithioacetal formation from various α-ketoaldehydes and *N*-substituted glutathiones are collected in Table 1. At the pH (ca. 6.60) usually used for glyoxalase I enzymatic studies K^{obs} needs little if any correction for the effect of pH on thiol ionization[44,48], but such corrections may be necessary at higher pH. It can be seen from Table 1 that even for GSH the equilibrium is displaced to the hemithioacetal side. Indeed, the hemithioacetals of some α-ketoaldehydes have been isolated[49,50].

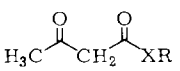
For acetaldehyde the equilibrium constant (K) is independent of the pK_a of the thiol[45,46]. However, values of K (determined from the saturation kinetics observed in the amine-catalyzed rearrangement of the hemithioacetal to thioester) for phenylglyoxal appear to have a small, but real dependence on thiol basicity. A plot of K^{obs} (from [48]) against pK_a of the thiol is linear with a slope -0.3 over ca. three thiol pK_a units. This is similar to the sensitivity of bridging methylene pK_a in acetoacetates **11**[51] to the pK_a

Table 1. Equilibrium constants (K^{obs}) at 25 °C for thiohemiacetal formation from an aldehyde (RCHO) and glutathione; K^{obs} is defined as [thiohemiacetal]/[RCHO][GSH].

R	K^{obs} [M^{-1}]	Ref.
H	667 [a]	[41]
CH_3CO	200 ± 10 [b]	[44]
	333 [c]	[54, 17]
PhCO	603 ± 31 [d]	[48]
	625 ± 75 [e]	[48]
X–C_6H_4–CO		
X=H	1667 [f]	[54]
p-CH_3	909 [f]	[54]
p-OCH_3	714 [f]	[54]
p-Br	667 [f]	[54]
p-Cl	278 [f]	[54]
p-Ph	1124 [f]	[54]
m-OCH_3	833 [f]	[54]
p-NO_2	833 [f]	[54]
p-OH	1075 [f]	[54]

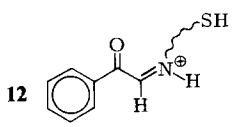
[a] At pH 8.0. [b] Corrected for thiol ionization. [c] Data from [17] at pH 6.6; data from [54] at pH 7.0, but the value was pH-independent from pH 5 to pH 9. [d] Measured at 280 nm, pH 6.67. [e] Measured at 250 nm, pH 6.67; the value decreases sigmoidally with increasing pH following ionization ($pK_{app} = 9.0$). [f] At pH 7.0, $\mu = 0.2$.

of the conjugate acid of the leaving group (for thiols and phenols).

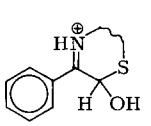


11, X = O,S

Table 2 summarizes the equilibrium constants (K^{obs}) for the reaction of α-ketoaldehydes with glutathione substituted at nitrogen. *N*-Acetylation appears to affect the K^{obs} value for methylglyoxal slightly, phenylglyoxal scarcely, and *p*-chlorophenylglyoxal not at all. For phenylglyoxals the data clearly exclude any significant contribution from Schiff base formation between the glutathione amino group and the aldehyde or keto group (**12** or **13**).



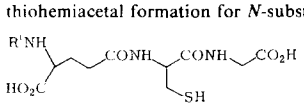
12



13

The equilibrium between glutathione and methylglyoxal is such that in the cell, where the level of GSH is quite high (often 10^{-3} M or greater[52]) and that of methylglyoxal is very low[53], nearly all the methylglyoxal is bound, leaving very little free electrophilic aldehyde. This favorable equilibrium must contribute significantly to the detoxification of this highly cytotoxic aldehyde, as it purchases time for the glyoxalase system to encounter the α-ketoaldehyde and act on it. In contrast to the (relative to GSH) low flux of the glyoxalase enzymes, the higher cellular level of GHS means that encounter of the α-ketoaldehyde with it is considerably more likely.

Table 2. Effect of the amino substituents R′ on the equilibrium constants for thiohemiacetal formation for *N*-substituted glutathiones.



R′ \ Aldehyde	CH_3COCHO	PhCOCHO K^{obs} [M^{-1}]	*p*-ClC_6H_4COCHO
H	333 [a]	1667 [b]	625 [b]
CH_3CO	1000 [b]	1111 [b]	625 [b]
$PhCH_2OCO$	571 [c]	—	—

[a] From [17] and [67]. [b] From [67]. [c] K. T. Douglas, C. D'Silva, unpublished (pH 6.60, 25 °C).

The apparent first-order rate constants for the reaction of GSH with a series of α-ketoaldehydes (25 °C, formate buffer, pH 3.0, [GSH]/[α-ketoaldehyde] ≈ 12) were found[54] to be essentially independent of the structure of the α-ketoaldehyde (including methylglyoxal and nine arylglyoxals). This behavior parallels the absence of substituent effects on the equilibrium constants for this system. Substituents also have little effect on the stretching frequency of the aldehyde carbonyl group (1727 cm^{-1}), whereas the keto group is markedly sensitive. The rate constants reported represent the approach to hemithioacetal equilibrium and also reflect the hydration equilibria[54].

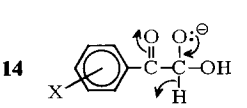
3.2. Model Systems for the Mechanistic Study of the Hemithioacetal-Thioester Rearrangement

The rearrangement of hemithioacetals derived from α-ketoaldehydes to the corresponding α-hydroxythioesters catalyzed by glyoxalase I occurs in the absence of enzyme in a number of model systems. In this section we review the chemistry of this rearrangement and apparent analogues (e.g. the Cannizzaro reaction) in model systems.

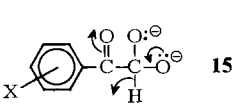
A number of systems have been considered as models for the glyoxalase I reaction. These include Franzen-type catalysts based on 2-(dialkylamino)ethanethiols[55–60], base-catalyzed rearrangement of hemithioacetals of simple thiols either with[61] or without[48,58,60] metal ion catalysis, as well as $OH^{\ominus}$-catalyzed rearrangements of arylglyoxals to mandelates[62] (intramolecular Cannizzaro reactions[62–65]) and analogues[66].

3.2.1. Models for the Study of Hydride Ion Transfer—Cannizzaro Type

It is fairly well established that the hydroxide ion catalyzed disproportionation of phenylglyoxal in aqueous media to give the mandelate ion involves internal hydride transfer[62,65] in the hydrate anion **14** and dianion **15**[*].



14



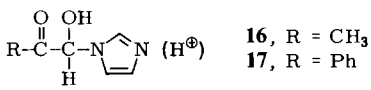
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For substituted phenylglyoxals the Hammett ρ-value is +2.0, indicating that the transition state is strongly stabilized by electron withdrawal from the α-keto group[65]. The reaction correlates well with the ketonic C=O stretching frequencies of both hydrated and free aldehyde forms[65].

[*] A free radical route for the benzaldehyde Cannizzaro reaction has recently been proposed: S.-K. Chung, *J. Chem. Soc. Chem. Commun. 1982*, 480.

3.2.2. General Base Catalysis

In the presence of the bases imidazole and $HPO_4^{2\ominus}$, the glutathione-derived hemithioacetals of methyl- and phenylglyoxal rearrange to the corresponding *S*-lactoyl- and *S*-mandeloylglutathiones, respectively[58,61]. Imidazole forms an adduct **17** with the α-ketoaldehyde, which probably does not rearrange to mandeloylimidazole[58]. The



16, R = CH_3
17, R = Ph

rearrangement was suggested to be general base catalyzed, since supported by more detailed kinetic studies[48], and, when run in D_2O it resulted in the incorporation of solvent deuterons at C-2 of the α-hydroxy acid product[58]. In contrast, under Cannizzaro conditions (strong base in D_2O) methylglyoxal is converted into lactate with no significant deuterium incorporation at C-2, i.e. hydride transfer occurred in the absence of thiol at high pH, but under milder, general base conditions (pH 7) proton transfer occurs in the presence of glutathione[58]. For the general base catalyzed reaction there was a kinetic solvent isotope effect (k_H/k_D) of 3.3 ± 0.5 for CH_3COCHO and 2.3 ± 0.2 for PhCOCHO, comparing the CDO derivatives in each case: the values are considerably less than those for $OH^{\ominus}$-catalyzed Cannizzaro reactions (typically 3.8 and 5.0[67]). The authors[58] suggested that glutathione has the role of a covalent catalyst whose sulfur atom acidifies the α-CH group and that there is a basic active-site amino acid residue in glyoxalase I for this purpose. The metal ion, if important, serves only to chelate the substrate to the active site[58].

The data of *Okuyama* et al.[48] show that the solvent isotope effects reported above are complex, having been obtained at a fixed concentration of thiol[58]. For the hemithioacetals from phenylglyoxal and β-mercaptoethanol or glutathione the rate of rearrangement to thioester shows hyperbolic dependence on thiol concentration, reflecting both the rearrangement and the thiol-aldehyde equilibrium. For the rearrangement the solvent isotope effect $k_{H_2O}/k_{D_2O} \approx 1.0$, whereas for the thiol-aldehyde equilibrium it is 0.38, although primary isotope effects were not reported[48]. The studies by *Hall* et al.[58] do not appear to allow for the solvent isotope effect on the aldehyde-thiol equilibrium, which should be felt in the kinetics of thioester formation (it was not stated whether primary isotope experiments with PhCOCDO were conducted in H_2O or D_2O). The kinetics follow equation (9)[48], in which K_h is the formation constant of the hemithioacetal and k_{max} the maximal rate constant at high thiol concentrations, ascribed by *Okuyama* et al.[48] to the rearrangement reaction.

$$k_{obs} = \frac{k_{max} \cdot K_h [RSH]}{(1 + K_h [RSH])} \tag{9}$$

At low thiol concentrations $K_h[RSH] \ll 1$, and we obtain equation (10).

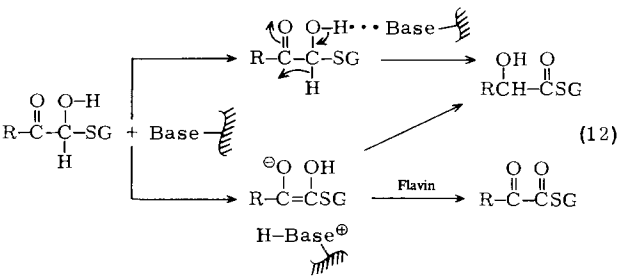
$$k_{obs} = k_{max} \cdot K_h [RSH] \tag{10}$$

Hence the primary isotope effect $k_{obs(H/D)}$ (e.g. comparing PhCOCHO in H_2O with PhCOCDO in D_2O) is given by equation (11)

$$k_{obs(H/D)} = k_{max(H/D)} \cdot K_{h(H/D)} \tag{11}$$

For phenylglyoxal a value of 6.1 for $k_{max(H/D)}$ is obtained for the rearrangement using a value of 2.3 for $k_{obs(H/D)}$ (assuming that the primary isotope effect will not be greatly affected by the solvent change) and using a value[48] of 0.38 for $K_{h(H/D)}$ (assuming that the change from PhCOCHO to PhCOCDO will not affect the value of K_h as much as the change from H_2O to D_2O). This k_{max} value is in line with extensive hydrogen transfer in the transition state but does not distinguish between hydride and proton transfer. However, the products is formed (in D_2O from PhCOCHO) with deuterium incorporated at the α-position (PhCD(OD)COSR) consistent with a proton transfer pathway as suggested by *Hall* et al.[58].

It is known that flavins are able to trap transient enediols oxidatively, while they do not serve as efficient hydride acceptors[59]. This implies that, if the reaction proceeds via an enediol intermediate, added flavin should inhibit the rearrangement and effect oxidation. In the presence of tetra-*O*-acetyl-3-methylriboflavin the rearrangement of hemithioacetals to α-hydroxythioesters was almost totally inhibited and the products were α-keto acids[59]. In accord with the results of *Hall* et al.[58], this finding supports the idea that the rearrangement occurs via an enediol intermediate [eq. (12)].

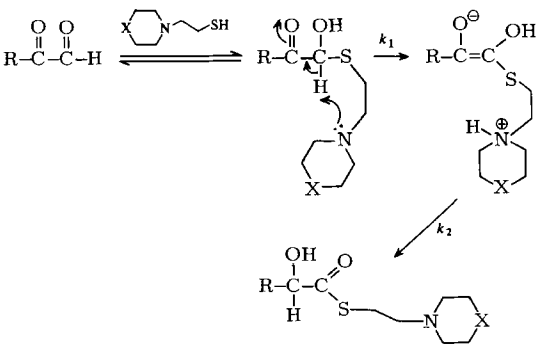


(12)

Kinetic studies established that the oxidation by the flavin was zero order with respect to flavin and first order with respect to thiols and glyoxals. Thus the reaction sequence consists of the rate-limiting deprotonation of the hemithioacetal to form the enediol intermediate, followed by its rapid oxidation by the flavin. The k_H/k_D values of 5—12 for C_6H_5COCHO/C_6H_5COCDO are apparently consistent with this proposal[59].

3.2.3. Intramolecular Catalysis

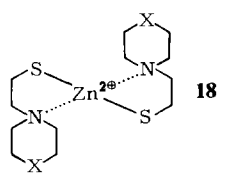
Franzen showed early on that β-amino-substituted thiols are effective intramolecular catalysts[55-57]. The Franzen catalysts (2-dialkylaminoethanethiols) have been reinvestigated kinetically and the reaction proceeds via a hemithioacetal initially formed between the catalyst and phenylglyoxal[60]. This hemithioacetal then rearranges in a general base catalyzed process to afford the product thioesters.



It was proposed that for X = O the rate-determining step was an intramolecular deprotonation (k_1) to form the enediolate. For X = CH_2, the rate-determining step at pH < 8 was deprotonation to form the enediolate, but at pH > 8 it was suggested that the rate-determining step was reprotonation of the enediol at C-2 (k_2) to give the thioester. Compared to intermolecular catalysis of the hemithioacetal rearrangement by amino groups[48], the intramolecular process shows low effective molarities (30 M (X = O) and 90 M (X = CH_2)). Low effective molarities are common for intramolecular general base processes[68], in line with this view.

3.2.4. Metal Ion Effects

In an early paper, *Hall* and *Poet* reported a highly effective catalysis by divalent metal ions of the rearrangement of hemithioacetals to thioesters in non-aqueous systems[61] which was not effective in aqueous media[58]. The absence of metal ion catalysis in aqueous media has been confirmed and proposed[60] to arise from inhibition of hemithioacetal formation since the 2-(dialkylamino)ethanethiol sequesters the metal ion as complex **18**.



18

On the basis of these results, the authors proposed[60] that the active site of glyoxalase is sufficiently nonpolar to be subject to metal ion catalysis and is highly protected against water molecules. While it is certainly the case that the active site of glyoxalase contains a large hydrophobic pocket[11,17,19-22,29,32,33] in the region of the "enediol" site (the S-site[69]), it has been reported that the metal ion in the active site of Mn^{II}-glyoxalase I binds two water molecules. Indeed, a mechanism has been proposed which incorporates both of these water molecules[70]. It is likely that the prevention of effective hemithioacetal formation in vivo or in the presence of the enzyme system by complexation of metal ions by glutathione presents fewer problems than in model systems. The metal ion active site of glyoxalase stereoselectively binds one of the diastereomeric hemithioacetals in preference to free GSH[95]. In the cell the lever of free GSH is likely to vastly exceed the levels of divalent metal ions freely available in the cell.

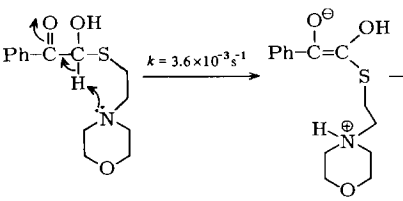
3.2.5. Conclusions from Model Systems

Whereas the intramolecular Cannizzaro reaction of arylglyoxals in sodium hydroxide is a hydride transfer, the analogous rearrangement of the hemithioacetals from α-ketoaldehydes to α-hydroxythioesters occurs via a proton transfer involving an enediolate intermediate as well as carbanion species. The rate-determining step may be deprotonation of hemithioacetal to the enediolate ion or reprotonation of the enediol at C-2 to afford an α-hydroxythioester, depending on the nature of the 2-(dialkylamino)ethanethiol catalyst. Metal ion catalysis is only significant in nonaqueous media.

The thiol presumably stabilizes the carbanion formed upon deprotonation of the hemithioacetal at C-1 (cf. mandeloylimidazole **17**, e.g., does not rearrange[58]). This deprotonation is assisted by the neighboring RCO-group.

3.3. Rate of Glyoxalase I Reaction

The v_{max} values for glyoxalase I are relatively independent of the nature of the α-ketoaldehyde, but do depend on the species from which the enzyme was isolated. For methylglyoxal and glyoxalase I isolated from rat liver, k_3 (the turnover number) has been reported[71] to be 2×10^3 sec^{-1} and about 1×10^3 sec^{-1} for the enzyme from human erythrocyte[72]. In a model system[60] in which the hemithioacetal of phenylglyoxal and *N*-(2-mercaptoethyl)morpholine rearranged as shown in equation (13) to the corresponding thioester of mandelic acid the rate constant was 3.6×10^{-3} sec^{-1}.



(13)

Even if rate-determining steps differ, in the unimolecular step the enzyme reaction is at least 10^6-fold faster than in the model system. The comparison is useful only if, as appears likely, both enzyme and model reactions follow the enediol route. If bimolecular rate constants of the glyoxalase I reaction (k_{cat}/K_m for glyoxalase[71] $= 4 \times 10^6$ M^{-1} sec^{-1}) and the *N*-methylmorpholine-catalyzed rearrangement[48] of the hemithioacetal from phenylglyoxal and 2-mercaptoethanol to thiomandelate ester ($k_B = 4.5 \times 10^{-4}$ M^{-1} sec^{-1}) are compared, the rate advantage of glyoxalase I is of the order of 10^{10}—a powerful catalysis.

4. Mechanism of the Enzyme Reaction

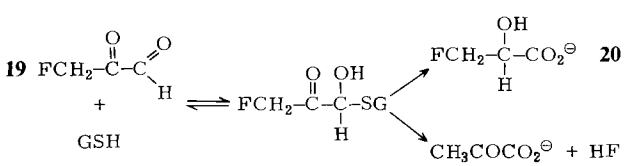
4.1. Proton Exchange

Assuming that the hemithioacetal is the substrate for the enzyme, a mechanism involving either a hydride transfer or proton transfer (enediol) can be envisaged. These two

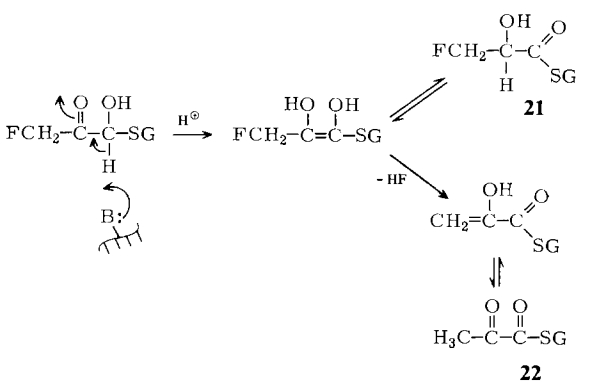
possibilities are usually distinguished in classical organic chemistry by a straightforward isotopic tracer experiment. The hydride route is indicated by absence of incorporation of a hydrogen isotope from labeled solvent into the product. Exchange into the product from labeled solvent is consistent with a proton transfer (the enediol) mechanism. For enzymes the situation is complicated by the problem of "buried bases"; these bases lie in the interior of the enzyme and can be totally protected against free proton exchange with the solvent either by the presence of tightly bound substrate or by the conformation of the protein itself. An added complication arises for substrates which are weakly acidic, e.g. CH acids. The rates of exchange of some of these substrates at neutrality can be quite slow. Consequently, lack of proton exchange for enzymic catalysis is not strong evidence for a hydride transfer.

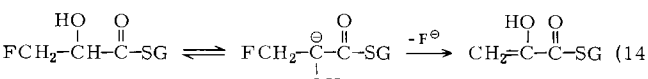
For glyoxalase I the hydride mechanism has been preferred until quite recently because of some early experiments which showed little, if any, deuterium (3% maximum)[55] or tritium incorporation (4%)[73] into the lactic acid product. However, at higher temperatures some recent NMR results have detected deuterium incorporation (ca. 15% at 25°C and ca. 22% at 35°C) into the lactate upon addition of glyoxalase II, which cleaved the initially-formed *S*-lactoylglutathione[74]: neither lactic acid nor *S*-lactoylglutathione incorporated deuterium under these conditions. In support of this, *Rose*[73] has reported no deuterium incorporation from solvent for *S*-lactoylglutathione. However, it has recently been reported that very high concentrations of glyoxalase I (human erythrocyte) catalyze H/D exchange at the C–H group in *S*-lactoylglutathione[78]. H/D Exchange for yeast glyoxalase I using phenylglyoxal/D_2O or [1-D]-phenylglyoxal/H_2O has also been reported[74]. If the glyoxalase I reaction does indeed proceed with isotopic incorporation, especially at higher temperatures[75], a shielded enzymic base and proton transfer mechanism may be indicated[*]. In the glyoxalase I catalyzed formation of fluorolactate from fluoromethylglyoxal (both [1-H] and [1-D]) practically no H/D exchange was observed[77].

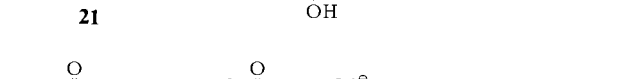
Kozarich et al.[78] have used fluoromethylglyoxal **19** as a substrate for yeast glyoxalase I and reported that, in addition to the normal enzymatic product (after glyoxalase II-catalyzed conversion to fluorolactate), pyruvate is also formed via elimination of HF.



This was explained[78] by postulating that a part of the enzymically-produced enediolate is reprotonated normally at C-2 and another part is converted by elimination of fluoride ion into the enol form of *S*-pyruvoylglutathione[78]. The same amounts of fluoride ion and pyruvate were produced, consistent with this hypothesis. More difficult to explain is the observation that thioester formation (followed at 240 nm) is complete long before $F^{\ominus}$ elimination. Whilst formation of **21** could be independent of $F^{\ominus}$ elimination, formation of **22**, also a thioester, should parallel it (or perhaps occur more slowly if the keto-enol transformation is slow). Moreover, the authors[78] point out in a footnote that the *S*-pyruvoylglutathione might arise fortuitously by an enzyme-catalyzed elimination of HF from **21** (which, need not have formed via an enediol). The reported reversibility[72] of the glyoxalase I reaction and the exchange of the lactate hydrogen atoms[76] (which should be easier for the fluorolactate **20**) in *S*-lactoylglutathione with glyoxalase I is consistent with this view. As pointed out[78], this "fortuitous" base effect in glyoxalase could also explain the low levels of hydrogen isotope incorporation. It is possible[77] that *S*-(fluorolactoyl)glutathione **21** undergoes nonenzymic β-elimination [eq. (14)]. The α-hydrogen of thioesters is markedly acidic and eliminations for such esters are known, although these usually involve thiol elimination[79–82] [eq. (15)].



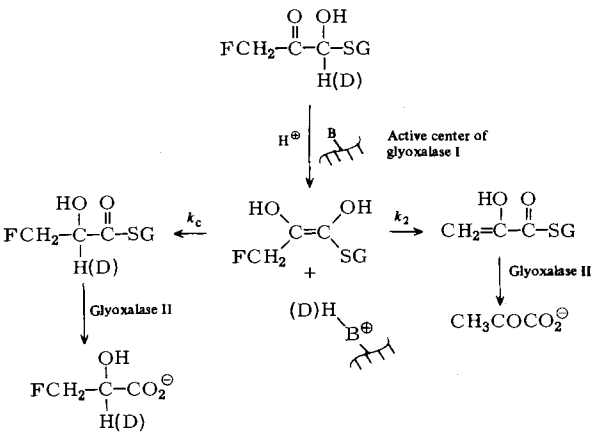




In an elegant analysis, *Chari* and *Kozarich*[77] suggested that it was conceivable that the enzymic reaction was a hydride transfer followed by an active-site dependent process. This "fortuitous" base could effect the proton exchange of *S*-lactoylglutathione with solvent or the elimination of fluoride ion from *S*-(fluorolactoyl)glutathione. In either case, they argued, the competing process would be release of product from the enzyme. They defined a partition ratio as the ratio of fluoride ion released from fluoromethylglyoxal/GSH by glyoxalase I and glyoxalase II (i.e. total fluoride releasable)[77]. They then studied the effect of deuterium substitution at C-1 of fluoromethylglyoxal and found that when [1-D]-fluoromethylglyoxal was used instead of the [1-H]-compound, the amount of fluoride ion released (i.e. the partition ratio) significantly increased for glyoxalase I from a number of species. *Chari*

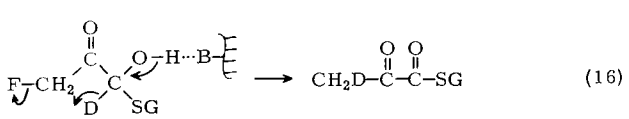
[*] As pointed out by *W. P. Jencks*, exchange at higher but not at lower temperatures is also in accord with an inherently slowly exchanging base, i.e. not specially "protected" from the environment. See: W. P. Jencks: *Catalysis in Chemistry and Enzymology*, McGraw-Hill, London 1969.

and *Kozarich* proposed that this could only be explained in terms of the enediol mechanism, as outlined in Scheme 3[77].



Scheme 3.

Any primary isotope effect in the formation of the enediol will not affect its subsequent partitioning to *S*-(fluorolactoyl)glutathione and *S*-pyruvoylglutathione. Solvent exchange of the active-site base is slow and the rate constant for fluoride elimination k_e should be largely the same irrespective of whether deuterium or hydrogen is present on the active-site base. However, the normal substrate conversion to *S*-(fluorolactoyl)glutathione k_c requires reprotonation by the active-site base at C-2, which is subject to a primary isotope effect. Thus, at the partitioning stage of reaction with this substrate analogue the presence of a deuterium will decrease the rate of formation of normal product relative to the protio-substrate whilst the fluoride elimination step should not be much affected by the H/D substitution. The net result would be a relative increase in the amount of fluoride eliminated for the deuterio substrate. The hydride transfer mechanism[77] predicts the opposite effect. However, if as in equation (16) one writes the fluoride elimination as a hydride (or deuteride) transfer, both normal substrate conversion (hydride transfer to C-2) and fluoride elimination (hydride transfer to C-3) are subject to (different) primary (H/D) isotope effects, making diagnostic use of the "partition" effect difficult. In this mechanism, however, deuterium labeling of the substrate would afford a deuterium labeled methyl group in the pyruvate formed, assuming that pyruvoylglutathione and pyruvate did not undergo H/D exchange at C-3 under the reaction conditions.

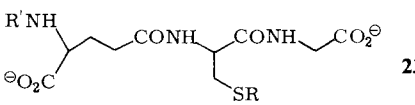


(16)

The trapping of the enediolate species in the nonenzymic rearrangement of hemithioacetals to α-hydroxythioesters by flavins has now been applied successfully[83] to the glyoxalase I catalyzed reaction. Since flavins do not function as hydride ion traps, an intermediate enediolate species is the most likely explanation. It has not yet been established whether the enediolate trapped is intercepted while still bound to the enzyme or reacts in the free form.

4.2. Role of the Metal Ion in the Active Center and Enzyme Flexibility

Early work suggested that glyoxalase I was a $Mg^{2\oplus}$-dependent enzyme[84], but it has now been established[85,86] that both yeast and mammalian enzymes are Zn-metalloenzymes. Yeast glyoxalase I is not amenable to metal ion replacement, in contrast to the mammalian enzyme[84–90]. Recently, zinc has been shown to be at the active site and it has been replaced by $Mn^{2\oplus}$ and $Co^{2\oplus}$ for spectroscopic studies[70,76,91]. High-resolution NMR studies of the $Mn^{2\oplus}$-enzyme with the bound product *S*-lactoylglutathione and the competitive inhibitor *S*-acetonylglutathione have indicated that in these complexes the oxygen atoms of the lactoyl and acetonyl groups are not in the first coordination sphere of the metal[76]. However, the structure of an enzyme/product or enzyme/inhibitor complex need not closely resemble the structures of either the enzyme/substrate complex or of any complexes involving high energy intermediates (e.g. enediols). There is considerable evidence for conformational flexibility in glyoxalase I. For example, fluorescence studies indicated a conformational change of the native enzyme on binding the strong competitive inhibitor *S*-(*p*-bromobenzyl)glutathione[89], and the EPR spectrum of the Co^{II}-enzyme is slightly perturbed on binding this inhibitor[91]. We have detected the perturbation on inhibitor binding of a tyrosine residue on yeast glyoxalase I by difference CD spectra[92] although there are no major peptide backbone changes in this process. Chemical evidence for flexibility in the glutathione-based peptide inhibitor backbone and/or glyoxalase I itself has been obtained[69] using a series of *N,S*-substituted glutathiones **23**.



23

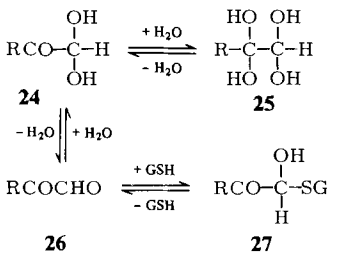
All of these derivatives proved to be competitive inhibitors but the degree of weakening of K_i for various *N*-acylations (e.g. on proceeding from $-NH_3^{\oplus}$ via $-COCH_3$ to $-COPh$) depended markedly on the substituent at the sulfur atom (comparing $SCH_2-C_6H_4-Br(p)$ and $SCH_2-C_6H_4-CF_3(m)$). Further indications of protein flexibility have been obtained from comparisons of steady-state and equilibrium binding parameters[93,94]. In addition, K_i values for *S*-(*m*-trifluoromethylbenzyl)glutathione[66] and *S*-(*p*-bromobenzyl)glutathione[33] are pH-independent for yeast glyoxalase I. In view of the significant effects[67] of pH on v_{max}/K_m and on K_m, such insensitivities of K_i values are surprising and possibly indicate that the enzyme can exist in more than one conformation. According to NMR studies, the bound conformations of *S*-lactoyl- and *S*-acetonylglutathione also differ[76].

Because of this possible conformational flexibility the role of the metal ion in glyoxalase I should be considered in more detail. Is the metal ion directly bonded to substrate oxygens at the S-site or do these oxygen atoms lie in the second coordination sphere of the zinc? It is reasonably well established[89–91] that the metal ion lies in the active site, quite close to the S-site. It is unlikely to be coordi-

nated to the N-terminal site of the glutathione substrate in view of NMR studies (which also exclude the Glu α-CO_2 site). The rather small effect of *N*-acetylation of inhibitors and substrates on the K_i value also suggests this[67,69]

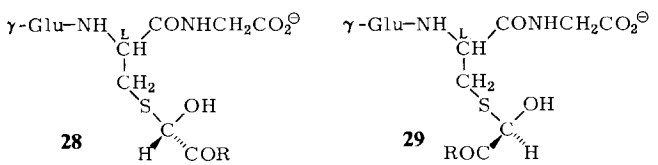
4.3. Stereochemical Aspects

It has already been pointed out that the nature of the glyoxalase I substrate is not yet fully clear. α-Ketoaldehydes exist largely as their hydrates (**24**, **25**) and not as the free aldehyde (**26**). Thus, equation (17) is a more realistic representation than equation (1). For phenylglyoxal, only

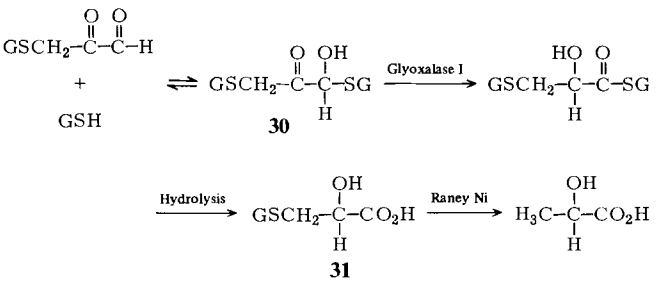


(17)

the monohydrate **24** was detectable by ^{1}H- and ^{13}C-NMR spectroscopy[95]. Three basic mechanisms have previously been proposed for glyoxalase I. In the two-substrate mechanism[18] the substrates are the free aldehyde form of the α-ketoaldehyde and GSH. For the one-substrate mechanism the substrate is the hemithioacetal[19]. The third possibility is a hybrid route, i.e. a branching, alternative one- and two-substrate mechanism in which the one-substrate is the hemithioacetal and the first of the two-substrates is GSH, with the α-ketoaldehyde the second[96]. The hemithioacetal from GSH and phenylglyoxal exists in two diastereomeric forms (see **28**, **29**, R = Ph) which can be detected by high resolution ^{1}H-NMR spectroscopy[95]. Addition of glyoxalase I at pD 4.4 led to selective disappearance of the signals from one of the diastereotopic methine protons (lower field signal). This directly establishes the asymmetric binding of the hemithioacetal as the origin of the stereospecificity of the glyoxalase I reaction, leading to formation of (*S*)-D-mandeloylglutathione[97] and (*S*)-D-lactoylglutathione[98]. If the enzyme mechanism involves a *cis*-enediolic intermediate or transition-state, the base of the enzyme's active site removes the proton from the (*S*)-configuration **28**. For a *trans*-enediol the (*R*)-configuration **29** would be the substrate involved. For a hydride transfer, assignment would not be possible.

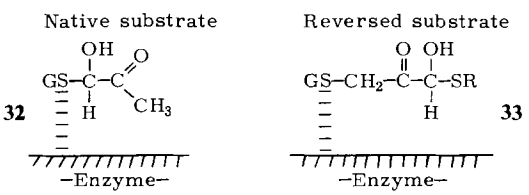


An interesting stereochemical trick has been performed with glyoxalase I[99]. The normal product from methylglyoxal[48] or phenylglyoxal[97] is the D-isomer of *S*-lactoylglutathione or *S*-mandeloylglutathione. The hemithioacetal formed between GSH and (glutathiomethyl)glyoxal, **30**,

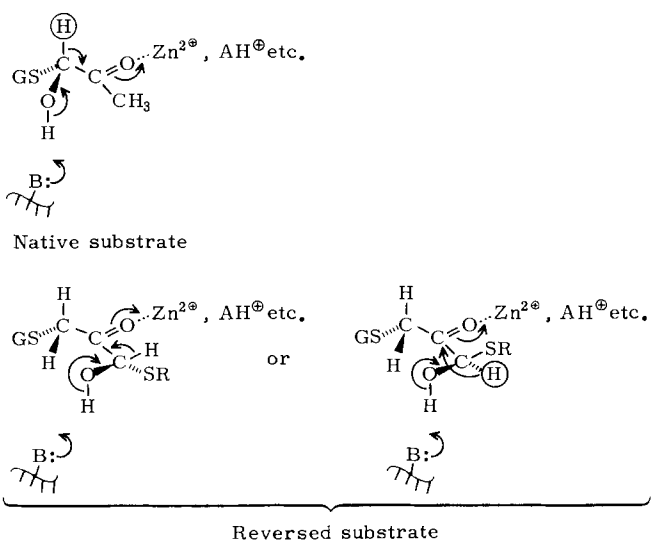


is also a substrate for yeast glyoxalase I and forms a thioester which is hydrolyzed to the 3-(glutathione)lactic acid **31**. Its stereochemistry was determined by Raney nickel desulfurization (relative amounts of D- and L-lactic acid determined by D- and L-lactate dehydrogenases).

Compound **30** gave predominantly D-lactate as might be expected. However, the hemithioacetals of **30** with ethanethiol and β-mercaptoethanol were also substrates, and this procedure (with mild base cleavage of thioesters) affords predominantly (≈4:1) the L-lactic acid - the opposite stereochemical result. Clearly, for the ethanethiol and β-mercaptoethanol binding of the hemithioacetal occurs in the opposite sense to that of the normal substrate, in each case binding specificity being determined by the glutathione moiety (see **32** and **33**)[99].



Although the authors rationalized their results in terms of the enediol mechanism[99], they can equally be explained by a hydride transfer route (Scheme 4).



Scheme 4. $AH^{\oplus}$ = acid.

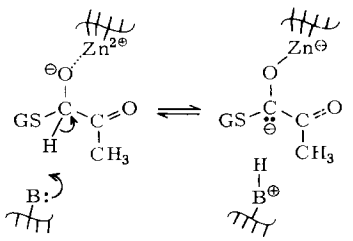
Immobilized forms of glyoxalase I and II have been used to synthesize optically active α-hydroxy acids from α-ketoaldehydes in high enantiomeric excesses[100].

4.4. Possible Mechanisms for the Glyoxalase I Reaction

The balance of evidence favors a proton-transfer pathway with an enediolate intermediate, and the discussion will be based on this. Two extreme types of mechanism must be considered: a) The substrate is bound directly to the active-site of the metal ion ($Zn^{2\oplus}$). b) The substrate is in the second coordination sphere.

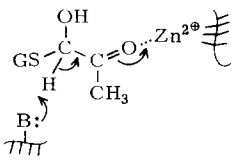
4.4.1. Substrate in the First Coordination Sphere of $Zn^{2\oplus}$

$Zn^{2\oplus}$ can bind to the substrate either via the oxygen atom at C-1 or that at C-2. In the first case the carbanion (and the transition-state) formed by deprotonation at C-1 is stabilized [eq. (18)].



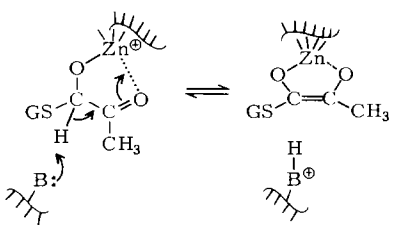
(18)

In the second case ionization of an enediolate intermediate is markedly supported by polarization of the ground state and by stabilization of the transition state (see **34**).



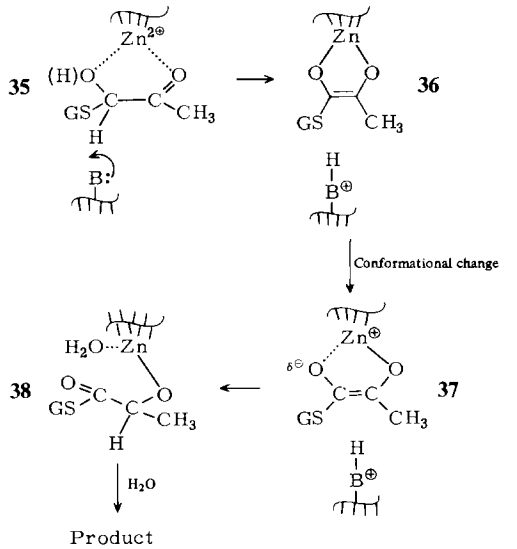
34

Finally, chelate binding via both oxygen atoms is possible. As is evident from equation (19) this would combine the C–H bond activation and transition-state stabilization.



(19)

Enediols form stable metal complexes, and at first sight such a reaction seems attractive. However, formation of a symmetrical $Zn^{2\oplus}$-enediolate of this type raises problems: If, as seems most reasonable, $Zn^{2\oplus}$ binding with the substrate is arranged to facilitate deprotonation and formation of enediol by chelation, then the converse process, reprotonation at C-2 to give product must be impaired by such a chelate. If a chelated enediol transition state were to form there would have to be a minor configurational change at the active-site to distort the chelate geometry (to favor reprotonation at C-2) and to realign the protonated base. Scheme 5 shows a reasonable minimal scheme for such a mechanism.

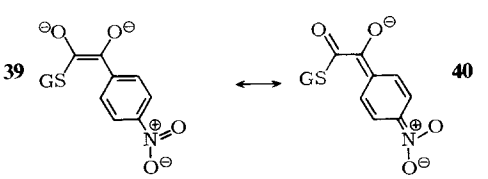


Scheme 5.

In this scheme, substrate binds with (**35**) $Zn^{2\oplus}$ facilitating proton transfer from C-1 to the buried active-site base B either by binding to C-1–O (protonated or deprotonated) and/or to C-2=O. Proton transfer leads to the almost symmetrical Zn-enediol chelate **36** (probably deprotonated at both oxygens as metal ions lower –OH pK_a values significantly). There may be considerable strain in such an enediol-$Zn^{2\oplus}$ chelate in view of the size of $Zn^{2\oplus}$ and this may aid the next step which is a conformational change to allow selective binding of Zn to the oxygen of C-2 aiding reprotonation by $-BH^{\oplus}$, which has been reoriented for attack at C-2, **37**. B might be a carboxylate ion which can transfer the proton that it sequesters from C-1 to C-2 by a simple rotation, as is known for triosephosphate isomerase[102]. The mechanism formulated in Scheme 5 requires a *cis*-enediol, for which there is no direct evidence[24–26] (but see Appendix).

In principle the first two mechanisms are possible for a *trans*-enediol bound only via one oxygen atom. The problems of a symmetrically chelated enediol-$Zn^{2\oplus}$ complex favoring deprotonation but inhibiting reprotonation are clearly not present for the *trans*-enediol mechanism, since no chelate is formed.

A mechanism involving partial or completely rate-determining deprotonation at C-1 to form the enediol intermediate is consistent with the observed[67] kinetic primary deuterium isotope effect at C-1 ($k_{cat}^{H}/k_{cat}^{D}=3.2$). However, it is difficult to reconcile such a mechanism with the absence of substituent effects reported[54] for substituted phenylglyoxals (k_{cat} varies approximately only 4-fold for ten of these compounds, including methylglyoxal). The enediol intermediate and, from the Hammond postulate, the transition state leading to it, should be stabilized by electron-withdrawing groups—especially if ionized at C-1—because of the conjugation in **39/40**. Furthermore, if such an interaction were to occur one would expect a correlation between the reaction rates and the Hammett σ^--constants.



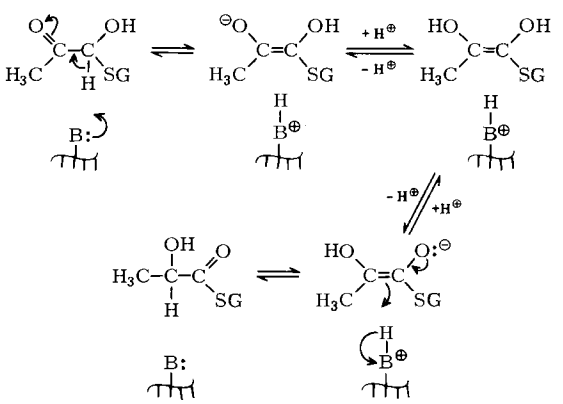
It is possible, however, that the enediolate is stabilized by the metal atom and that this "swamps" such resonance effects, or that there is rate-determining deprotonation of C-1–H. Reprotonation of the enediol at C-2 would also be expected to exhibit marked substituent effects, since the resonance interaction would be lost on protonation. The absence of substituent effects is consistent with the hydride mechanism[67], or with a rate-determining conformational change of the enzyme (e.g. on substrate binding, in the switch in site of enediol-metal polarization or on rate-determining product desorption), or rate-determining deprotonation at C-1–H.

4.4.2. *Substrate in Second Coordination Sphere of* $Zn^{2\oplus}$

In the previous section we discussed the range of mechanistic options available to glyoxalase I if the metal ion is directly coordinated to the ketoaldehyde oxygen atoms of the substrate. Recent NMR evidence indicates that these oxygen atoms lie in the second coordination sphere of the metal ion in the enzyme-product[76] and enzyme-*S*-acetonylglutathione complexes[103]. We shall now discuss the possible mechanisms available.

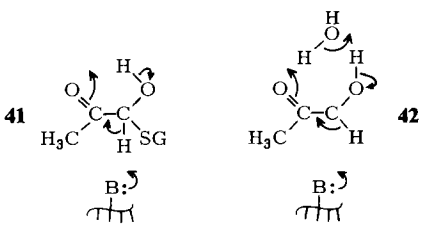
Reactions Involving a Single Base

A single base probably deprotonates C-1 which has been activated by the adjacent sulfur atom and possibly by $Zn^{2\oplus}$ polarization (Scheme 6).



Scheme 6.

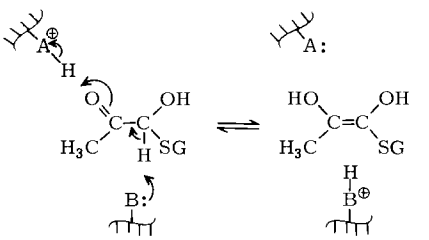
For the overall reaction a series of proton transfers is necessary. These may be avoided in the case of a *cis*-enediol either by direct "intramolecular" proton transfer (**41**) or by a water-mediated analogue (**42**).



The base B can either be an amino acid side-chain or $[Zn(OH)]^{\oplus}$. In the water-mediated proton transfer the H_2O molecule may be Zn-bound, but this would require that the Zn simultaneously act as a source of hydroxide ion (base) and promote proton donation by water.

Reactions Involving One Acid and One Base

The cooperative action of an active-site acid and base is possible for either a *cis*- or *trans*-enediol intermediate (Scheme 7) (the Zn-bound water molecule is a special case of $AH^{\oplus}$).

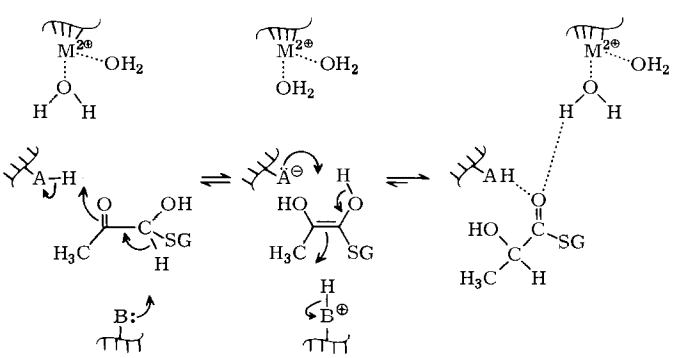


Scheme 7.

Deprotonation at C-1 would then rely on the acidity of the OH group; the minor conformational change necessary to relocate B for protonation at C-2 might also relocate A for deprotonation of C_1–OH. If $AH^{\oplus}$ in Scheme 7 were $[Zn(H_2O)]^{2\ominus}$, it could serve not only as an acid-base catalyst in the Brønsted sense by activating proton transfers but also as a Lewis acid by polarizing the substrate for the initial C–H cleavage.

Mechanisms of this type, in which the substrate is located in the second coordination sphere of the metal ion, i.e. with an intervening water molecule or hydroxide ion, have been proposed for a number of metalloenzymes[104].

One mechanism suggested by *Sellin* et al.[76] is shown in Scheme 8. In addition to the proton shift from C-1 to C-2



Scheme 8.

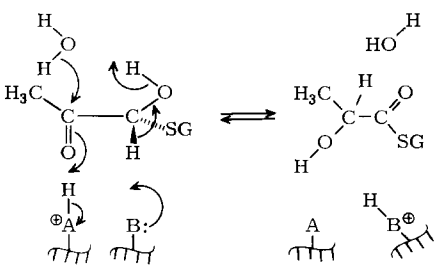
there is also a proton transfer to the keto site of the hemithioacetal substrate, which is converted into an –OH group during catalysis. The authors suggested[76] that although a metal-bound water molecule could polarize the carbonyl site, protolysis of the bound water could not supply the proton transferred to the oxygen of the substrate keto group as proton dissociation from $Co^{2\oplus}$, $Zn^{2\oplus}$, $Mn^{2\oplus}$ and $Mg^{2\oplus}$ (based on pK_a values) is orders of magnitude slower than is v_{max} for glyoxalase I[76]. However, proton transfer from an enzyme-bound acid to an essentially contiguous *enzyme-bound* base within the confines of an active site is effectively an intramolecular reaction and will

be limited not by diffusion rates or other bimolecular features, but will be a unimolecular rate constant. The upper limit on unimolecular rate constants is ca. 10^{-13} sec^{-1}, determined by the vibration frequency of the molecular bonds. Clearly, intramolecular proton transfers between neighboring electronegative atoms could be very rapid indeed relative to v_{max} for the enzyme reaction, and the AH species in Scheme 8 may yet be a metal-bound water molecule buried under the substrate. The authors also suggested that AH may be the OH group of the substrate[76] (cf. **41**).

An alternative second sphere mechanism has also been proposed by *Sellin* et al.[70]. This pathway involves participation of two ligand water molecules on the metal ion and incorporates a conformational change associated with product formation. Fluorescence studies suggest that the hemithioacetal substrate, glutathione itself, or the competitive inhibitor *S*-(*p*-bromobenzyl)glutathione, but *not* the product *S*-D-lactoylglutathione induces a conformational change on binding to the enzyme. Using circular dichroism, we have detected a minor configurational change in a tyrosine residue on binding *S*-(*p*-bromobenzyl)glutathione to yeast glyoxalase I[105].

Concerted Proton Transfer

In principle, there would be no need for an enediol intermediate if the proton transfer were concerted, as shown in Scheme 9. However, such a mechanism is not consistent with the lack of hydrogen exchange with solvent, nor with the flavin reduction studies in which a carbanion was trapped.



Scheme 9.

5. Summary and Prognosis

It is now clearly established that the substrate of glyoxalase I is the α-ketoaldehyde-derived hemithioacetal of glutathione, which is converted into *S*-D-lactoylglutathione by a proton transfer mechanism and not via a hydride ion route. There is a good body of evidence now implicating an enediolate intermediate. Armed with such knowledge, the avenue is clear for the design of novel tailor-made inhibitors. The inhibition of glyoxalase I by cytotoxins appears promising, at least in tissue culture. Antiglyoxalase I activity in a compound is, at the very least, a useful prescreening step in the search for elusive biological activity.

A number of questions remain. Does antiglyoxalase I activity cause the cytotoxic activity of some of these compounds, either as the sole or as a contributing factor? Can very powerful and specific inhibitors be designed to help such studies? In line with this question are some basic remaining problems about the mechanism of action of glyoxalase I. Is the enediol a *cis*- or *trans*-compound? Which diastereomer is the substrate? Does catalysis require one, two, or indeed any of the water ligands detected by NMR spectroscopy at the active-site metal? How is the conformational flexibility of the enzyme related to mechanism? Does the dimeric nature of mammalian glyoxalase I, in contrast to monomeric structure of the yeast enzyme, hold any functional significance? The application of powerful modern techniques (e.g. NMR) has already shed considerable light on aspects of the interaction of products with the enzyme and on the nature of the metal site. It is to be hoped that the rapid progress in recent years in this field continues apace.

6. Appendix

After completion of the manuscript a number of aspects of the glyoxalase I mechanism have been clarified. The conformations of four derivatives of glutathione bound at the active site have been computed from NMR data. The tripeptide inhibitors were found to be bound in an extended Y-shape, reminiscent of the structure of GSH determined by theoretical calculation and by X-ray diffraction. The distances between the active-site and the metal substrate- and product-complexes are different; an ionic inhibitor *S*-(methoxycarbonyl)glutathione was bound in the third coordination sphere, in contrast to the second coordination sphere occupancy of other bound inhibitors[106]. In addition, there has been a report of nonstereospecific substrate conversion by glyoxalase I[107], which implies that the enzyme can convert one of the substrate diastereomers into the other, yielding the *cis*-enediol intermediate, and this intermediate has now been detected by NMR spectroscopy[108]. Theoretical calculations have been carried out on the structure of the transition state mimics of glyoxalase I such as maltol[109]. Finally, EXAFS studies have revealed some of the ligands around the Zn atom of the active site[110].

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A Simple Notation System for Transition-Metal Clusters**

By *Tien-Yau Luh**, *Henry N. C. Wong*, and *Brian F. G. Johnson*

The description of the spatial distribution of metals and ligands in metal clusters is a nontrivial problem[1]. Here, we wish to propose a relatively simple system of notation which hopefully will facilitate a more useful method of describing clusters.

There are ample examples in the literature demonstrating that the ligands in clusters occupy positions that define the vertices of regular and semiregular polyhedra[2,3]. One of us has used Föppl notation[4] to illustrate the structure and fluxional behavior of carbonyl ligands in various clusters[2,3]. This approach considers a metal polyhedron[5] sitting inside a ligand polyhedron envelope. We felt that this concept can be used to represent cluster structures pictorially, and formulate the following rules:

Rule 1. The structures of metal and ligand polyhedra are described by appropriately modified Föppl notation (Table 1) written in sequence in square brackets with a hyphen between the brackets. The notation therefore has the general form $[m_1:\ldots m_p:\ldots:m_n]$-$[l_1:\ldots:l_i:\ldots:l_z]$.

Table 1. Modified Föppl notation [2—4].

n	designates a planar polygon with n vertices.
(n)	designates a planar polygon with n vertices which is in an anti-prismatic configuration to a previously assigned n-vertex polygon [a].
n′	designates a polygon of n vertices which is not strictly planar [b].

[a] Cf. rule 4 and Figure 1. [b] n′ must be even. An n′ polygon can therefore also be described as two anti-prismatic n′/2 polygons. For example, the chairform of a hexagon, which consists of two anti-prismatic triangles, is named 6′ rather than 3 : (3).

Rule 2. All metal polyhedra are numbered along the principal rotation axis.

Rule 3. A metal polyhedron is considered as a basic set. The orientation of the planes defined by the polygons in the ligand polyhedron is related to this basic set.

Rule 4. If the polyhedron is viewed along its principle rotation axis, two eclipsed lines, or one polygon[6] having at least one edge parallel to a line, or two polygons[6] having at least one pair of eclipsed edges are considered to be prismatic. Otherwise, they are denoted as anti-prismatic (see Table 1). Graphical representations of various arrangements are shown in Figure 1.

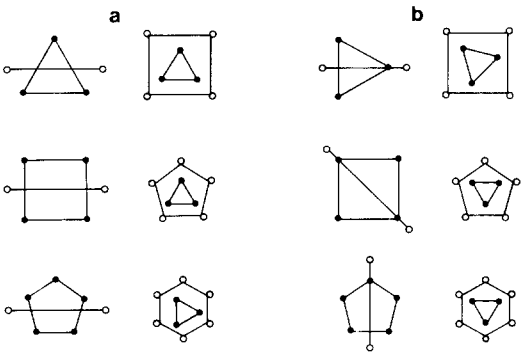


Fig. 1. Graphical representations of some a) prismatic and b) anti-prismatic arrangements.

Rule 5. The plane of the polygon (or the line) defined by the first number l_i greater than or equal to 2 in the modified Föppl notation of the ligand polyhedron should be parallel to the plane of the polygon (or the line) defined by the first number m_l greater than or equal to 2 of the metal polyhedron. Hence, the polygon m_l defines the orientation of the polygon l_i, which, in turn, defines the orientation of the rest of the polygons in the ligand polyhedron.

Examples of the application of these rules are given in Table 2. The notations for mononuclear metal complexes are straightforward (Nos. 1—3). The notation [1 : 1] rather than [2] is used to define the metal polyhedron in binuclear

Table 2. Notations for some metal clusters.

No.	Formula	Notation	Ref.
1	$Ni(CO)_4$	[1]-[1 : 3]	[7]
2	$Fe(CO)_5$	[1]-[1 : 3 : 1]	[8]
3	$Mo(CO)_6$	[1]-[1 : 4 : 1]	[9]
4	$Co_2(CO)_8$	[1 : 1]-[3 : 2 : 3]	[10]
5	$Fe_2(CO)_9$	[1 : 1]-[3 : (3) : 3]	[11]
6	$Mn_2(CO)_{10}$	[1 : 1]-[1 : 4 : (4) : 1]	[12]
7	$Mn_3(CO)_{14}^{\ominus}$	[1 : 1 : 1]-[1 : 4 : (4) : 4 : 1]	[13]
8	$Fe_3(CO)_{12}$ **2**	[3]-[(2) : 2 : (4) : 2 : (2)]	[33]
9	$Os_3(CO)_{12}$	[3]-[3 : 6 : 3]	[14]
10	$Re_3Cl_{12}^{3\ominus}$	[3]-[3 : (6) : 3]	[15]
11	$Ni_3(CO)_6^{2\ominus}$	[3]-[(6′)]	[16]
12	$Co_4(CO)_{12}$ **1**	[1 : 3]-[(3) : 6′ : 3]	[32]
13	$Ir_4(CO)_{12}$	[1 : 3]-[(3) : (6) : 3]	[17]
14	$Fe_4(CO)_{13}^{2\ominus}$	[1 : 3]-[(3) : 3 : 6 : 1]	[18]
15	$H_4Ru_4(CO)_{12}$	[1 : 3]-[(3) : (6) : 3]	[19]
16	$Re_4(CO)_{16}$	[4]-[4 : 8 : 4]	[20]
17	$HFe_4(CO)_{13}^{\ominus}$	[2 : (2)]-[4 : 1 : (4′) : 4]	[21]
18	$Ni_5(CO)_{12}^{2\ominus}$	[1 : 3 : 1]-[(3) : 6 : (3)]	[22]
19	$Fe_5C(CO)_{15}$	[1 : 4]-[3 : 8 : 4]	[23]
20	$Os_5(CO)_{16}$	[1 : 3 : 1]-[(3) : 3 : 4 : 3 : (3)]	[24]
21	$Mo_5Cl_{13}^{\ominus}$	[1 : 4]-[1 : (4) : (8′)]	[25]
22	$Ni_6(CO)_{12}$	[3 : 3]-[(6′) : (6′)]	[16]
23	$Pt_6(CO)_{12}$	[3 : 3]-[(6) : (6)]	[26]
24	$Co_6(CO)_{14}^{4\ominus}$	[1 : 4 : 1]-[1 : (4) : 4 : (4) : 1]	[27]
25	$Rh_6(CO)_{16}$	[1 : 4 : 1]-[2 : (2) : 4 : 4 : 2 : (2)]	[28]
26	$Os_6(CO)_{18}^{2\ominus}$	[1 : 4 : 1]-[3 : 6′ : (6′) : 3]	[29]
27	$[(Nb_6Cl_{12})Cl_6]^{2\ominus}$	[1 : 4 : 1]-[1 : 4 : (8) : 4 : 1]	[30]

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metal complexes (Rule 2). Similarly, [1 : 1 : 1] is employed to represent a linear arrangement of three metal atoms.

The CO ligands in either $Co_4(CO)_{12}$ **1** (Table 2, No. 12)[32] or $Fe_3(CO)_{12}$ **2** (No. 8)[33] form an eicosahedron (Fig. 2). The notation for the metal polyhedron in **1** is [1 : 3] rather than [3 : 1]; $m_l = 3$. The ligand polyhedron can be

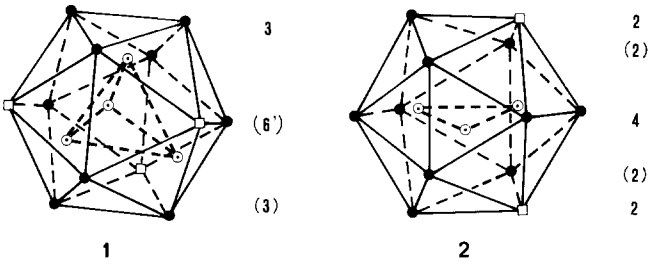


Fig. 2. Structures of $Co_4(CO)_{12}$ **1** and $Fe_3(CO)_{12}$ **2**. ⊙: Metal atom, ○: terminal CO ligand, □: bridging CO ligand.

represented by [3 : (6') : (3)], where $l_i = 3$ and the triangle defined by the last number (3) is anti-prismatic relative to that defined by l_i. Furthermore, the two triangles defined by m_l and by l_i are also anti-prismatic. It follows that the notation for **1** should be [1 : 3]-[(3) : 6' : 3]. It should be noted that the 6'-polygon in the ligand envelope is also anti-prismatic with respect to the 3-polygon, or triangle, in the metal polyhedron. In other words, three of the six vertices of the ligand 6'-polygon are anti-prismatic to the three vertices of the metal 3-polygon. Three CO ligands therefore function as bridging ligands. On the other hand, the ligand eicosahedron in **2** can be represented by [2 : (2) : 4 : (2) : 2], and l_i is anti-prismatic to the triangle defined by the three metal atoms. Hence, the notation for **2** should be [3]-[(2) : 2 : (4) : 2 : (2)].

At the present stage, interstitial atoms or groups and bridging hydrides are not included in our notation, since they do not, in general, affect the geometry of clusters (cf. Nos. 15, 17, 19 in Table 2)[31]; however, they can be treated as substituents[34].

To specify the structure of a metal cluster, we propose combining its formula and notation. For example, **2** can be written as $Fe_3(CO)_{12}$:[3]-[(2) : 2 : (4) : 2 : (2)] or triiron[3]-dodecacarbonyl[(2) : 2 : (4) : 2 : (2)].

In summary, using our notation cluster structures can easily be drawn and the nature of the ligands unequivocally assigned. We are currently extending this system to describe the structure of other heteronuclear and heteroligand clusters as well as nontransition-metal clusters such as boranes.

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Hydrogenobyrinic Acid and Vitamin B_{12}**

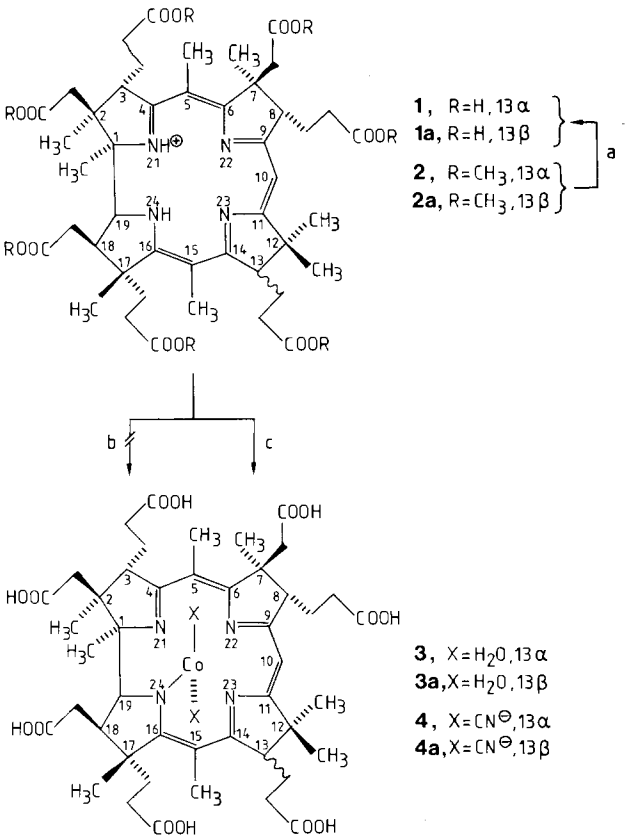
By *Trutz E. Podschun* and *Gerhard Müller**

The final step in the biosynthesis of the vitamin B_{12}-precursor cobyrinic acid **3** could be the insertion of cobalt into the cobalt-free analogue, the so-called hydrogenobyrinic acid **1**. Compound **1** has hitherto never been detected, neither in studies on the biosynthesis of **3** nor in photosynthesizing bacteria, which form cobalt-free corrinoids[1a]. In order to check whether **1** is a precursor of **3**, we have converted the hydrogenobyrinic acid amides described by *Koppenhagen* et al.[1] into the free acids **1** and then allowed these to react with enzyme preparations which catalyze a cobalt insertion and enable the de-novo synthesis of **3**.

A mixture of mono-, di-, and triamides of **1** was prepared, as described in ref. [1b], using *Rhodopseudomonas sphaeroides* (yield: ca. 200 μg/L culture medium). Methanolysis of the amide mixture led to formation of a 3 : 2 mixture of the 13α- and 13β-hydrogenobyrinic acid heptamethyl esters **2** and **2a**, respectively, together with some byproducts. 1 μmol of the mixture of hydrogenobyrinic acid amides was allowed to react with 26.5 μmol $BF_3 \cdot 2MeOH$ in 11 mL MeOH for 48 h at 55 °C in the absence of light and oxygen. After addition of $CHCl_3$ the mixture was neutralized with $NaHCO_3$ and washed with

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Scheme 1. [a]: 1 μmol **2** or **2a** in 2 mL 2M piperidine (degassed), 4 h, room temperature, in the dark. [b]: Enzyme + $^{57}Co(NO_3)_3$, pH 7, 32°C, 16 h [5]. [c]: 1 μmol **1** or **1a** + 1.5 μmol $Co(NO_3)_2$ in 2 mL NH_4OH, pH 11, 20 min boiling-water bath under argon, finally room temperature, pH 7 (HCN + CH_3COOH), electrophoresis pH 8.6 and 2.7.

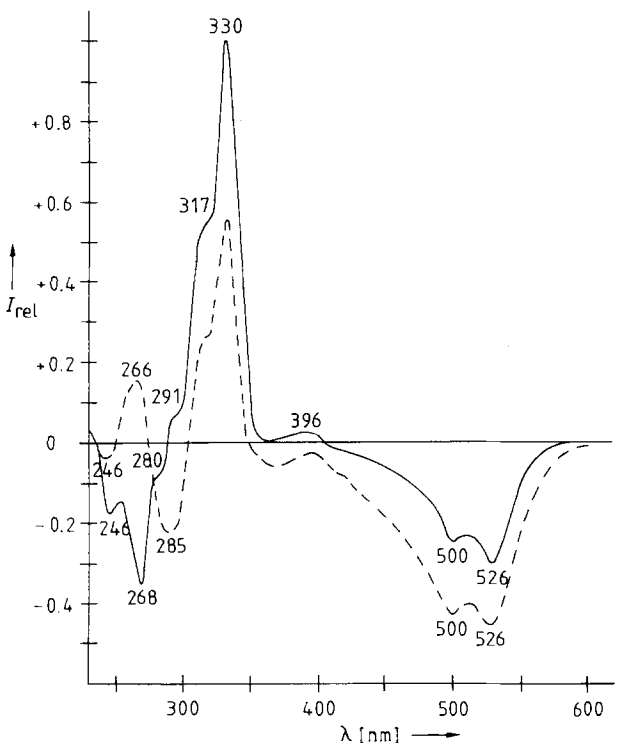


Fig. 1. CD spectra of 13α-hydrogenobyrinic acid heptamethyl ester **2** (——) and 13β-hydrogenobyrinic acid heptamethyl ester **2a** (------). Solvent: $CHCl_3$.

H_2O. The $CHCl_3$ phase was then dried over Na_2SO_4, concentrated by evaporation, and chromatographed on Merck silica gel 60 (CH_2Cl_2/MeOH (9:1, v/v)). The epimeric mixture **2**/**2a** ($R_F = 0.7$; yield 56%) occurring as main zone afforded **2** ($R_F = 0.55$) and **2a** ($R_F = 0.64$) on rechromatographic separation (toluene/*i*PrOH/MeOH (5:3:2, v/v/v)). The spectra and analytical values[2] of **2** and **2a** (UV/VIS, fluorescence, FD-MS and ^{1}H-NMR, and, after hydrolysis, electrophoresis) were characteristic for **2** and **2a** and showed no significant differences. According to the CD spectra (Fig. 1) **2** is the 13α isomer[3]. The CD spectra after chemical insertion of cobalt into **1** and **1a** (see Scheme 1, c) were decisive for verification of the correctness of the assignment, for they did indeed correspond to those of the heptamethyl esters of **4** and **4a**[1b,4].

Does **1** play a significant role in the biosynthesis of vitamin B_{12}? To answer this question, we checked with $^{57}Co^{2+}$ whether tetrapyrrole-free cell extracts from *Propionibacterium shermanii*[5] catalyze the insertion of cobalt into **1** (and **1a**) (Table 1, Experiments 1—4). Incubations, and isolation of **4** (transformation product of **3**) and its quantitative determination by reversed isotope dilution were carried out as described in ref. [5].

Table 1. Formation of **3** with enzyme preparations from *P. shermanii* [5], $^{57}Co^{2+}$, and substrates [a].

Experiment	1	2	3	4
		Cobyrinic acid **3** [nmol]		
a	42	17	17	80 [b]
b	—	5 [c]	7 [d]	32 [b, d]
c	—	10 [e]	14 [f]	57 [b, f]
d	5.8 [g]	—	—	—

[a] In each case the same enzyme preparation per series of experiments (a—d), (25 g moist bacteria/experiment); substrates: 3.3 μmol $^{57}Co(NO_3)_2$, specific radioactivity: 104 Bq/nmol and [b] 15 μmol 5-aminolevulinate and 37 μmol *S*-adenosyl-L-methionine, [c] 0.6 μmol **1**, [d] 0.4 μmol **1**, [e] 0.6 μmol **1a**, [f] 0.4 μmol **1a**, and [g] 1.3 μmol **1** + **1a**.

From Table 1 it follows that the formation of **3** from precursors still present in the enzyme preparations (Experiments 1a—3a) is markedly inhibited if **1** (2b and 3b), **1a** (2c and 3c), or **1**/**1a** (1d) is added. This effect is the strongest in the case of **1**, but is also manifested in the case of added species which additionally contain precursors of **3** (4b and 4c compared to 4a).

From theses findings it follows that **1** does not play any significant role in the biosynthesis of vitamin B_{12} by *P. shermanii*. The question of when the cobalt ion is inserted during the formation of vitamin B_{12} remains open.

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CAS Registry numbers:
1, 23599-55-5; **2**, 94042-20-3; **2a**, 94131-79-0; **3**, 33593-50-9; vitamin B_{12}, 68-19-9.

[1] a) V. B. Koppenhagen in D. Dolphin: *Vitamin B_{12}, Vol. 2.* Wiley, New York 1983, p. 106—149; b) B. Dresow, G. Schlingmann, L. Ernst, V. B. Koppenhagen, *J. Biol. Chem. 255* (1980) 7637.

[2] Spectroscopic data of **2**: UV/VIS ($CHCl_3$): $\lambda_{max} = 270$ (rel. int. = 0.80), 319 sh (0.81), 330 (1.00), 378 (0.16), 400 (0.16), 500 (0.48), 527 nm (0.52); FD-MS: $m/z = 979$ (M^+); ^{1}H-NMR ($CDCl_3$): $\delta = 3.65$, 3.68, 3.69, 3.695, 3.70, 3.71, 3.76 (7s/7OCH_3), 1.25, 1.32, 1.35, 1.40, 1.43, 1.61 (6s/6CH_3), 2.16 (s/CH_3-5), 2.22 (s/CH_3-15), 5.49 (s/H-10), 4.53 (br. s/H-19).

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[5] a) H.-O. Dauner, G. Müller, *Hoppe Seyler's Z. Physiol. Chem. 356* (1975) 1353; b) R. Deeg, H.-P. Kriemler, K.-H. Bergmann, G. Müller, *ibid. 358* (1977) 339.

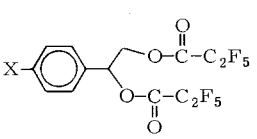
Direct Enantiomer Resolution of Hydroxy and Carbonyl Compounds by Gas Chromatography on Chirasil-Val**

By *Bernhard Koppenhoefer**, *Hans Allmendinger*, and *Graeme Nicholson*

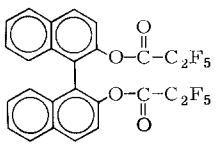
New methods for the chemical and biotechnological synthesis of chiral active substances[1] have led to extraordinarily high enantiomeric excesses (*ee*), which can be accurately determined only by sensitive, direct methods. Gas chromatography on chiral stationary phases[2] such as Chirasil-Val[3] is the method of choice, providing the substances are sufficiently volatile and have favorable chromatographic properties (retention time, separation factor α, peak shape).

Polar compounds are, as a rule, derivatized in order to shorten the time of analysis and avoid peak tailing. Recourse to acylation of hydroxy compounds[4] leads to small separation factors, since the donor functions for hydrogen bonding with the stationary phase are eliminated. A complete separation on Chirasil-Val is only observed if at least two ester carbonyl groups are present; aromatic π-systems additionally promote the separation. Arylethanediols, which are formed in high enantiomeric yields (*ee* = 99.4%) by reduction with bakers' yeast[5], and the atropisomeric chiral reagent[1e] 2,2'-dihydroxy-1,1'-binaphthyl are chromatographed as diperfluoropropionates **1** and **2**, respectively[6]. (The respective separation factor α, the column temperature, and the more strongly retained enantiomers are given in brackets under the formulas; in some cases, however, the order of elution of the enantiomers has not been determined.) Cyclic carbonates obtained from diols and phosgene have only one carbonyl group and are separable only under carefully optimized conditions[7].

The derivatization of hydroxy groups with nitrogen-containing reagents also has disadvantages: Admittedly, the separation factors are increased by N–H donor functions, but the volatility is considerably reduced. Furthermore, the conversion into urethanes[8] includes the danger of side reactions and racemization (e.g. in the case of mandelic acid), often accompanied by an unsatisfactory conversion.

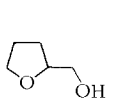


1a, X = H (1.043, 80 °C, *R*)
1b, X = F (1.050, 80 °C, *R*)
1c, X = Cl (1.050, 80 °C, *R*)
1d, X = Br (1.050, 80 °C, *R*)

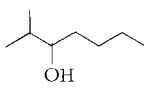


2 (1.038, 180 °C, *R*)

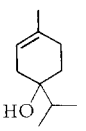
By using suitably deactivated glass capillaries (e.g. with diphenyltetramethyldisilazane), the functionalization of the hydroxy groups can be dispensed with in a number of classes of compounds, since the peak tailing caused by absorption on the column wall is largely suppressed. Thus, enantiomeric alcohols[9] can now be resolved on amide phases without recourse to derivatization. This method is applicable to primary (**3**), secondary (**4**), and tertiary (**5**) alcohols. The surprising resolution of **4** demonstrates that *one strong attractive interaction* (e.g. hydrogen bridges of the type O–H···O=C) can lead to a satisfactory discrimination of the enantiomers, since **4** contains neither a hetero atom like **3** nor a π system like **5**.



3 (1.129, 50 °C)

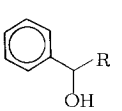


4 (1.036, 50 °C)

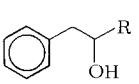


5 (1.067, 80 °C)

From these findings, we can derive a model of the separation mechanism. In the thin-film capillary (film thickness ca. 0.1 μm) there are about 10^2 superjacent chiral polymer chains (selectors of the order of magnitude of 1 nm). Hence, there is a stationary liquid phase which *completely* surrounds the substrate. By rapid reversible inclusion of the enantiomeric selectands from the gas phase in the chiral cavities of the condensed phase (which are already present or are formed by a change in conformation), the entropy is reduced at the expense of the (more favorable) enthalpy[6]. Moreover, since the changing shape of the cavities is averaged over all orientations of the selectands accomodated within them, usually only small differences in free energies of interaction of the enantiomers result ($-\Delta\Delta G_{333} = 0.1$ J/mol for **4**). The mobility, however, is already sufficiently restricted by *one* hydrogen bridge, for even on rotation about this axis the enantiomers of **4** always differ regarding the sum of the various van der Waals interactions (attractive and repulsive) with the boundaries of the virtual chiral cavities. In combination with the high efficiency of the capillary columns employed (10^5 theoretical plates), even such an unspecific mechanism enables the clean separation of a large variety of enantiomeric pairs on the same stationary phase. For instance, 1-menthen-4-ol **5** was detected in the pheromone bouquet of bark beetles[10].



6a, R = Me (1.034, 50 °C, *R*)
6b, R = Et (1.040, 50 °C, *R*)
6c, R = *i*Pr (1.051, 50 °C, *R*)
6d, R = *t*Bu (1.074, 50 °C, *R*)



7a, R = Et (1.034, 50 °C, *R*)
7b, R = *i*Pr (1.061, 70 °C, *S*)
7c, R = *t*Bu (1.130, 70 °C, *S*)

The enantiomers of the phenyl-substituted alcohols **6** and **7** have been obtained by asymmetric synthesis[1e] from the corresponding ketones. In addition, we have been able to assign the absolute configuration by reduction with bakers' yeast. In **6**, the preference given by the stationary phase for the *R*-enantiomers increases with the size of the alkyl groups (see also Fig. 1). The homologous benzyl derivatives **7** show an analogous trend (in both series, the L-configurated alcohol is eluted later[11]). The average relative retention time of **7c** is only 0.09 at 110 °C, referred to the corresponding isopropylurethane[12].

Also in the case of the mesityl derivative **8** (hindered rotation), the separation factor α is astonishingly high. The corresponding naphthyl and anthryl derivatives behave similarly to **6a**. Even dihydroxy compounds, e.g. the phe-

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[**] We thank Prof. Dr. *W. Francke*, Hamburg, and Dr. *D. A. Schooley*, Palo-Alto, CA (USA), for kindly supplying reference substances.

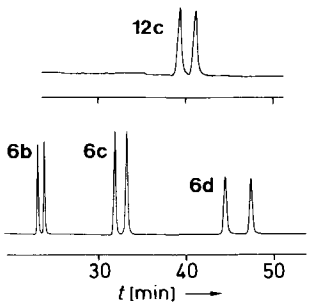
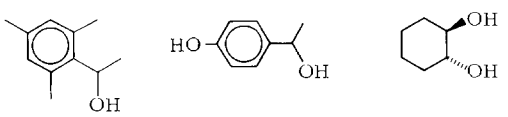


Fig. 1. Derivatization-free enantiomer resolution of hydroxy compounds on Chirasil-Val, carrier gas 0.6 bar H_2, Duran glass capillary 37 nm × 0.25 nm, number of theoretical plates 1.3×10^5. Top: suicide substrate **12c**, 110 °C isotherm; bottom: increasing separation factors in the phenyl alkanols **6b**—**6d**, 60 °C isotherm.

nol **9** or *trans*-1,2-cyclohexanediol **10**, can be separated. The same applies for lactones containing one hydroxy



8 (1.064, 80 °C) **9** (1.035, 100 °C) **10** (1.036, 60 °C)

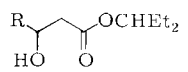
group, e.g. pantolactone **11** or mevalonolactone **12a**. Compounds **12a** and **12b** are key building blocks in the biosynthesis of juvenile hormones in insects. The fluoro-compound **12c** (see Fig. 1) has been employed as suicide substrate for the inhibition of hormone production in parasites (e.g. the tobacco horn worm *Manduca sexta*)[13]; this is an interesting alternative to biological pest control with pheromones.

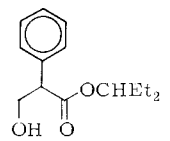


11 (1.158, 80 °C, *R*)



12a, R = Me (1.033, 110 °C, *S*)
12b, R = Et (1.033, 110 °C, *S*)
12c, R = CH_2F (1.043, 110 °C)



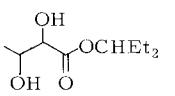


13a, R = Et (1.035, 70 °C, *S*)
13b, R = *i*Pr (1.044, 70 °C, *R*)
13c, R = Ph (1.041, 120 °C, *R*)

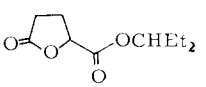
14 (1.039, 100 °C, *S*)

Consequently, open-chain hydroxy acids require only a simple racemization-free[14] esterification of the carboxy group. Similarly, as in the case of the 2-hydroxy acids[14], 3-pentanol proves to be the most suitable alcohol component in the case of 3-hydroxy acids with regard to separation factor, volatility, and polarity of the derivatives. The separation factors α increase with the size of the main chain. In contrast to the 2-hydroxy acid esters, however, the L-enantiomer of the 3-hydroxy esters (e.g. *S*-**13a** or *R*-**13b**) usually undergoes the stronger interaction with L-Chirasil-Val. Tropanoic acid, a 3-hydroxy acid with an asymmetry center on C-2 (cf. **14**), is the chiral component of the alkaloids atropine and hyoscyamine.

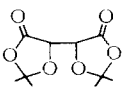
Polyfunctional hydroxycarboxylic acids such as *threo*-2,3-dihydroxybutanoic acid or 2-hydroxyglutaric acid lactone are separated as 3-pentyl esters **15** and **16**, respectively; the preparatively useful enantiomers of tartaric acid are best separated by way of the bisacetonide **17**. As was demonstrated some years ago[6], even diketones can be completely resolved into the enantiomers without resorting to derivatization. On the basis of theoretical considerations, the 3,4-diphenyl-2,5-hexanedione **18** with C2 symmetry has been chosen as example.



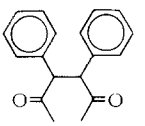
15 (1.133, 80 °C, 2*S*, 3*R*)



16 (1.039, 80 °C, *S*)



17 (1.040, 80 °C, 2*S*, 3*S*)



18 (1.031, 130 °C)

Thus, the scope of application of peptide phases partially overlaps that of complexation gas chromatography[9], which is still indispensable in the case of less polar compounds, e.g. pheromones with a spiroketal structure[15]. On the other hand, the thermally stable polymeric phase Chirasil-Val has also proven useful for many polar, less volatile compounds.

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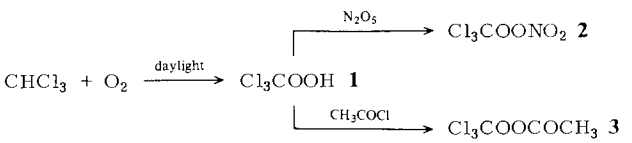
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[10] W. Francke, P. Sauerwein, J. P. Vité, D. Klimetzek, *Naturwissenschaften 67* (1980) 147.
[11] The CIP nomenclature is less helpful for describing the uniform elution behavior of the alcohols **6** and **7**; due to the priority sequence ethyl < benzyl < isopropyl, the descriptor of the absolute configuration is interchanged within the homologous series. The D/L nomenclature is more consistent in describing the fact that the substituents phenyl (benzyl), alkyl, and H are always arranged in a clockwise manner in the more strongly retained enantiomer when viewed from the direction of the OH group (referred to L-Chirasil-Val).
[12] Prepared from 1 mg of **7c** with 100 µl of isopropylisocyanate in 200 µl of dichloromethane (1 h, 110 °C); yield 40%.
[13] G. B. Quistad, D. C. Cerf, D. A. Schooley, G. B. Staal, *Nature (London) 289* (1981) 176.
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Photooxidation of Chloroform: Isolation and Characterization of Trichloromethyl Hydroperoxide

By *Siegmar Gäb* and *Walter V. Turner*

A series of thorough studies since the beginning of this century has shown that a peroxide is formed in the photooxidation of chloroform. Formulated as Cl_3COOH **1**, this peroxide is stable enough to build up over several months at room temperature; nevertheless, until now all attempts to isolate it by distilling out the chloroform have failed[1].

We have found that stripping photooxidized chloroform on a rotary evaporator at 0°C yields a peroxidic oil[2], which on the basis of its physical and chemical properties is identified as trichloromethyl hydroperoxide **1** [^{13}C-NMR ($CDCl_3$, 20 MHz): $\delta = 116.4$; ^{1}H-NMR ($CDCl_3$, 80 MHz): $\delta = 9.9$, broad; IR (CCl_4): strong bands at $\nu = 3500$, 1370, 1025, 900 cm^{-1}]. Iodometric titration of the oil in glacial acetic acid showed a peroxide content of ca. 90% of that calculated for **1**. Cryoscopy in benzene gave a slightly too high molecular weight (calc., 151.3; found, 160).



On reaction with N_2O_5 and $NaHCO_3$ in $CHCl_3$ at −25°C, **1** is converted in high yield into **2** [^{13}C-NMR ($CDCl_3$): $\delta = 116.1$; IR (CCl_4): strong bands at $\nu = 1750$, 1300 cm^{-1}[3]]. The ^{13}C-NMR signals of **1** and **2** lie close together, but can be distinguished in a mixture of the two compounds.

Treatment of **1** with acetyl chloride leads to the perester **3**[4] [^{13}C-NMR ($CDCl_3$): $\delta = 164.9$, 114.6, 16.8; ^{1}H-NMR ($CDCl_3$): $\delta = 2.21$; IR (CCl_4): strong bands at $\nu = 1818$, 1160, 1025 cm^{-1}]. The colorless product **3** melts above 6°C and can be chromatographed on silica gel with hexane/chloroform (2:1). The elemental analyses were correct. The molecular weight was determined as 191 by cryoscopy and 185 by iodometric titration (calc. 193.4). Perester **3** can readily be prepared in gram quantities without isolating **1**, by exposing a solution of acetyl chloride in alcohol-free chloroform under oxygen to either direct or diffuse sunlight[5].

Hydroperoxide **1** is more stable than CH_3CCl_2OOH[6]; a considerable portion survives even several hours' refluxing in $CHCl_3$. IR measurements showed that **1** slowly decomposes in CCl_4 at ca. 35°C to yield CO_2 (an additional absorption at 2345 cm^{-1}) and $COCl_2$ (additional absorptions at 1815 and 850 cm^{-1}); under these conditions **2** forms $COCl_2$. In a sealed tube under O_2, **3** was found by ^{1}H-NMR to have a half-life of ca. 10 h at 60°C. Several perchlorinated dialkyl peroxides have also recently been shown to be more stable than expected[7]; there may be important implications here for the photochemical degradation of organochlorine compounds in the atmosphere.

Caution! *Although small quantities of* **3** *have been distilled in a miniature sublimator, the compound exploded on one occasion when an attempt was made to remove a few droplets from the cold finger with a capillary pipette.*

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CAS Registry numbers:
1, 94089-33-5; **2**, 70490-93-6; **3**, 94089-34-6; $CHCl_3$, 67-66-3.

[1] A. M. Clover, *J. Am. Chem. Soc.* 45 (1923) 3133; A. T. Chapman, *ibid.* 56 (1934) 818; 57 (1935) 416, 419; J. W. Schulte, J. F. Suttle, R. Wilhelm, *ibid.* 75 (1953) 2222.

[2] Commercial analytical grade $CHCl_3$ was shaken with H_2SO_4, then H_2O, dried over Na_2SO_4, and distilled. Portions of 100 mL were stirred under O_2 in 1 L Pyrex flasks and exposed to diffuse daylight until iodometric titration in glacial acetic acid revealed a peroxide content of ca. 0.1 mmol/mL (at least a week). Portions of 20 mL of the photooxidized solution were stripped at 0°C and 15 torr to **1**, a viscous oil. In this concentrated state, **1** is far less stable above 0°C than in dilute solution.

[3] These absorptions correspond to those of **2** in the gas phase, where its formation in the chlorine-sensitized oxidation of $CHCl_3$ in the presence of NO_2 was studied by IR spectroscopy. H. Niki, P. D. Maker, C. M. Savage, L. P. Breitenbach, *Chem. Phys. Letters* 61 (1979) 100; R. Simonaitis, J. Heicklen, *ibid.* 62 (1979) 473; O. Morel, R. Simonaitis, J. Heicklen, *ibid.* 73 (1980) 38.

[4] Perester **3** is also obtained by reaction of acetyl chloride with the product (presumably **1**) from ozonolysis of either trichloro- or tetrachloroethylene in the presence of HCl.

[5] Over several weeks the concentration of **3** in a solution of $CHCl_3$ and acetyl chloride (1:1) rises to more than 0.2 mmol/mL. After removal of the solvent, the oily residue was chromatographed.

[6] S. Gäb, W. V. Turner, *J. Org. Chem.* 49 (1984) 2711.

[7] S. Gäb, W. V. Turner, F. Korte, L. Born, *J. Org. Chem.* (1982) 173.

Reductive Trimerization of the Trioxo Half-Sandwich Complex $[(\eta^5\text{-}C_5Me_5)ReO_3]$ with Deoxygenation: The Electron-Deficient Cluster Ion $[(\eta^5\text{-}C_5Me_5)_3Re_3(\mu\text{-}O)_6]^{2+}$ **

By *Wolfgang A. Herrmann**, *Ricardo Serrano*, *Manfred L. Ziegler*, *Heike Pfisterer*, and *Bernd Nuber*

Dedicated to Professor Gerhard Fritz on the occasion of his 65th birthday

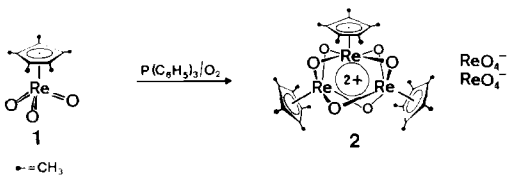
The readily accessible, unusually stable Re^{VII} complex $[(\eta^5\text{-}C_5Me_5)ReO_3]$ **1**[1] is functionalized by Lewis acids and Lewis bases with partial deoxygenation and reduction of the transition metal[2–4]. A particularly useful reaction from a synthetic point of view proved to be the reductive coupling of **1** by means of PPh_3 to give the binuclear Re^V derivative $[(\eta^5\text{-}C_5Me_5)_2Re_2O_4]$, whose synthesis, however, could only be achieved under rigorous exclusion of air[2,3]. We have now found that on reaction of **1** with PPh_3 in the presence of atmospheric oxygen, a further type of reaction surprisingly takes place, leading via intermediates to an unusual electron-deficient cluster compound.

Treatment of a solution of **1** in *aerated* tetrahydrofuran (THF) with an excess of PPh_3 rapidly leads to a gradual deepening in color of the solution from yellow to brown

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[**] Multiple bonds between main group elements and transition metals, Part 14. This work was supported by the Deutsche Forschungsgemeinschaft, the Fonds der Chemischen Industrie, Degussa AG, Herbert Quandt-Stiftung der VARTA AG, and the Spanish Ministry of Education (Fellowship grant for *R. S.*, 1982–84).—Part 13: W. A. Herrmann, J. Rohrmann, H. Nöth, C. K. Nanila, I. Bernal, M. Draux, *J. Organomet. Chem.*, in press.

until, after ca. 20 min, bluish green crystals of the novel complex compound **2** precipitate which are completely air-stable. That **2** must be a salt follows from the equivalent conductivity, $\Lambda = 134\ cm^2\ \Omega^{-1}\ mol^{-1}$ (dilute nitromethane solution, 25 °C), which value is characteristic of completely dissociated 2:1 electrolytes. The complex, which is isolable in 70–90% yield, is diamagnetic and shows only *one* sharp methyl signal at $\delta = 2.22$ in the ^{1}H-NMR spectrum (270 MHz, $CDCl_3$, 25 °C); and even in the ^{13}C-NMR spectrum, only the simple set of signals of chemically equivalent C_5Me_5 ligands is observed ($\delta(C_5Me_5) = 118.75$, $\delta(CH_3) = 11.18$). Since a total analysis gave an empirical formula $C_{30}H_{45}O_{14}Re_5$ and the signal pattern of correct intensity for the trinuclear cluster species $[(C_5Me_5)_3Re_3O_6]$ reproducibly occurred in the FD mass spectrum ($M/z = 1056$, ^{185}Re), it was suspected that this compound consists of a dication which is associated with two perrhenate anions. This presumption was further strengthened by an X-ray structure analysis of a single crystal having the composition $[(C_5Me_5)_3Re_5O_{14}]\cdot 1/2\,CH_2Cl_2$ (obtained from dichloromethane/THF).



The trinuclear dication of **2** consists of three chemically equivalent $[(\eta^5\text{-}C_5Me_5)ReO_2]$ structural groups coupled via angular symmetrical oxo bridges in such a way that an empty "trigonales Trigonprisma" of C_3 symmetry is formed (Fig. 1). The six bridge ligands occupy the corners of a trigonal prism whose faces form two equilateral triangles and three almost square rectangles. There are no bonding interactions between the oxo ligands ($d(O\ldots O) = 263$ pm, mean value). Each rhenium atom is symmetrically arranged above each rectangle which, taking into consideration the pentamethylcyclopentadienyl ligands oriented almost parallel to the threefold axis of the molecule, lies at the center of an only slightly distorted square-pyramidal coordination polyhedra. In each case, four oxygen atoms with angles summing up to 320.1° form the basal ligand set. The angles at the oxo-bridges average 89.3°, and the bond lengths of 193–197 pm between the rhenium and the oxygen atoms fall within the typical range for such structural units[2–5].

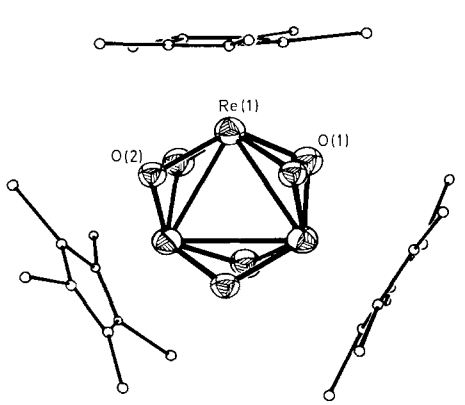


Fig. 1. Structure of the C_3-symmetrical cluster ion $[(\eta^5\text{-}C_5Me_5)_3Re_3(\mu\text{-}O)_6]^{2+}$ in the complex **2** (from THF/CH_2Cl_2); cubic, space group $T^4\text{-}P2_13$; $a = b = c = 1613(1)$ pm, $V = 4197 \times 10^6$ pm^3; $R_{iso} = 0.050$, $R_w = 0.035$. Selected bond lengths [pm] and angles [°]: Re–Re 274.7(2), Re–O(1) 197(2), Re–O(1′) 195(2), Re–O(2) 197(2), Re–O(2′) 195(2), Re–C(C_5Me_5) 219–237, C–C 124–148 (C_5 rings); O(1)–Re–O(1′) 89(1), O(1)–Re(1)–O(2) 73(1), O(1)–Re(1)–O(2′) 132(2), O(1′)–Re(1)–O(2) 133.0(2), O(1′)–Re(1)–O(2′) 72.1(10), O(2)–Re(1)–O(2′) 88.3(13), Re–O–Re 89.3 (mean value).—The two perrhenate counterions and the solvent molecule are not involved in bonding interactions, either between themselves or with the cation.—Further details of the crystal structure investigation are available upon request from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2, on quoting the depository number CSD 51024, the names of the authors, and the journal citation.

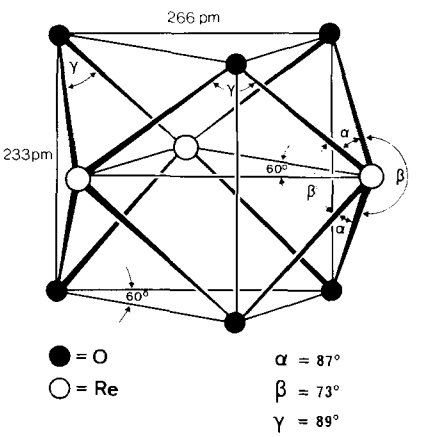
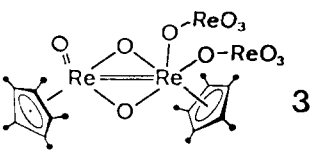


Fig. 2. The Re_3O_6 geometry in the cluster ion of **2** consists of a trigonal prismatic coordination polyhedron of six oxygen atoms, whose three rectangular faces are each bridged symmetrically by a rhenium atom ("trigonales Trigonprisma"). The ReORe triangular faces form an interplanar angle of 123° with the Re_3 framework; the interplanar angle of the ReORe and ReO′Re planes is 114°.

With regard to their inconclusively interpretable bond order, the metal-metal distances (274.7(2) pm) compare with the length of double bonds or of shortened single bonds[3]. Since the complex cation $[(\eta^5\text{-}C_5Me_5)_3Re_3(\mu\text{-}O)_6]^{2+}$ of **2**, with only 46 valence electrons, is an electron-deficient species, four bonding electrons are left over after taking into account the nine ligands for the Re_3 cluster structure, thus giving a formal bond order of 2/3. Whether there is any bonding interaction at all between the metal atoms, despite the relatively short metal-metal distances, must be checked by an MO calculation[6]. The metal atoms of the cluster ion have a formal oxidation state of $+5\frac{2}{3}$.

Despite the facile formation of **2**, the reaction mechanism is still unclear. On the basis of control experiments, it can be concluded that the complex **3**, formed from **1**, PPh_3 and a little oxygen[2], does not react with excess **1**.



3

The electronically unsaturated cluster ion of **2** is not only the first example of a square-planar complex of the type $LReO_4$, it also represents a novel M_3O_6 skeletal geometry in organometallic chemistry.

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1, 90695-83-3; **2**, 93806-04-3; **3**, 91129-20-3.

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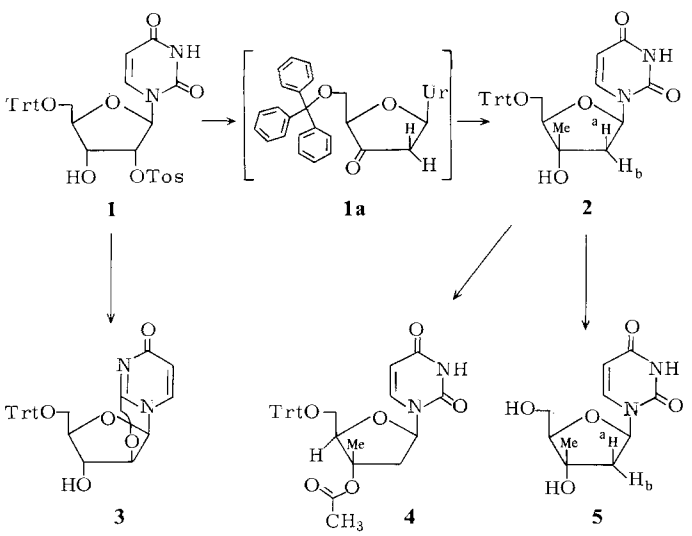
[1] a) W. A. Herrmann, R. Serrano, H. Bock, *Angew. Chem. 96* (1984) 364; *Angew. Chem. Int. Ed. Engl. 23* (1984) 383; b) see also R. Dagani, *Chem. Eng. News 62* (1984) No. 30, p. 28; c) A. H. Klahn-Oliva, D. Sutton, *Organometallics 3* (1984) 1313.
[2] W. A. Herrmann, R. Serrano, U. Küsthardt, M. L. Ziegler, E. Guggolz, T. Zahn, *Angew. Chem. 96* (1984) 498; *Angew. Chem. Int. Ed. Engl. 23* (1984) 515.
[3] W. A. Herrmann, R. Serrano, A. Schäfer, U. Küsthardt, M. L. Ziegler, E. Guggolz, *J. Organomet. Chem. 272* (1984) 55.
[4] W. A. Herrmann, R. Serrano, U. Küsthardt, M. L. Ziegler, T. Zahn, *J. Organomet. Chem.*, in press.
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[6] P. Hofmann, Technische Universität München.

Synthesis of 3′-*C*-Methyl-2′-deoxyribonucleoside with Methylmagnesium Iodide**

By *A. Grouiller, H. Essadiq, H. Pacheco, S. Juntunen,* and *J. Chattopadhyaya**

Branched-chain sugar nucleosides have previously been prepared by reaction of Grignard reagents with pentofuranosuloses and hexopyranosuloses followed by coupling with a suitable base[1].

We report here a more convenient route to a new branched-chain sugar nucleoside **5** via a one-step preparation of 2′-deoxy-3′-*C*-methyl-5′-*O*-trityluridine **2** by Grignard reaction of 2′-*O*-tosyl-5′-*O*-trityluridine **1** with methylmagnesium iodide (Scheme 1).



Scheme 1. Procedure for **2**: To a stirred solution of **1** [5] (1 g, 1.56 mmol) in anhydrous tetrahydrofuran (50 mL) was gradually added a freshly prepared solution of MeMgI (15 equiv.) in diethyl ether at 0 °C under N_2. The mixture was then stirred for 90 min at 25 °C and subsequently heated to 65 °C for 30 min. After cooling, 10% aqueous NH_4Cl (18 mL) was added. The organic layer was separated, dried, and concentrated to give a syrup, which was chromatographed on a short silica gel column with 2% ethanol/chloroform mixture to afford **2** (280 mg, 37%).—The reaction of **1** with 7 equivalents of MeMgI gave essentially **3** [6].

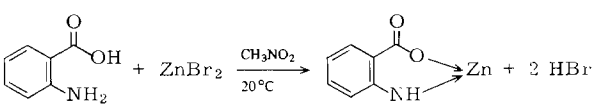
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[**] We gratefully acknowledge financial support through Swedish MFR and INSERM exchange program (*A. G.* and *J. C.*); two of us (*J. C.* and *S. J.*) also acknowledge generous financial supports by Swedish Natural Science Research Council (NFR).

The synthesis of 3′-branched-chain 2′-deoxysugar nucleosides of this type is important in view of the biological properties of the corresponding ribofuranosyl derivatives[2]. The availability of these compounds would enable the synthesis of corresponding DNA analogues which should assist in our understanding of the conformational role of the 2′-deoxysugar residue in protein-DNA interactions. To our knowledge, there are only two reports of such branched, deoxysugar nucleosides: *Acton* et al.[3] have reported the preparation of α- and β-2′,3′-dideoxy-3′-(hydroxymethyl)thioguanosine starting from a modified sugar and *Ueda* et al. have described a multistep synthesis of 2′,3′-dideoxy-3′-(hydroxymethyl)uridine starting from 1-(3-amino-2,3-dideoxy-β-D-glucopyranosyl)uracil[4].

The structure of **2** was determined by spectroscopy[7]. **2** was assigned the *erythro*-configuration by comparison with similar reactions of carbohydrates[1a–c, 8] and also from the downfield shift ($\delta = 0.3$) of 4′-H in **4** (m.p. = 183 °C), obtained by acetylation of the tertiary hydroxyl group in **2**[1c]. According to *Kawana* et al.[9] Grignard reaction of methyl-5-*O*-benzyl-2-*O*-tosyl-β-D-ribofuranoside led to a mixture of the *threo*- and *erythro*-isomers of the 2′-deoxy-3′-*C*-methyl derivatives in 57 and 20% yields, respectively, in contrast to our present example with the ribonucleoside **1** where we isolated exclusively the *erythro*- isomer **2**. Such stereoselective control is desirable for the preparation of DNA analogues. This result may be rationalized as arising from steric hindrance of the α-side of the 3′-carbonyl carbon atom by the 5′-*O*-trityl group, facilitating stereoselective nucleophilic attack from the β-side and giving **2**. Previously we observed[10] a similar "steric blocking" in the regioselective preparation of a 2′-*O*-methylribonucleoside.

Finally, compound **2** was detritylated to obtain **5**[11] (Scheme 2). We presume that under these acidic conditions a complex such as **6** is formed which releases anhydrous HBr that in turn acts as a detritylating agent.



Scheme 2. Preparation of **5** by detritylation of **2** with $ZnBr_2$ and anthranilic acid (molar ratio 1 : 1.6 : 4) in anhydrous nitromethane (24 mL/mmol), 3 h, yield 54%.

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CAS Registry numbers:
1, 6206-09-3; **2**, 94042-10-1; **3**, 3249-94-3; **4**, 94042-11-2; **5**, 94042-12-3; 2′,3′-di-*O*-tosyl-5′-*O*-trityluridine, 94042-13-4; 5′-*O*-trityluridine, 6554-10-5.

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[5] **1** was obtained in 41% yield in addition to 2′,3′-di-*O*-tosyl-5′-*O*-trityluridine (27%) when 5′-*O*-trityluridine was treated with *p*-toluenesulfonyl chloride in pyridine (1.1 equiv., 25 °C, 24 h).
[6] K. K. Ogilvie, D. Iwacha, *Can. J. Chem. 47* (1969) 495.

[7] **2**: UV: λ_{max} = 262 nm (pH 7 and 4); 259 nm (pH 12). $M^{\oplus\ominus}$ at *m/z* 484 (2.2%). ^{1}H-NMR (400 MHz, $CDCl_3$, TMS): δ = 7.93 (d, 8.4 Hz, 1 H), H-6; 7.50—7.23 (m, 15 H), trityl; 6.10 (dd, $J(1',2'H_a)$ = 7.7 Hz, $J(1',2'H_b)$ = 2.1 Hz), H-1'; 5.56 (d, 1 H, H-5); 3.83 (m, 1 H, H-4'), 3.57 (m, 2 H, H-5'), 2.40 (dd, $J(2'H_a,H_b)$ = 14 Hz, 1 H, 2'-H_a); 2.25 (dd, 1 H, 2'-H_b), 1.30 (s, 3 H, 3'-CCH_3). ^{13}C-NMR ($CDCl_3$, TMS): δ = 164.9, 150.6, 143.5, 141.9, 128.7, 127.2, 100.5, 87.3, 85.8, 76.1, 62.2, 46.9, 24.2.

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[9] M. Kwana, T. Koresawa, H. Kuzuhara, *Bull. Chem. Soc. Jpn. 56* (1983) 1095.

[10] J. Heikkilä, S. Björkman, B. Öberg, J. Chattopadhyaya, *Acta Chem. Scand. B36* (1982) 715.

[11] UV: λ_{max} = 262 (pH 7 and 14); 259 (pH 12); $M^{\oplus\ominus}$ at *m/z* 242 (78.1%). ^{1}H-NMR (350 MHz, [D$_6$]DMSO, TMS): δ = 7.95 (d, 8.4 Hz, 1 H), H-6; 5.98 (dd, $J(1'2'H_a)$ 7.7, $J(1'2'H_b)$ 2.1 Hz, 1 H, H-1'); 5.62 (d, 1 H, H-5); 3.55—3.73 (m, 2 H, H-4', 5'); 2.40 (dd, $J(2'H_a,H_b)$ = 14 Hz, 1 H, 2'-H_a); 1.96 (dd, 1 H, 2'-H_b); 1.28 (s, 3 H, 3'-CCH_3).

Phosphaalkenylrhenium Complexes—a Novel Class of Substances with P=C Bonding**

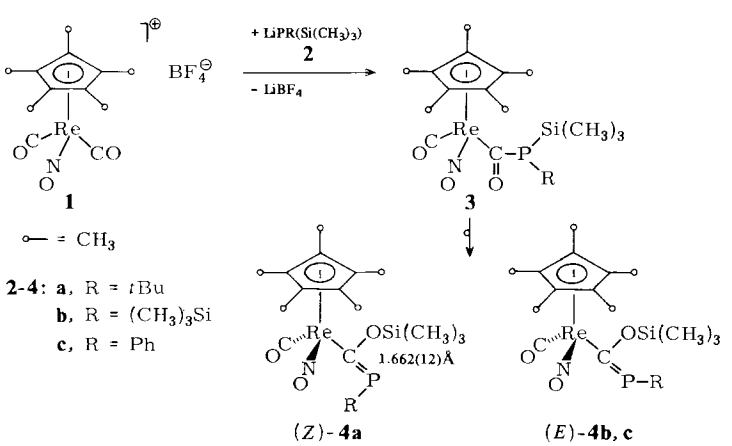
By *Lothar Weber** and *Klaus Reizig*

Dedicated to Professor Gerhard Fritz on the occasion of his 65th birthday

Compounds containing phosphorus-carbon multiple bonds are very interesting, both from the theoretical as well as the preparative point of view[1-6]. The synthesis of the P=C unit is generally accomplished by reaction of organically bound carbonyl groups with polysilylated phosphanes. However, the preparation of carbon-phosphorus multibonded systems from carbonyl ligands which are coordinated to transition metals has so far not been reported in the literature.

We report here on the first reaction sequence of this kind, which leads to a novel class of compounds, the phosphaalkenyl complexes **4**.

The silylated lithium phosphides **2a—c** react with an ethereal suspension of the complex cation **1** at −78 °C to give an orange-yellow solution which turns reddish brown on warming to room temperature. The phosphaalkenylrhenium complexes **4a—c** are isolated from this reaction solution as dark-red crystalline solids[7]. The initial step of the reaction could be the nucleophilic addition of the phosphide to a CO ligand of **1**. In the phosphinocarbonyl complexes formed in the reaction, a 1,3-Si(CH$_3$)$_3$-shift with formation of **4** takes place at elevated temperatures.



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The reaction of **1** with **2a** can be monitored by ^{31}P-NMR spectroscopy. A singlet at δ = 43.2 (−60 °C) is assigned to **3a**[8]. Above −40 °C, this signal diminishes in intensity and at −10 °C can no longer be detected. In place of it, a new signal is recorded at δ = 240.1. At 20 °C, in the course of several hours a further singlet appears at δ = 272.8, while that at δ = 240.1 disappears.

The complex **4a** isolated shows a ^{31}P-NMR signal at δ = 271.7 in C_6D_6. The Re(CO)(NO) group is recognizable by strong bands at 1970 (ν(CO)) and 1685 cm^{-1} (ν(NO)) in the IR spectrum (n-hexane). A medium-strong band at 1050 cm^{-1} (Nujol) is assigned to the ν(SiOC) vibration. Aside from the downfield shift in the ^{31}P-NMR spectrum, the vapor pressure osmometric M_r determinations as well as the $M^{\oplus}$ ion in the mass spectrum also verify the monomeric structure of the complex. The configuration at the P=C bond was ascertained by analysis of the ^{13}C-NMR spectra. Besides the doublet for the carbon atom of the P=C moiety (δ = 241.9; ^1J(PC) = 80.7 Hz), a singlet is observed at δ = 211.0 for the CO ligand. The signal of the (CH$_3$)$_3$Si group is recorded as a doublet (δ = 1.87, ^4J(PC) = 8.4 Hz). Assuming that this PC coupling is transferred by the free electron pair on the phosphorus atom[9], **4a** has *Z*-configuration. This is confirmed by the X-ray structure analysis[10].

We presume, therefore, that the ^{31}P-NMR signal at δ = 240.1 is due to the *E*-isomer initially formed from **3a**, which slowly rearranges into the isolated *Z*-isomer. On the basis of similar findings we assign **4b** and **4c** the *E*-configuration[7].

The complexes **4a—c** are the first phosphorus analogues of the η^1-alkenyltransition-metal class of complexes of the type $L_nM-C(R^1)=CR^2R^3$[11]. Disregarding the posphavinylidene complex $(C_5H_5)(CO)_2Mo=P=C(Si(CH_3)_3)_2$[12], all the previously known phosphaalkene transition-metal compounds[13-16] contain the intact $R^1P=CR^2R^3$ structure unit.

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1, 86497-29-2; **2a**, 89982-51-4; **2b**, 59624-91-8; **2c**, 79908-20-6; **4a**, 93984-98-6; **4b**, 93984-99-7; **4c**, 93985-00-3.

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[7] Procedure: **4a**: A 0.48 M ethereal solution of **2a** (9.1 mL, 4.37 mmol) was added dropwise and slowly to a suspension of **1** (2.160 g, 4.37 mmol) in ether (50 mL) at −78 °C. On warming to 20 °C a dark-brown solution was obtained. This was stirred for 30 min, evaporated to dryness in vacuo, and the solid residue extracted with petroleum ether (40 mL, boiling range 40—60 °C). The filtered extract was concentrated to ca. 10 mL. On allowing to stand for 12 h at −25 °C dark-red crystals were formed. After pipetting off the mother liquor, the crystals were dried in vacuo. Yield: 0.750 g (30%) **4a**, readily soluble in ether, dichloromethane, tetrahydrofuran, benzene, moderately soluble in petroleum ether; m.p. 64 °C.—^{1}H-NMR (200 MHz, C_6D_6, 22 °C): δ = 0.52 (d, ^5J(PH) = 1.7 Hz, 9 H, OSi(CH$_3$)$_3$), 1.51 (d, ^3J(PH) = 10.7 Hz, 9 H, P—C(CH$_3$)$_3$), 1.63 (s, 15 H, C$_5$(CH$_3$)$_5$).—^{13}C{^{1}H}-NMR (C_6D_6, 22 °C): δ = 1.9 (d, ^4J(PC) = 8.4 Hz, OSi(CH$_3$)$_3$), 10.0 (s, C$_5$(CH$_3$)$_5$), 31.7 (d, ^2J(PC) = 12.8 Hz, C(CH$_3$)$_3$), 33.8 (d, ^1J(PC) = 39.0 Hz, C(CH$_3$)$_3$), 104.2 (s, C$_5$(CH$_3$)$_5$), 211.0 (s,

Re–C≡O), 241.9 (d, ^1J(PC) = 80.7 Hz, P=C). – ^{31}P{^{1}H}-NMR (C_6D_6, 22°C): δ = 271.7 (s). – IR (*n*-hexane): 1970 (s, ν(CO)), 1685 cm^{-1} (s, ν(NO)). – MS (CI), Varian MAT 312: $MH^{\oplus}$ (*m/z* 570). – **4b** and **4c** were prepared analogously. **4b**: dark-red crystals, m.p. 88°C, yield 25.5%. – ^{31}P-NMR: δ = 212.4 (s). – ^{13}C-NMR: δ = 252.5 (d, ^1J(PC) = 113.5 Hz, C=P), 207.3 (d, ^3J(PC) = 19.7 Hz, C≡O), 1.7 (s, $(CH_3)_3SiO$). – **4c**: dark-red crystals, m.p. 99°C, yield 37%. – ^{31}P-NMR: δ = 194.4 (s). – ^{13}C-NMR: δ = 230.7 (d, ^1J(PC) = 106.1 Hz, C=P), 210.5 (d, ^3J(PC) = 21.7 Hz, C≡O), 0.40 (s, $(CH_3)_3SiO$).

[8] Stable phosphinocarbonyl complexes of the type $(C_5(CH_3)_5)(CO)_2M-C(O)P(t\text{Bu})(Si(CH_3)_3)$ of iron (δ^{31}P = 75.1 (C_6D_6): L. Weber, K. Reizig, *Chem. Ber.*, in press) and of ruthenium (δ^{31}P = 67.4 (C_6D_6): L. Weber, K. Reizig, unpublished) are also known.

[9] A similar behavior is observed in the case of the *E/Z*-isomers of 2,4,6-$(t\text{Bu})_3C_6H_2-P=C(Ph)OSi(CH_3)_2(t\text{Bu})$: M. Yoshifuji, K. Toyota, K. Shibayana, N. Inamoto, *Chem. Lett. 1983*, 1653.

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Crystal Structures of Potassium Ozonide and Rubidium Ozonide**

By *Wolfgang Schnick* and *Martin Jansen**

In the case of main group elements, bond systems with uneven numbers of electrons are an exception to the rule; on the other hand, a host of such systems appears to exist in the case of triatomic units with 19 valence electrons. This may be a coincidence. But there are also indications of such systems being especially stable: for example, the markedly low tendency for chlorine dioxide to dimerize. As further supporting evidence of this concept, one could mention the tendency of N_2F_4 to dissociate into NF_2 radicals, or the exceptionally long S–S bond in the dithionite ion (239 pm, bond order noticeably less than one), indicating a tendency for decomposition into two SO_2^- moieties. The group of 19-electron systems also includes the ozonide ion O_3^-. However, despite intensive studies over the past twenty years and more[1], the existence of this anion has still not been unequivocally settled. In particular, there has been lack of reliable data on its geometry: thus, the data on experimentally determined O–O bond lengths vary between 119 and 142 pm, with the O–O–O angle being quoted as 100°[1a]. Theoretically, values of between 128 and 135 pm are predicted for the bond lengths and between 108 and 120° for the bond angle. We have now determined the dimensions of the ozonide ion by X-ray structure analyses on single crystals of KO_3 and RbO_3.

Of the possible strategies available for the preparation of alkali-metal ozonides[1c], it was found from detailed preliminary investigations that the reaction of solid potassium or rubidium hyperoxide with O_2/O_3 mixtures was the most suitable. The hyperoxides of potassium and rubidium, obtained by oxidation of the alkali metals with O_2[2], were ozonized for 1 h in a fluidized bed reactor (capacity ca. 100 mL) with O_2/O_3 mixtures (6 vol.-% ozone). About 0.02 mol of hyperoxide was converted per run. Optimal reaction temperatures are 5°C and 20°C for KO_3 and RbO_3, respectively. The reaction can be monitored by the change in color of the reaction mixture from yellow to intense red.

For the growth of single crystals the ozonides were extracted at –40°C with liquid ammonia, while unreacted hyperoxide remained undissolved. The solvent was then removed under argon with cooling; the alkali-metal ozonides precipitated as transparent deep-red crystals. The single crystals for the X-ray structure analysis were prepared under an inert gas at 10°C.

The X-ray structure analyses[3] confirm the predicted composition of the alkali-metal ozonides. Isolated angular O_3^- ions are present whose dimensions in RbO_3 (O–O(averaged) 134.1(15) pm, bond angle 114.6(13)°) and KO_3 (135.7(5) pm, bond angle 113.4(8)°) agree within the standard deviations[3]. Thus, packing effects seem to have no significant impact on the geometry of the anion. With respect to the bond lengths and angles previously determined on the basis of inadequate data[1c] (RbO_3: 142(9) pm, 101(5)°, KO_3: 119 pm, 100°), there are considerable discrepancies.

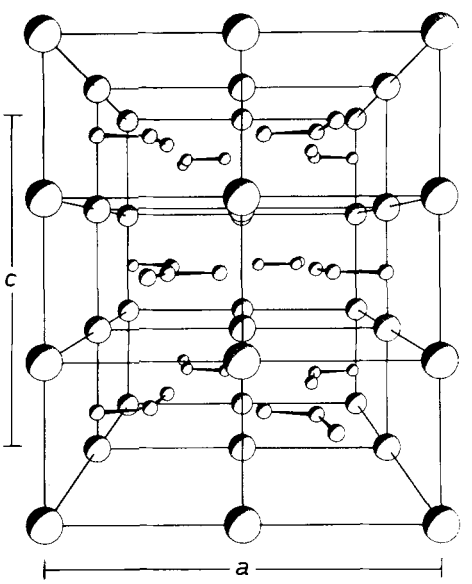


Fig. 1. Perspective diagram of the crystal structure of KO_3, viewed along [100]; large circles denote potassium, small circles oxygen.

The O–O bonds are longer than in ozone (127.8 pm)[4]. Since the additional electron occupies an antibonding molecular orbital, this tendency is consistent with expectation. The bond angle is reduced slightly from 116.8° to 114.0°. The distance between the two terminal oxygen atoms increases significantly from 218 to 226 pm.

With considerable simplification the packing of K^+ or Rb^+ and O_3^- to a three-dimensional crystal array can be rationalized as the CsCl-type structure (Fig. 1). The shortest contacts between oxygen and alkali-metal ions are, in the case of KO_3 exclusively and in the case of RbO_3 predominantly, those at the terminal O-atoms of the anion. This structural feature enables qualitative conclusions to be drawn about the polarity of the ozonide ion. Common to both ozonides is a marked deviation (86 pm (KO_3), 58 pm (RbO_3)) of the anion from the center of the polyhedron that is formed by the eight alkali-metal ions. There is still

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no satisfactory explanation for the complete order of the ozonide anions at room temperature, which is in contrast with the comparable $RbNO_2$[5]. Intermolecular interactions between the ozonide ions (dimerization) can be ruled out on the grounds of the large intermolecular distances[3]. Also still inexplicable are the marked differences in the stability of the compounds with 19-electron systems (NF_2, SO_2^-, O_3^-, S_3^-, ClO_2) towards dimerization. Whichever of the conceivable criteria is analyzed for an explanation (repulsion of non-bonding electron pairs, differences in electronegativity[6], charge of the monomer, state of aggregation) there are inconsistencies.

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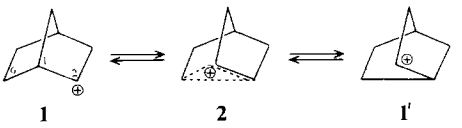
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Destabilized 2-Norbornyl Cations

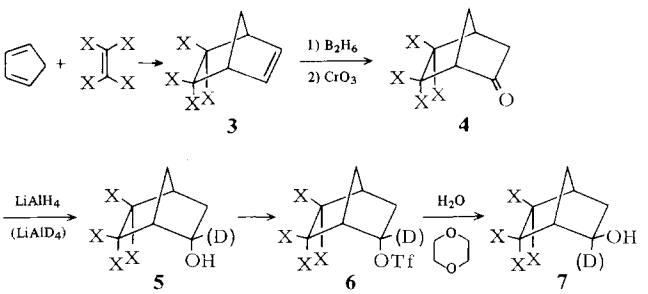
By *Wolfgang Kirmse**, *Uwe Mrotzeck*, and *Rainer Siegfried*

A conspicuous property of the 2-norbornyl cation **1** (≡ **1′**) is the equivalence of C-1 and C-2 in its spectra and reactions[1], as expressed by the σ-delocalized ("nonclassical") structure **2**. If an acceptor substituent is present at C-6, Wagner-Meerwein rearrangement and attack by the solvent appear to compete with each other; norbornyl cations of this type are considered to be unsymmetrically



1 **2** **1′**

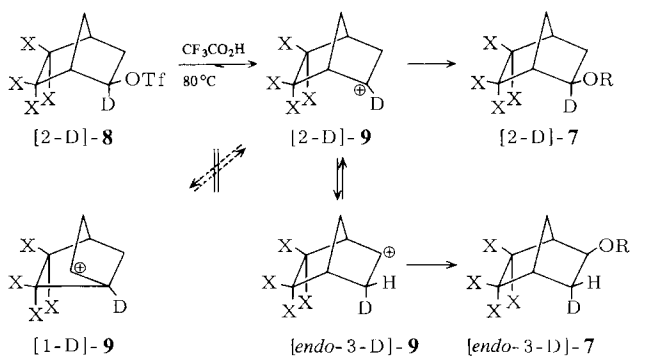
bridged[2]. The presence of four fluorine atoms or four trifluormethyl groups[3] at C-5 and C-6 should intensify the electron deficiency and at the same time maintain the symmetry of the parent system. We have found that the Wagner-Meerwein rearrangement is completely forestalled by such a substitution pattern—largely with retention of the *exo*-selectivity.



3 **4** **5** **6** **7**

Scheme 1. **a**, X = F; **b**, X = CF_3. Tf = trifluoromethylsulfonate.

The reactions of the substituted norbornenes **3**[4] sketched in Scheme 1 proceeded in good yields. Solvolysis of the *endo*-trifluoromethylsulfonate(triflate) **6** in dioxane-water afforded predominantly the *exo*-alcohols **7** (Table 1) without scrambling of a 2D-label. The *exo*-triflate **8a**



[2-D]-**8** [2-D]-**9** [2-D]-**7** [1-D]-**9** [*endo*-3-D]-**9** [*endo*-3-D]-**7**

Scheme 2. **a**, X = F; **b**, X = CF_3.

Table 1. Distribution of products upon solvolysis of the triflates **6** and **8**.

Educt	Conditions	**3**	**7**	**5**	*exo* : *endo*
endo-Series					
6a	Dioxane-H_2O (1 : 1), 80°C	8.6	91.2	0.2	—
6a	CF_3CO_2H, CF_3CO_2Na, 110°C	1.9	96.1	2.0	—
6b	Dioxane-H_2O (1 : 1), 100°C	1.3	98.7	—	—
6b	HCO_2H, HCO_2Na	trace	>99	—	—
exo-Series					
8a	Dioxane-H_2O (7 : 3), 80°C	69.0	5.3	25.7	0.21
8a	Dioxane-H_2O (1 : 1), 80°C	71.8	6.4	21.7	0.29
8a	Dioxane-H_2O (3 : 7), 80°C	60.0	14.4	25.6	0.56
8a	CF_3CO_2H, CF_3CO_2Na, 80°C	58.1	36.6	5.3	6.85
8b	Dioxane-H_2O (1 : 1), 100°C	>99	trace	—	—
8b	HCO_2H, HCO_2Na, 100°C	36.3	62.4	1.3	48
8b	CF_3CO_2H, CF_3CO_2Na, 65°C	59.2	40.7	trace	>100

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(Scheme 2) reacts only three- to four-times more rapidly than the *endo*-triflate **6a** and 20-times slower than 7-norbornyl triflate (ca. 10^{11}-times slower than *exo*-2-norbornyl triflate). The strongly solvent-dependent product ratio 7 : 5 (Table 1) suggests a competition between an S_N2 and an S_N1 reaction; the S_N1 reaction dominates only in trifluoroacetic acid. In contrast, in dioxane-water the *exo*-triflate **8b** underwent practically only elimination to give the alkene **3b**; in formic acid and trifluoroacetic acid **8b** reacted with high *exo*-selectivity (S_N1) (Table 1). In trifluoroacetic acid or formic acid the labeled triflates [2-D]-**6** and [2-D]-**8** led to a scrambling of D in **7** (Table 2). As indicated by the

Table 2. Deuterium scrambling in **7** upon solvolysis of [2-D]-**6** and [2-D]-**8**.

Educt	Conditions	*endo*-2-D	*endo*-3-D
endo-Series			
[2-D]-**6a**	CF_3CO_2H, CF_3CO_2Na, 80°C	95	5
[2-D]-**6b**	HCO_2H, HCO_2Na, 100°C	85	15
exo-Series			
[2-D]-**8a**	CF_3CO_2H, CF_3CO_2Na, 80°C	61	39
[2-D]-**8b**	CF_3CO_2H, CF_3CO_2Na, 80°C	84	16
[2-D]-**8b**	HCO_2H, HCO_2Na, 100°C	78	22

chemical shift in the ^{2}H-NMR spectrum and the coupling in the ^{1}H-NMR spectrum[5], the rearrangement product bore deuterium at the *endo* 3-position, but not at the bridgehead (C-1). A Wagner-Meerwein rearrangement had therefore not occurred, but rather an *exo,exo*-3,2-H shift. Scrambling of D in the solvolysis of [2-D]-**6a** is less than in [2-D]-**8a**, which indicates a higher S_N2 contribution in the reaction of **6a**; the difference is less pronounced for **6b**/**8b**. 3,2-H shifts are also known in 2-norbornyl cations; however, here they have the highest activation energy of all rearrangements and are insignificant under solvolysis conditions[6]. As indicated by the behavior of the cations **9**, the bridged structure **2** is more destabilized by F or CF_3 substituents than the open form **1**. The absence of Wagner-Meerwein rearrangement unequivocally characterizes **9a**, **b** as open ("classical") cations. The *exo*-selectivity of the 3,2-H shift cannot be accounted for here by σ-delocalization, but must have its origins elsewhere. The steric effects of the *endo*-substituents[1,6], torsional effects along the C1–C2 bonds[7], and deformation of the p-orbital at C-2 ("nonequivalent orbital extension")[8] have all been discussed in this connection.

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3a, 2822-56-2; **3b**, 94137-40-3; **5a**, 94137-41-4; **6a**, 94137-42-5; **6b**, 94137-43-6; **7a**, 94137-44-7; **7b**, 94137-45-8; **8a**, 94137-46-9; **8b**, 94137-47-0.

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[5] **7a**: 1-H (δ = 2.63 br. s), 2-H (δ = 4.34, d, J = 6.5 Hz), *endo*-3-H (δ = 2.28, dd, J = 14 and 6.5 Hz), *exo*-3-H (δ = 1.49, dq, J = 14 and ca. 2 Hz). The assignment was confirmed by comparison with [*exo*-3-D]-**7a** (from **3a** and B_2D_6). **7b**: 1-H (δ = 2.82 br, s), 2-H (δ = 4.56, d, J = 6.6 Hz), *endo*-3-H (δ = 2.65, ddd, J = 15.3, 6.6 and 3.5 Hz), *exo*-3-H (δ = 1.55, br, d, J = 15.3 Hz). The mixtures of [2-D]-**7** and [*endo*-3-D]-**7** exhibited singlets for 2-H and doublets (geminal coupling) for *endo*-3-H.

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Nitrile Imines: Thermal Generation, Direct Observation, and Subsequent Trapping**

By *Curt Wentrup**, *Stephan Fischer*, *André Maquestiau*, and *Robert Flammang*

Nitrile imines are important intermediates for 1,3-dipolar cycloadditions in solution[1]. Diphenyl- and *N*-phenylnitrile imine have been observed by IR and UV spectroscopy following low-temperature irradiation of matrix-isolated precursors[2]. Also trapping with protic solvents and use of an intramolecular cycloaddition reaction have been described[2c]. However, no direct observation of a thermally generated nitrile imine has been reported, there is no evidence for the existence of discrete nitrile imines in the gas phase, and the crucial link between the gas-phase or matrix-isolated species and the solution-phase intermediates, trappable in intermolecular 1,3-dipolar cycloaddition reactions and presumed to be nitrile imines, has not been established. We now wish to report evidence for each of these points.

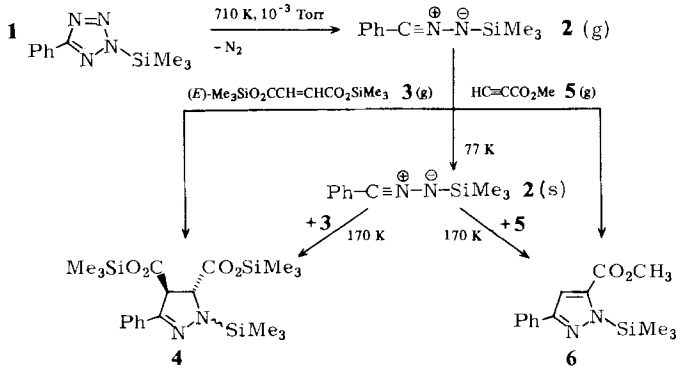
In order to observe a nitrile imine in thermal reactions, gas-phase generation with short contact times and subsequent low-temperature isolation are appropriate. However, nitrile imines with *N*-aryl groups undergo rapid cyclization to indazoles in the gas phase, thereby precluding direct observation[3]. Furthermore, *N*-methyl and related nitrile imines isomerize in the gas phase to azines and carbodiimides[4]. A nonisomerizing *N*-substituent is therefore required, and *N*-silyl substituents proved to be the best in this respect.

Flash vacuum pyrolysis of *C*-phenyl-2-trimethylsilyltetrazole **1**[5] at 710 K/10^{-3} torr gave gaseous *C*-phenyl-*N*-trimethylsilylnitrile imine **2**, which was led directly into the ion source of a mass spectrometer situated ca. 1 cm from the exit of the pyrolysis tube, or trapped on a KBr window at 77 K as the neat solid for IR spectroscopy. For UV spectroscopy the nitrile imine was co-condensed with isopentane on a quartz window at 77 K.

The molecular ion from **1** disappeared as a result of the pyrolysis, leaving an intense signal of the molecular ion of **2** (*m/z* 190). The collisionally induced dissociation (CID) mass spectrum of the latter ion was significantly different

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from those of the isomeric species 1-phenyl-3-trimethylsilylcarbodiimide and phenyl(trimethylsilyl)diazomethane (Table 1).

Table 1. Mass and IR spectra of **2** and isomeric compounds.

Compd.	Mass spectrum [a]			CID mass spectrum of *m/z* 190 [b]				IR [cm^{-1}], 77 K
m/z	218	190	175	175	162	147	73	
1	3	54	100	100	1.0	2.3	2.2	—
2 [c]	—	46	100	100	0.6	2.7	1.2	2230
Ph–N=C=N–Si(CH_3)$_3$	—	38	100	100	—	—	2	2175
Ph–C(N_2)Si(CH_3)$_3$	—	8	—	17	100	12	1	2045

[a] 70-eV electron ionization mass spectrum (Varian MAT 311A instrument). Ion abundancies in percent of the base peak. [b] CID mass spectrum of *m/z* 190 from the electron ionization mass spectrum, obtained on a triple sector (*E/B/E*) modified MS 902 instrument at an accelerating potential of 8 kV using air as the collision gas at a pressure of ca. 5×10^{-5} torr. [c] Obtained by pyrolysis of **1** at 700 K.

When the pyrolysis gas was mixed with bis(trimethylsilyl)fumarate **3** or methyl propiolate **5** vapor at the exit of the pyrolysis tube, the adducts **4**[6] and **6**[7] were isolated in 90—100% and 70—80% yield, respectively.

The solid nitrile imine **2** (s) exhibited strong IR absorptions at 2955, 2230 cm^{-1} (asymmetrical stretch), 1375 and 1355 (symmetrical stretch), 1245, 1098, 835, 750, and 680 cm^{-1}. The UV spectrum in an isopentane matrix showed a maximum at 303 nm. The nitrile imine was stable indefinitely at 77 K, but disappeared irreversibly on warming to 170—180 K.

Proof of the identity of the isolated nitrile imine **2** (s) was obtained by co-condensing the compound at 77 K with the trapping agent **5**. The IR spectrum of the nitrile imine was still observable at 77 K, but on warming to 170 K the spectrum was replaced by that of the 1,3-dipolar cycloaddition product **6**. In particular, bands due to **2** at 2230, 1375, 1355, and 1098 cm^{-1} disappeared synchronously with the development of new bands from **6** at 1140, 1073, and 635 cm^{-1}. After warming to room temperature the adduct **6** was isolated in essentially quantitative yield and its identity with the previously isolated material from the gas-phase reaction established. Similar results were obtained using **3** as the trapping agent.

Other *N*-silylated nitrile imines have been generated, observed, and trapped in analogous reactions, e.g. *N*-dimethylsilyl-*C*-phenylnitrile imine (2230 ($C\equiv\overset{\oplus}{N}-\overset{\ominus}{N}$), 2117 (Si–H) cm^{-1}); *C*-phenyl-*N*-triphenylsilylnitrile imine (2242 cm^{-1}; $\lambda_{max} = 310$ nm); *N*-methyldiphenylsilyl-*C*-phenylnitrile imine (2242 cm^{-1}); *N*-trimethylsilyl-*C*-methylnitrile imine (2259 cm^{-1}).

These results unambiguously demonstrate the existence of discrete nitrile imines, indefinitely at 77 K[2], and at least for several ms in the gas phase, and thus open the possibility of securing precise structural information and ionization potentials, the latter of which are of paramount importance for the determination of HOMO energies for use in theoretical treatment of 1,3-dipolar reactivity.

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1, 17591-51-4; **2**, 94136-16-0; **3**, 17962-03-7; **4**, 94136-17-1; **5**, 922-67-8; **6**, 94111-13-4; Ph–N=C=N–Si(CH_3)$_3$, 30543-46-5; Ph–C(N_2)Si(CH_3)$_3$, 24379-49-5; 5-phenyl-2-(dimethylsilyl)tetrazole, 94111-14-5; 5-phenyl-2-(triphenylsilyl)tetrazole, 94111-15-6; 5-phenyl-2-(methyldiphenylsilyl)tetrazole, 94111-16-7; 5-methyl-2-(trimethylsilyl)tetrazole, 94111-17-8; *N*-(dimethylsilyl)-*C*-phenylnitrilimine, 94111-18-9; *N*-(triphenylsilyl)-*C*-phenylnitrilimine, 94136-18-2; *N*-(methyldiphenylsilyl)-*C*-phenylnitrilimine, 94136-19-3; *N*-(trimethylsilyl)-*C*-methylnitrilimine, 94136-20-6; 5-phenylpyrazol-3-carboxylic methyl ester, 56426-35-8.

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[6] **4** was identical with the product isolated in 66% yield from the solution reaction described by Birkofer et al. [5]: B.p. = 150°C (0.05 torr). ^{1}H-NMR ($CDCl_3$): $\delta = 0.14$ (s, 9H), 0.295 (s, 9H), 0.302 (s, 9H), 4.46 (d, 1H), 4.77 (d, 1H), 7.22 (t, 1H), 7.30 (t, 2H), 7.70 (d, 2H). ^{13}C-NMR ($CDCl_3$): $\delta = -0.60$ ($SiMe_3$), -0.53 ($SiMe_3$), -0.36 ($SiMe_3$), 56.3, 66.8, 126.1, 127.6, 128.0, 132.3, 143.8, 169.9 (C=O), 171.9 (C=O).

[7] a) **6**: M.p. = 67°C; IR (KBr) 1742 (s), 1250 (s), 1237 (s), 840 (s); ^{1}H-NMR ($CDCl_3$): $\delta = 0.6$ (s, 9H), 3.9 (s, 3H), 7.25 (s, 1H), 7.36 (t, 2H), 7.4 (t, 3H), 7.9 (d, 2H); ^{13}C-NMR ($CDCl_3$): $\delta = 0.35$ ($SiMe_3$), 51.7 (CH_3), 109.4 (C=C–H), 125.7 (arom.-*m*), 127.9 (arom.-*p*), 128.6 (arom.-*o*), 132.9, 140.6, 153.8, 160.9 (C=O); $M^{\oplus\ominus}$: *m/z* = 274. Hydrolysis of **6** gave methyl 5-phenylpyrazole-3-carboxylate, which was identical with a sample prepared from phenyl(trimethylsilyl)diazomethane in CCl_4 with a threefold excess of methyl propiolate at room temperature; after standing overnight, the needles are filtered off and recrystallized from ethanol: yield 95%; m.p. = 184°C; [7b]: 182°C; [7c]: 182—183°C; b) K. von Auwers, C. Mausolf, *Chem. Ber. 60* (1927) 1730; c) U. Felcht, M. Regitz, *Liebigs Ann. Chem. 1977*, 1309.

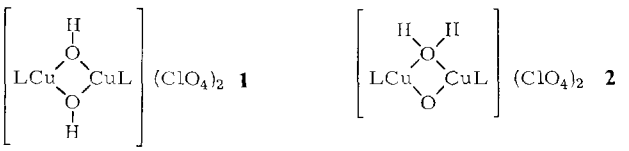
Preparation, Magnetism, and Crystal Structures of the Tautomers [LCu(μ_2-OH)$_2$CuL](ClO$_4$)$_2$ (Blue) and [LCu(μ_2-OH$_2$)(μ_2-O)CuL](ClO$_4$)$_2$ (Green): μ-Aqua-μ-oxo vs. Di-μ-hydroxo Linkage

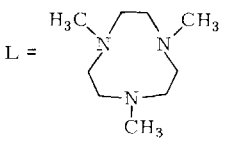
By *Phalguni Chaudhuri**, *Dirk Ventur*, *Karl Wieghardt*, *Eva-M. Peters*, *Karl Peters*, and *Arndt Simon*

Binuclear, di-μ-hydroxo-bridged complexes of almost all the transition metals have been prepared and their structures and chemistry thoroughly investigated. Antiferromagnetic and ferromagnetic intramolecular interactions of the unpaired electrons of the metal centers are the objects of numerous studies, in which particularly the relationships between structure and magnetism are being studied[1]. For compounds of copper(II) of this type *Hodgson*

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and *Hatfield* et al. have discovered a correlation between the spin interaction parameter $2J$ and the Cu–O–Cu bond angle ϕ[2]. Unsymmetrical tautomeric bridging through an oxo and an aqua ligand was previously not known.





We obtained *blue* single crystals of **1**[4] from aqueous reaction solutions of $Cu(ClO_4)_2 \cdot 6H_2O$ and the cyclic amine *N,N',N''*-trimethyl-1,4,7-triazacyclononane[3]. Interestingly, after addition of an aqueous solution of $NaClO_4$ to methanolic solutions of $CuCl_2 \cdot 2H_2O$ (but *not* of $Cu(ClO_4)_2 \cdot 6H_2O$) and the amine, we obtained *green* crystals of **2**, which are identical in composition with those of **1**[4]. Aqueous solutions of **2** are *blue*, and **1** can be crystallized from them. The UV spectra of **1** and **2** in the solid state are slightly different: **1**: $\lambda_{max} = 620$, 950 nm; **2**: 630, 1070 nm. Aqueous solutions of **1** and **2** are blue and their UV spectra are identical: $\lambda_{max} = 636$ nm ($\varepsilon = 138$ L mol^{-1} cm^{-1}), ≈ 1000 (70).

X-ray structure analysis of **1** reveals[5] that the blue crystal consists of $[LCu(\mu\text{-}OH)_2CuL]^{2\oplus}$ ions of C_i symmetry and of isolated $ClO_4^{\ominus}$ ions (Fig. 1). The positions of the H atoms of the OH groups were clearly recognizable as maxima in the difference Fourier synthesis.

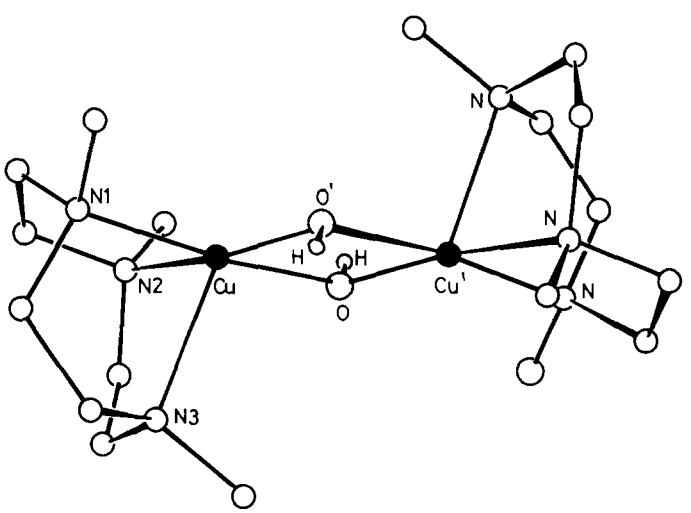


Fig. 1. Structure of the dimeric cation in the crystal of **1**. Selected distances [pm] and angles [°] (values for **2** in parentheses): Cu–O 193.9(4) (222.0(5)), Cu–O' 193.6(4) (219.9(5)), Cu–N1 208.3(4) (207.3(7)), Cu–N2 206.0(5) (206.4(7)), Cu–N3 223.8(4) (222.1(7)), Cu–Cu' 297.1(1) (303.2(1)); Cu–O–Cu' 100.1(2) (88.6(2)), O–Cu–O' 79.9(2) (91.4(2)), N1–Cu–O' 97.0(2) (91.1(2)), N1–Cu–N2 85.7(2) (86.3(3)), N2–Cu–O 96.6(2) (90.8(2)), O–Cu–N3 102.6(2) (107.8(2)), N2–Cu–N3 83.6(2) (84.0(3)).

Surprisingly, **2** crystallizes in the same space group as **1** and has very similar lattice constants[5]. According to a structure analysis, the packing of binuclear dications and $ClO_4^{\ominus}$ ions in **2** is almost identical to that in **1**. However, in **2** the O atoms of the bridges between the Cu^{II} centers are disordered (described with marked anisotropic temperature factors) and the H atoms on the O atoms could not be localized. The results of differential thermal analysis indicate that in the solid state **1** and **2** are not interconvertible. Significant differences between **1** and **2** are revealed by their IR spectra in the regions 3700—3000 and 1800—1600 cm^{-1}. **1** displays a sharp ν(OH) vibration at 3600 cm^{-1}, which is consistent with the absence of H bonds and of water of crystallization. In contrast, **2** exhibits a very broad ν(OH) band at 3400 and a ν(H–O–H) deformation mode at 1630 cm^{-1}; both of these are absent in the spectrum of **1**.

Since **2** also crystallizes free of water of crystallization, we suggest that this finding arises from the presence of an unsymmetrical μ-aqua-μ-oxo bridge between the two Cu^{II} centers. This type of bridging has not been described previously; pure μ-aqua bridging between transition metals is also rare[9]. In the crystal, the cation of **2** is statistically disordered, and no H bonds from the aqua bridge to $ClO_4^{\ominus}$ are formed.

1 and **2** are tautomeric complexes; in aqueous solution the equilibrium lies completely to the side of **1**.

The magnetic susceptibilities of **1** and **2**[6] differ markedly. The expression for the temperature-dependent susceptibility was derived from the general, isotropic spin Hamiltonian operator $H = -2J \cdot S_1 \cdot S_2$ for $S_1 = S_2 = 1/2$[7].

$$\chi_M = 2Ng^2\beta^2/3kT \cdot [1 + 1/3\exp(-J/kT)]^{-1}$$

ESR studies of **1** indicated a $\langle g \rangle$ value of 2.13[8]; the same value was assumed for **2**. By means of a fitting procedure using least-squares analysis, J values of -45 and $+37$ cm^{-1} were estimated for **1** and **2**, respectively. **1** is therefore antiferromagnetic (singlet ground state), whereas **2** is ferromagnetic (triplet ground state). The $2J$ value calculated for **1** fits the $2J/\Phi$-correlation well[2].

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1, 93806-56-5; **2**, 93841-98-6.

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[4] Procedure: **1**: 4 mL of a methanolic 1 M solution of *N,N',N''*-trimethyl-1,4,7-triazacyclononane is added to 40 mL of an aqueous solution of $Cu(ClO_4)_2 \cdot 6H_2O$ (0.90 g). The solution immediately became deep blue. Analytically pure crystals of **1** grew slowly (24 h) from this solution; the crystals were filtered off, washed with ethanol and ether, and dried in the air. Yield 50—75% relative to $Cu(ClO_4)_2 \cdot 6H_2O$.—**2**: $CuCl_2 \cdot 2H_2O$ (1.2 g) was added to 20 mL of a 1 M methanolic solution of the cyclic amine and refluxed for 30 min. 10 mL of water and 1 mL of an aqueous 1 M solution of $NaClO_4$ were added to the cooled solution (25 °C). Upon cooling this solution to 2 °C, analytically pure, green crystals of **2** precipitated out, which were filtered off, washed with ethanol and ether, and dried in air. Attempts to recrystallize **2** from the aqueous solution were unsuccessful; instead, **1** crystallized out. Both salts gave almost identical elemental analyses in excellent agreement with the calculated values.

[5] X-ray structure analysis of **1** and **2** (data for **2** in parentheses) $P2_1/n$ ($P2_1/n$), $a = 2041(2)$ (2067(2)), $b = 825.7(4)$ (827.04(4)), $c = 867.1(6)$ (874.7(6)) pm, $\beta = 91.44(6)$ (91.20(6))°, $Z = 2(2)$, $V = 440.0$ (450.3) cm^3 mol^{-1}; $\rho_x = 1.597$ (1.561) g cm^{-3}; $R = 0.061$ (0.096) for 2877 (2843) independent reflections ($F_0 > 3\sigma(F_0)$); $Mo_{K\alpha}$-radiation, Syntex R3. Further details on the crystal structure analysis can be obtained from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leo-

poldshafen 2, by quoting the depository number CSD 51119, the names of the authors, and the journal citation.
[6] Magnetic measurements: The molar susceptibilities of **1** and **2** were measured on powdered samples in the temperature region 93–293 K using the Faraday method. Diamagnetic corrections for the ligands and $ClO_4^{\ominus}$ were carried out by means of Pascal's constant.
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Quantitative HPLC Analysis and Thermodynamics of Sulfur Melts**

By *Ralf Steudel**, *Reinhard Strauss*, and *Lothar Koch*

Dedicated to Professor Gerhard Fritz on the occasion of his 65th birthday

Because of its unique thermal behavior, liquid sulfur has been the subject of numerous physicochemical and theoretical investigations. As a rule, it is assumed that, below the polymerization temperature (159°C), the melt essentially consists of S_8 molecules. However, we have already previously shown by means of vibrational spectra[1] that rings other than S_8 (mainly S_7, S_6, and S_n with $n > 8$) are present at all temperatures in liquid sulfur, and that these—in comparison with S_8—are considerably more reactive species and strongly influence the properties of the melt[2].

The separation of sulfur homocycles by means of high-pressure liquid chromatography (HPLC)[3] now enables a much more accurate quantitative analysis. Using this technique, we have now found that, after establishment of the equilibrium

$$n/8\,S_8 \rightleftharpoons S_n \quad (n \neq 8) \qquad (1)$$

at constant temperature (23 samples, 13 temperatures) and then quenched in liquid nitrogen, accurately weighed at 20 °C (4.1–7.2 g), and immediately extracted quantitatively with ca. 200 mL CS_2[4]. After filtration and dilution to a prescribed volume, the solution was analyzed quantitatively by HPLC. The insoluble residue (polymeric sulfur, S_μ) was washed with CS_2, dried, and weighed.

In the chromatograms[5], the areas A of 18 S_n ring-molecules ($n = 6$–23) could be measured by electronic integration. For the calibration, at least ten solutions of different concentration c of each of the pure compounds were measured in the case of S_6, S_7, S_8, S_{10}, S_{12}, and S_{20}. The calibration curve was linear ($c = aA$) with a correlation coefficient better than 0.9999 over the range 5–500 μg S/mL CS_2. Since the slope a is proportional to the number of S atoms in the molecule (except in the case of S_7), the calibrations could be calculated for the remaining molecules.

Representative analytical values at 13 different temperatures are listed in Table 1. As expected[6], the concentrations of the S_n rings ($n \neq 8$) pass through a maximum at 159°C: besides 3% S_μ, only 83.4% S_8 is present. The missing "rest" of the 100% assay is ascribed to soluble S_n molecules ($n > 23$) and analytical errors (maximally 3%). Molecules with $n < 6$ were not detectable.

After S_8 and S_7, the most frequently occurring molecules in the melt are S_6, S_9, and S_{12}. The relevant reaction enthalpies $\Delta H(1)$ of Equation (1) can be calculated from the temperature-dependence of the concentrations of the molecules listed in Table 1. From the linear regressions in the temperature range 116–159°C the values shown in Table 2 are obtained.

Assuming an equally strong intermolecular interaction (per atom) for all molecules in the melt (zero enthalpy of mixing), the mean bond energies (m.B.E.) in the sulfur rings shown in Figure 1 can be calculated from the $\Delta H(1)$

Table 1. Composition [mass%] of quenched liquid sulfur, after equilibration between 116–387°C.

T[°C]	S_8	S_μ	S_6	S_7	S_9	S_{10}	S_{11}	S_{12}	S_{13}	S_{14}	S_{15}	S_{16}	S_{17}	S_{18}	S_{19}	S_{20}	S_{21}	S_{22}	S_{23}	$\sum S$
116	93.63	0.17	0.51	3.05	0.30	0.10	0.03	0.39	0.02	0.03	0.06	0.03	0.03	0.06	0.08	0.07	0.05	0.04	0.02	98.67
122	93.08	0.24	0.56	3.29	0.35	0.10	0.04	0.42	0.03	0.04	0.07	0.03	0.03	0.07	0.08	0.07	0.06	0.04	0.02	98.62
141	92.69	0.31	0.75	4.51	0.54	0.17	0.06	0.48	0.05	0.06	0.09	0.05	0.05	0.09	0.12	0.10	0.07	0.05	0.03	100.27
159	83.43	3.01	0.93	5.20	0.62	0.21	0.07	0.49	0.06	0.07	0.11	0.06	0.06	0.09	0.13	0.12	0.08	0.05	0.03	94.82
178	68.82	19.91	0.89	4.87	0.57	0.14	0.07	0.45	0.05	0.07	0.10	0.06	0.06	0.07	0.12	0.10	0.08	0.06	0.04	96.53
197	60.64	28.42	0.91	4.86	0.51	0.12	0.07	0.42	0.04	0.06	0.10	0.06	0.06	0.11	0.12	0.11	0.09	0.06	0.04	96.80
220	54.33	34.21	0.89	4.55	0.58	0.19	0.07	0.40	0.05	0.07	0.10	0.06	0.06	0.09	0.11	0.08	0.06	0.04	0.03	95.97
243	51.48	39.85	0.91	4.73	0.61	0.20	0.07	0.40	0.05	0.07	0.10	0.07	0.06	0.10	0.12	0.11	0.08	0.06	0.03	99.10
269	50.70	38.96	0.89	4.44	0.58	0.20	0.07	0.39	0.05	0.07	0.10	0.06	0.06	0.06	0.11	0.08	0.06	0.04	0.02	96.94
293	54.02	37.80	0.90	4.61	0.61	0.20	0.08	0.40	0.05	0.07	0.10	0.06	0.06	0.08	0.11	0.08	0.06	0.04	0.03	99.36
316	54.89	35.22	0.81	3.87	0.51	0.18	0.07	0.41	0.04	0.06	0.10	0.05	0.05	0.06	0.11	0.08	0.06	0.03	0.02	96.62
339	56.40	34.47	0.83	4.18	0.56	0.19	0.07	0.39	0.04	—	0.10	0.05	0.06	0.08	0.10	0.08	0.06	0.04	0.02	97.72
387	56.28	33.91	0.86	4.13	0.50	0.18	0.06	0.40	0.04	0.06	0.09	0.05	0.05	0.09	0.10	0.09	0.07	0.05	0.03	97.04

in the temperature range 116–387°C, liquid sulfur contains between 6.2 and 13.6 mass-% S_n ($n \neq 8$) ring molecules. The sulfur was equilibrated in an aluminum furnace

Table 2. Reaction enthalpies $\Delta H(1)$ for the reaction (1) at 116–159°C (1.013 bar).

n	$\Delta H(1)$ [kJ·mol^{-1}]	n	$\Delta H(1)$ [kJ·mol^{-1}]
6	22.4±0.5	16	30±3
7	21.2±0.6	17	34±1
9	28±2	18	22±1
10	30±3	19	25.3±0.4
11	33±3	20	28±3
12	12±1	21	24±2
13	31±3	22	21±3
14	30±2	23	27±2
15	26±1		

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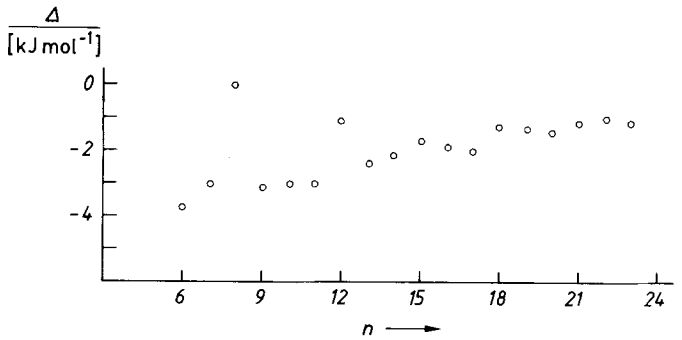


Fig. 1. Difference Δ between the mean bond energies (m.B.E.) of the ring molecules S_n ($n = 6$—23) dissolved in liquid S_8 and the m.B.E. of S_8:

$$\Delta = \text{m.B.E.}\ (S_n) - \text{m.B.E.}\ (S_8) = -\Delta H(1)/n$$

According to [7], m.B.E. (S_8) = 226.6 kJ mol^{-1} (atomization energy of gaseous S_8 at 25°C).

values and the bond energy of S_8. It emerges that S_{12} is the next most stable molecule after S_8, while the smallest ring (S_6) detectable in the melt has the smallest mean bond energy. Thus, for the first time, accurate thermodynamic data for sulfur molecules with more than 8 atoms are now known.

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CAS Registry numbers:
S_6, 13798-23-7; S_7, 21459-04-1; S_8, 10544-50-0; S_9, 18808-47-4; S_{10}, 19269-86-4; S_{11}, 60349-28-2; S_{12}, 14999-38-3; S_{13}, 77152-68-2; S_{14}, 60349-29-3; S_{15}, 77152-69-3; S_{16}, 60349-30-6; S_{17}, 77152-70-6; S_{18}, 41371-12-4; S_{19}, 77152-71-7; S_{20}, 42817-30-1; S_{21}, 77152-72-8; S_{22}, 77152-73-9; S_{23}, 77152-74-0.

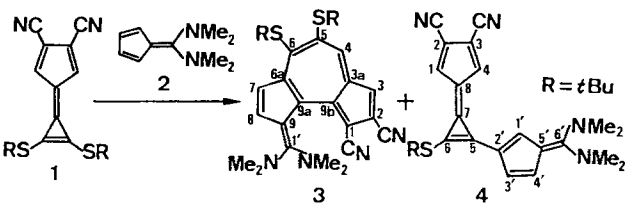
[1] R. Steudel, H.-J. Mäusle, *Z. Anorg. Allg. Chem. 478* (1981) 156, 177.
[2] R. Steudel, *Phosphorus Sulphur 16* (1983) 251.
[3] For the separation of sulfur molecules S_n, with $n = 6$—30, by means of reverse phase chromatography see: R. Steudel, H.-J. Mäusle, D. Rosenbauer, H. Möckel, T. Freyholdt, *Angew. Chem. 93* (1981) 402; *Angew. Chem. Int. Ed. Engl. 20* (1981) 394; R. Steudel, R. Strauss, *J. Chem. Soc. Dalton Trans. 1984*, 1775.
[4] Duration of heating 6.5—48 h, quenching rate 0.6 g min^{-1}, extraction time 10—150 min; for experimental details of furnace etc. see: [1].
[5] HPLC pumps, Series 2, with gradient control (Perkin-Elmer), sample loop 10 μL, Radical-Pak 10C18-column (Waters), eluent methanol-cyclohexane/ethanol, UV detector LC 75 (Perkin-Elmer), Integrator 3390A (Hewlett-Packard).
[6] The decrease in concentrations above 160°C is largely due to the decreasing S_8-concentration, which reaches a minimum of 51% at ca. 250°C. The maximal polymer content of 40% found by us is consistent with the values found by Schenk (P. W. Schenk, *Z. Anorg. Allg. Chem. 280* (1955) 1), but is ca. 10% lower than that found by other groups ([1]; K. C. Koh, W. Klement, *J. Phys. Chem. 74* (1970) 4280), which we ascribe to a more effective extraction as a result of the smaller particle diameters of the quenched melts in the experiments described here.
[7] K. C. Mills: *Thermodynamic Data for Inorganic Sulphides, Selenides and Tellurides*, Butterworths, London 1974, p. 65.

A Novel Transformation of a Calicene to an Azulenofulvene

By *Zen-ichi Yoshida**, *Mitsuhiro Shibata*, *Eiji Ogino*, and *Toyonari Sugimoto*

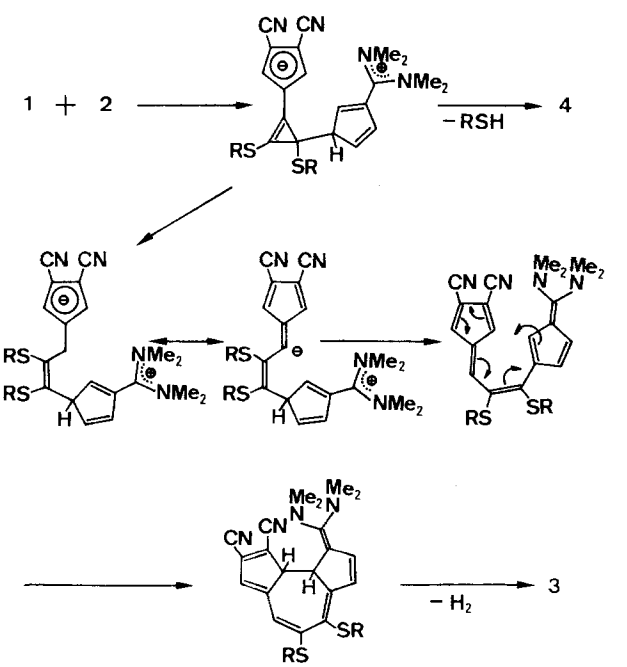
Calicenes (cyclopropenylidenecyclopentadiene) exhibit interesting reaction behavior, as expected from their novel structural features. For example, methyl-1-(dipropylcyclopropenylidene)-3-indenecarboxylate[1], 9-(dimethylcyclopropenylidene)fluorene and 5-(dimethylcyclopropenylidene)-1,2,3,4-tetraphenylcyclopentadiene[2] are converted into naphthalene derivatives by reaction with dimethyl acetylenedicarboxylate. In contrast, we have now found a novel skeletal conversion of 4-[bis(*tert*-butylthio)cyclopropenylidene]-1(5),2-cyclopentadiene-1,2-dicarbonitrile **1**[3] into the azulene derivative **3** upon reaction with 6,6-bis(dimethylamino)fulvene **2**.

Treatment of tetramethylammonium 1,2-dicyanocyclopentadienide[4] with tris(*tert*-butylthio)cyclopropenylium perchlorate[5] in dichloromethane gave **1** in 97% yield[3]. When **1** was allowed to react with **2** in refluxing tetrahydrofuran, 5,6-bis(*tert*-butylthio)-9-[bis(dimethylamino)methylene]-1,2-cyclopent[*e*]azulenedicarbonitrile **3** (dark blue crystals, m.p. = 250—251°C, 11% yield) and the substitution product **4** (yellow crystals; m.p. = 130—132°C, 52% yield) were obtained (Scheme 1). Both compounds possess novel π-electronic structures.



Scheme 1.

The structure of **4** was easily determined from the ^{1}H-NMR spectroscopic data. The IR spectrum of **3** shows no absorption attributable to the cyclopropene stretching vibration around 1800 cm^{-1}, suggesting cleavage of the three-membered ring. Also, in the ^{1}H-NMR spectrum, two protons on the fulvene moiety and one proton on the di-



Scheme 2.

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cyanocyclopentadienyl moiety appear as two doublets and a singlet, respectively. These results, together with the mass and ^{13}C-NMR spectroscopic data[6], suggest that **3** is an azulenofulvene derivative[7] with two *tert*-butylthio groups and two cyano groups.

A formation scheme involving 1) attack by the 2-position of **2** at the 5-position of **1**, 2) opening of the three-membered ring, 3) proton transfer, 4) disrotatory 10π-electrocyclic reaction, and finally 5) dehydrogenating aromatization is shown in Scheme 2[8].

Table 1. Spectral data for **3** and **4**.

	IR (KBr) [cm^{-1}]	UV (CH_2Cl_2) λ_{max} [nm] (logε)	^{1}H-NMR ($CDCl_3$) [a] δ-values
3	2203, 2175, 1580, 1520	258 (4.58), 293 (4.62), 328 (4.37), 350 (4.35), 404 (4.31), 575 (3.96)	8.10 (s, 1H, H-4), 7.87 (s, 1H, H-3), 7.50 (d, 1H, H-8, J=5.0 Hz), 7.03 (d, 1H, H-7, J=5.0 Hz), 3.26 (s, 6H, NMe_2), 2.76 (s, 6H, NMe_2), 1.38 (s, 9H, *t*Bu), 1.30 (s, 9H, *t*Bu)
4	2200, 1810, 1497	247 (4.62), 266 (4.59), 335 (4.53), 408 (4.85)	7.12 (s, 2H, H-1,4), 7.05 (t, 1H, H-1′, J=2.0 Hz), 6.73 (dd, 1H, H-3′ or -4′, J=4.5, 2.0 Hz), 6.36 (dd, 1H, H-3′ or -4′, J=4.5, 2.0 Hz), 3.22 (s, 12H, NMe_2), 1.71 (s, 9H, *t*Bu)

[a] 100 MHz, 25°C.

Other calicenes, e.g., the analogue of **1** with NO_2 and H instead of 2CN[9], gave only the substitution product of type **4**[10].

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CAS Registry numbers:
1, 94138-30-4; **2**, 703-24-2; **3**, 94138-31-5; **4**, 94138-32-6.

[1] A. S. Kende, P. T. Izzo, *J. Am. Chem. Soc. 87* (1965) 4162.
[2] H. Prinzbach, U. Fisher, *Helv. Chim. Acta 176* (1967) 1692.
[3] **1**: pale pink crystals; m.p. = 205–207°C; ^{1}H-NMR ($CDCl_3$): δ = 7.05 (s, 2H), 1.70 (s, 18H).
[4] O. W. Webster, *J. Am. Chem. Soc. 88* (1966) 3046.
[5] Z. Yoshida, S. Miki, S. Yoneda, *Tetrahedron Lett. 14* (1973) 4731.
[6] **3**: ^{13}C-NMR ($CDCl_3$): δ = 168.9 (C-1′), 145.7, 143.1, 141.4, 138.5, 134.8, 131.9 (C-9b,3a,5,6,6a,9a), 137.5 (C-4), 129.1 (C-3), 122.1, 117.6 (C-7,8), 119.2, 117.2 (CN), 111.2 (C-2), 108.9 (C-1), 107.4 (C-9), 49.6, 49.2 ($C(CH_3)_3$), 42.7, 42.4 ($N(CH_3)_2$), 31.9, 31.7 ($C(CH_3)_3$).
[7] Very recently we synthesized an unsubstituted cyclopent[*e*]azulenide and some of its derivatives (diaminomethylene- and diaminocyclopropenylidenecyclopent[*e*]azulenes); Z. Yoshida, M. Shibata, T. Sugimoto, *Tetrahedron Lett. 24* (1983) 4585; Z. Yoshida, M. Shibata, A. Sakai, T. Sugimoto, *J. Am. Chem. Soc. 106* (1984) 6383.
[8] It has been established that a carbene of the Wanzlick type, which readily accepts protons, can be easily generated under mild conditions from the cyclopropene intermediate formed in the reaction of thiocyclopropenylium ions with various nucleophiles (S. Miki, Dissertation, Kyoto University 1978; H. Hirai, Dissertation, Kyoto University 1980; S. Yoneda, H. Hirai, Z. Yoshida, *Chem. Lett. 1976*, 1051; *Heterocycles 15* (1981) 865). However, at present other routes cannot be ruled out.
[9] **5** was synthesized in 6% yield by reaction of sodium nitrocyclopentadienide with 1,2-bis(*tert*-butylthio)-3,3-dichlorocyclopropene: yellow crystals; m.p. = 156°C; ^{1}H-NMR ($CDCl_3$): δ = 7.42 (dd, 1H), 6.89 (dd, 1H), 6.48 (dd, 1H), 1.68 (s, 18H).
[10] Analogue of **4** with NO_2 and H instead of 2CN; yield 51%, yellow oil, ^{1}H-NMR ($CDCl_3$): δ = 7.60 (t, 1H), 7.15 (t, 1H), 6.95 (dd, 1H), 6.85 (dd, 1H), 6.65 (dd, 1H), 6.40 (dd, 1H), 3.25 (s, 12H), 1.75 (s, 9H).

Probing the Structure and Crystallinity of a Lithium Silicate Glass by ^{29}Si Magic-Angle-Spinning NMR Spectroscopy

By *C. N. R. Rao*, John M. Thomas*, Jacek Klinowski, U. Selvaraj, K. J. Rao, G. Robert Millward,* and *Subramaniam Ramdas*

It is now well established that high-resolution magic-angle-spinning NMR spectroscopy (MASNMR) can monitor the nature of short-range order in both non-crystalline and crystalline solids[1,2]. ^{29}Si-MASNMR studies of silicates have shown that the ^{29}Si chemical shift is related to the Si–O–Si angles and to interatomic distances[3]. In glasses, where a wide range of such structural parameters are simultaneously present, lineshapes provide information about the nature of the distribution functions[4]. We have found that useful information on the distribution of Si–O–Si angles may be obtained from ^{29}Si-MASNMR spectra of glasses in which the crystallinity varies from zero to 100%, as gauged by electron microscopy.

We have chosen lithium disilicate glass, thermally treated to yield a range of materials extending between the two extremes of 100% crystallinity and 100% non-crystallinity. Lithium disilicate, $Li_2O \cdot 2\,SiO_2$, is a particularly suitable material for such a study since its crystal structure is known[5], and no change of composition is observed on devitrification. Crystalline lithium disilicate consists of a double-chain arrangement of apex-shared SiO_4^{4-} tetrahedra in such a way that each Si atom has three equivalent silicon neighbors. Partly crystalline $Li_2O \cdot 2\,SiO_2$ contains minute microcrystals immersed in an amorphous matrix, apparent even in scanning electron micrographs, and is readily detectable by electron diffraction.

In recording the ^{29}Si-NMR spectra, we noted that the spin-lattice relaxation times T_1 of the nucleus were very different in the microcrystalline and non-crystalline regions; in the former case this was of the order of seconds while in the latter of the order of hours. This large difference in relaxation times makes it possible to distinguish between the two regions and measure the relative amounts of material in each. Whereas the spectrum of the crystalline part of the mixture can be obtained relatively easily, a spectrum comprising signals of both the amorphous and crystalline regions can be measured only if short pulses and long pulse delays are used, and we used 30° pulses separated by 90 min delays.

Even those samples which, by microscopy, appeared largely (80%) non-crystalline, contained traces of microcrystallinity, and hence the resulting spectrum (Fig. 1a) contains the characteristic, though somewhat broader signal at $\delta = -92$ from tetramethylsilane (TMS) superimposed upon a much broader background resonance, the chemical shift of which ranges from $\delta = -70$ to -120 and which is attributable to non-crystalline regions of the sample.

The total range of ^{29}Si-NMR chemical shifts in silicates lies between $\delta = -60$ and -120. This is split up into five intervals[2] corresponding to Si atoms in monosilicates, i.e. to isolated SiO_4^{4-} groups (denoted by Q^0), disilicates and

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chain end groups (Q^1), middle groups in chains (Q^2), chain branching sites (Q^3), and fully crosslinked framework sites (Q^4). Within each structural category the ^{29}Si chemical shift is correlated with the Si–O–Si bond angles and the interatomic distances. We conclude that, in agreement with the established structure, the sharp resonance at $\delta = -92$ is attributable to Q^3 groupings (chain branching sites), and the chemical shift corresponds to an Si–O–Si angle of ca. 135°. The single sharp resonance at $\delta = -61$ (x) is due to Q^0 (monosilicate) present as binder in the ZrO_2 magic-angle spinner.

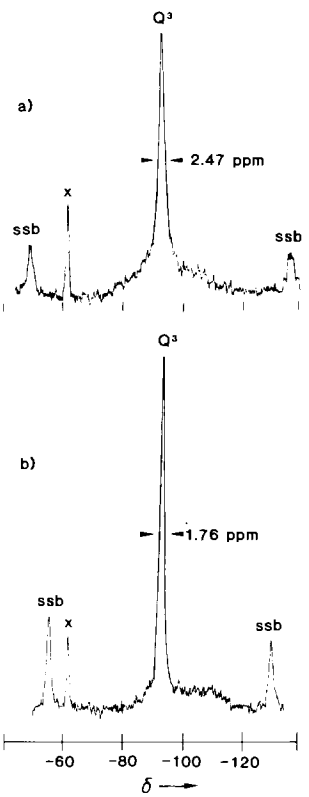


Fig. 1. ^{29}Si-MASNMR spectra (59.60 MHz, Bruker CXP-300). a) Partially crystallized lithium disilicate glass; b) almost completely crystalline $Li_2O \cdot 2SiO_2$. Samples spun at ca. 3.5 kHz in Andrew-Beams spinners made of Delrin. δ-values given in ppm relative to TMS branching sites.

There are also distinct spinning sidebands (ssb) equidistant from the main signal, which are due to chemical shift anisotropy. Their presence supports our assignment of the main signal as arising from Q^3 units; Q^4 (fully cross-linked framework sites) units resonate at a higher field and involve much smaller chemical shift anisotropy. Spinning sidebands from Q^4 sites in framework silicates are much less distinct than in the present Q^3 case. Finally, no Q^2 signals (corresponding to the termination of the double chain) are visible in the spectra, indicating that their concentration is low.

The range of resonances ($\delta = -70$ to -120) for the noncrystalline regions can be interpreted in several ways: 1) Q^1, Q^2 and Q^3 groups are present, 2) the Si–O–Si angles range from ca. 120 to 180° in the Q^3 groupings, and 3) the interatomic distances vary. Of these possibilities, a combination of 2) and 3) is the most likely explanation. The fact that the spectrum of the largely crystalline sample (electron diffraction studies) also contains a broad background resonance signifies the presence of some crystallographically disordered material. When the composition of a lithium silicate glass $Li_2O \cdot x\,SiO_2$ is varied by increasing x, a broad NMR signal is observed whose chemical shift approaches that of Q^4 units.

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[2] E. Lippmaa, M. Mägi, A. Samoson, G. Engelhardt, A.-R. Grimmer, *J. Amer. Chem. Soc. 102* (1980) 4889.
[3] J. M. Thomas, J. Klinowski, S. Ramdas, B. K. Hunter, D. T. B. Tennakoon, *Chem. Phys. Lett. 102* (1983) 158; S. Ramdas, J. Klinowski, *Nature 308* (1984) 521; J. V. Smith, C. S. Blackwell, *Nature (London) 303* (1983) 223; G. Engelhardt, R. Radeglia, *Chem. Phys. Lett. 108* (1984) 271; A.-R. Grimmer, R. Radeglia, *Chem. Phys. Lett. 106* (1984) 262.
[4] R. Dupree, R. F. Pettifer, *Nature (London) 308* (1984) 523.
[5] A. K. Pant, D. W. J. Cruickshank, *Acta Crystallogr. Sect. B 24* (1968) 13.

Photooxygenolysis of Vitamin B_{12}**

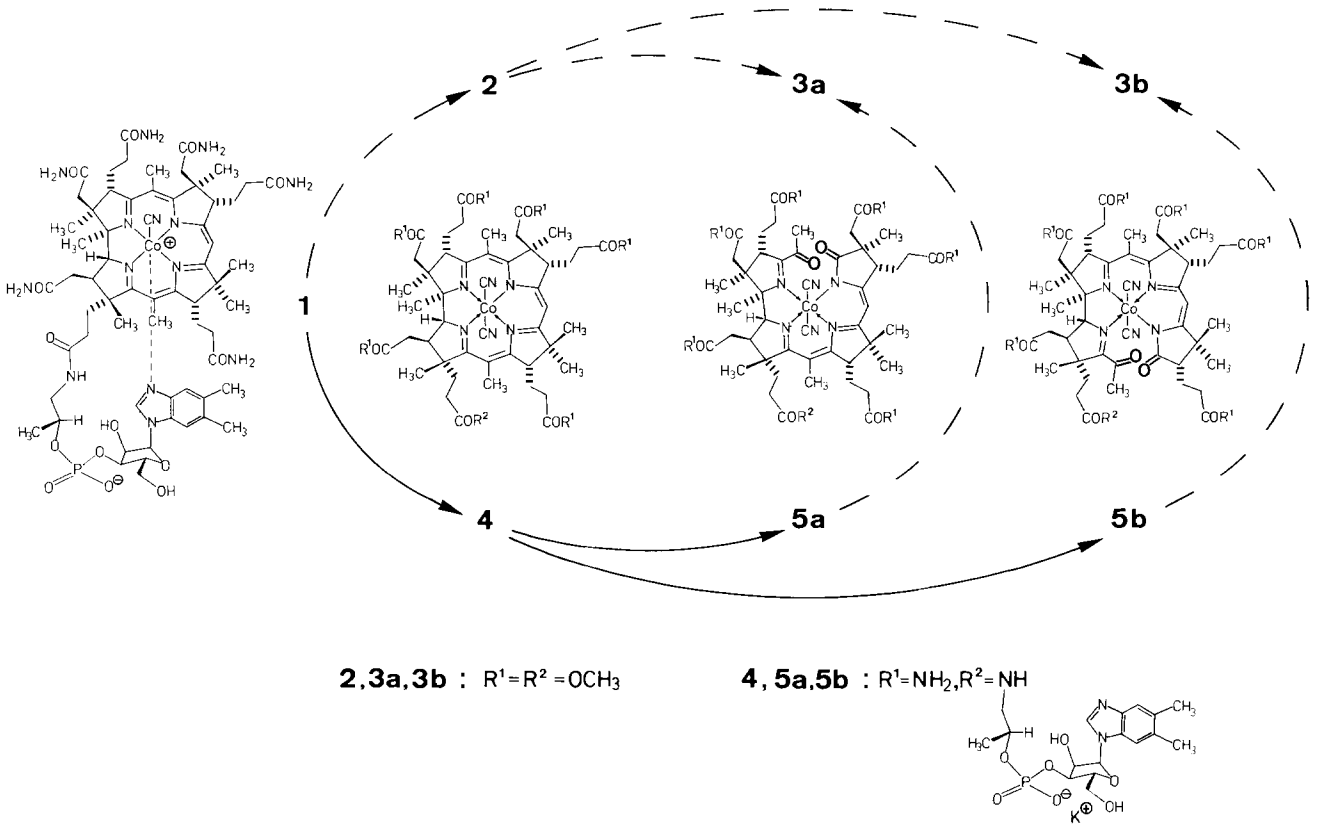
By *Bernhard Kräutler** and *René Stepánek*

Studies of the action of singlet oxygen ($^1O_2$) on vitamin B_{12} **1** are still outstanding, but should be of interest because of the medical[1], biological[1,2], and preparative[2,3] role of $^1O_2$. We recently found that heptamethyl-dicyano-Co^{III}-cobyrinate **2** ("cobester"[4]), the nucleotide-free methanolysis product of vitamin B_{12}, undergoes selective photooxygenolysis to afford the dioxosecocobyrinates **3a** and **3b**[5]. This degradation reaction with $^1O_2$[5] opened an efficient route to **3a** and **3b**, the former of which *Inhoffen* et al.[6] had already prepared via partial ozonolysis of heptamethyl-dicyano-Co^{III}-10-bromocobyrinate. We now report on the photooxygenolytic cleavage of the corrin macrocycle of vitamin B_{12} (see Scheme 1).

Upon irradiation with visible light, vitamin B_{12}, dissolved in oxygen-saturated CD_3OD, exhibited considerable inertness, even in the presence of the $^1O_2$-sensitizer methylene blue (MB). Only after addition of KCN (1 mol per mol **1**) to a solution of **1** (λ_{max} is shifted from 548 to 584 nm, corresponding to the conversion **1** → potassium dicyanocobalamin **4**) and of MB in CD_3OD did the photolysis lead to degradation of the corrin within a few hours[7]. In CH_3OH, but otherwise under the same conditions, the photolysis proceeded approximately 7 times more slowly[8]. Irradiation[9] of an oxygen-saturated solution of **1**, KCN, and MB (molar ratio 1 : 1 : 0.005) in CD_3OD at ca. −70 °C with a 150-W tungsten lamp led after 45 min to ca. 50% degradation of the educt and to formation of products which absorb at shorter wavelengths (λ_{max} ca. 490 nm). Work-up of the reaction mixture and HPLC separation[9] allowed recovery of 31% of **1** and afforded potassium dicyano-5′,6′-dimethylbenzimidazolyl-5,6-dioxo-5,6-secocobamide **5a** (10%) and its regioisomer **5b** (24%). The structures of the noncrystalline photooxygenolysis products **5a** and **5b** result from comparison of their UV/VIS, CD, IR,

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Scheme 1. **1**→**2** methanolysis [4]; **2**→**3a**+**3b**: photooxygenolysis [5]; **1**→**4**: see text; **4**→**5a**+**5b**: photooxygenolysis [9]; **5a**→**3a** and **5b**→**3b**: methanolysis [10].

^{1}H-, and ^{13}C-NMR, as well as of their FAB-MS spectra with those of **3a**[5,6] and of **3b**[5] (see Table 1). Moreover, upon acid-catalyzed methanolysis[10] **5a** is converted into **3a** and **5b** into **3b**. The characteristic regioselectivity and the ratio of **5a** : **5b** ≈ 0.4 : 1 can be interpreted as the outcome of electrophilic attack of $^1O_2$[8] that occurs to a similar extent at the *meso*-positions C-5 and C-15 of the corrin ligand (in comparison: photooxygenation of **2** afforded **3a** : **3b** ≈ 2 : 1[5]).

Table 1. Selected spectroscopic data for **5a** and **5b**.

5a, M.p. > 205 °C (decomp.)

UV/VIS [a]: λ_{max} (logε) = 278 (4.08), 288 (4.07), 324 (3.92), 360 sh (3.46), 477 (3.88) nm

CD [a]: λ_{max} ($\Delta\varepsilon$) = 269 (−9.9), 296 sh (3.1), 328 (25.9), 356 sh (12.1), 421 (−19.6), 466 (−22.4), 550 (6.3) nm; λ_0 at 289, 378, 522 nm

IR [b]: ν = 2130 (w), 1715 (m), 1665 (s), 1620 (s), 1555 (m), 1495 (m), 1455 (m), 1400 (s), 1225 (m), 1185 (m) cm^{-1}, etc.

^{1}H-NMR [c]: δ = 0.97, 1.19 (2s, 6H); 1.25 (d, J = 6, 3H); 1.28, 1.36, 1.39, 1.75, 2.24, 2.44, 2.46, 2.69 (8s); overlapped by 1.4—2.8 (m), in total ca. 61H; 3.01 (m, 1H), 3.15 (m, 2H), 3.3 (m, 2H), 3.7–4.0 (m, 4H), 4.36 (m, 1H), 4.54–4.9 (m, ca. 2H); 4.97 (t, J = 5, 1H); 5.90 (s, 1H); 6.60 (d, J = 5, 1H); 7.64, 7.68, 9.19 (3s, 3H)

^{13}C-NMR [d]: δ = 17.7, 19.0, 20.3, 20.6 (4q); 21.3 (q, double intensity); 22.0, 22.4, 22.7 (3q); 24.7, 26.9, 28.7 (3t); 29.5, 31.9 (2q); 34.4, 34.6, 35.2, 36.1, 36.7, 37.2 (6t); 42.4 (d); 44.2, 44.6, 47.5 (3t); 49.6, 51.0, 51.8 (3s); 55.2, 56.3, 61.8 (3d); 61.9 (s); 63.9 (t); 74.3, 74.8, 77.4, 77.5, 88.5, 89.9 (6d); 90.2 (s); 98.6 (d); 112.9 (s); 115.4, 117.1 (2d); 131.8, 132.3, 138.8, 139.6, 139.8 (5s); 141.3 (d); 142.2, 163.7 (2s); 177.5 (s, double intensity), 178.2, 178.6 (2s); 180.3 (s, double intensity); 180.7 (s); 180.9 (s, double intensity); 186.3, 190.1, 191.7, 200.8 (4s)

FAB-MS [e]: m/z 1414 (71, $[M+2-K]^{\oplus}$); 1387 (100, $[M+1]^{\oplus}$ − KCN); 1361 (95, $[M+1]^{\oplus}$ − KCN − CN); 1095 (12, $[M+1]^{\oplus}$ − KCN − CN − ring A); etc.

5b, M.p. > 230 °C (decomp.)

UV/VIS [f]: λ_{max} (logε) = 278 (4.05), 288 (4.02), 325 (3.94), 360 sh (3.35), 477 (3.89), 555 sh (3.26) nm

CD [f]: λ_{max} ($\Delta\varepsilon$) = 273 (−6.2), 295 sh (2.2), 327 (37.8), 357 sh (10.9), 416 (−15.3), 478 (−29.5), 560 (6.9) nm; λ_0 at 288, 375, 529 nm

IR [b]: ν = 2130 (w), 1710 (m), 1665 (s), 1620 (s), 1565 (s), 1542 (s), 1498 (s), 1455 (m), 1403 (s), etc.

^{1}H-NMR [c]: δ = 1.23 (d, J = 6, 3H), 1.27, 1.29, 1.33, 1.38, 1.42, 1.62, 2.20, 2.44, 2.46, 2.72 (10s), overlapped by 1.5—2.8 (m), in total ca. 69H; 3.15 (dd, J_1 = 10; J_2 = 4, 1H); 3.26 (m, 2H); 3.8—4.0 (m, 3H); 4.27 (m, 1H); 4.5—4.9 (m, ca. 3H); 4.97 (t, J = 5, 1H); 5.91 (s, 1H); 6.59 (d, J = 5, 1H); 7.62, 7.68, 9.16 (3s, 3H)

^{13}C-NMR [d]: δ = 17.5, 18.6, 21.2, 21.6, 21.8 (5q); 22.2 (q, double intensity); 22.6 (q), 24.0 (t); 25.7 (q); 27.3 (t); 27.7 (q); 28.2, 34.0, 34.4 (3t); 34.6 (q), 35.1, 35.9, 36.3, 37.3 (4t); 40.2 (d); 44.6, 46.7, 47.4 (3t); 48.4, 49.7, 53.1 (3s); 54.0, 58.2, 59.2 (3d); 63.9 (t); 65.0 (s); 74.4, 74.6, 77.4, 84.2 (4d); 87.1 (s); 88.8, 89.7, 99.4 (3d); 111.9 (s); 115.2, 116.7 (2d); 131.5, 131.9, 139.3, 139.5 (4s); 140.2 (s); 140.9 (d); 142.8, 163.5 (2s); 176.9, 177.3, 177.8, 178.1, 179.9, 180.3, 180.4, 180.9, 181.4, 186.0, 189.7, 194.6, 201.5 (13s)

FAB-MS [e]: m/z 1414 (50 $[M+2-K]^{\oplus}$); 1387 (72 $[M+1]^{\oplus}$ − KCN); 1361 [100 $[M+1]^{\oplus}$ − KCN − CN); 710 (45 $[M+1]^{\oplus}$ − KCN − CN − (ring D + f-side-chain)); etc.

[a] c = 2.289 · 10^{-5} mol/L, CH_3OH, 0.02% HCN. [b] 1 mg/300 mg KBr. [c] 300 MHz, D_2O, δ(HDO) = 4.71, J in Hz. [d] 75 MHz, H_2O with 20% D_2O, $\delta(TSP)_{ext}$ = 0.0. [e] Glycerin-SeO_2 matrix, argon atmosphere, 8.4 keV; cation spectrum m/z [%]. [f] c = 1.413 · 10^{-5} mol/L, CH_3OH, 0.02% HCN.

The photooxygenolysis therefore points to the degradability of the corrin macrocycle of vitamin B_{12} by $^1O_2$ and opens a facile route to secocorrinoid cleavage products (of **1**), which may be of interest for the preparation of cobalt-free, natural corrins[6,11] and from the point of view of enzyme mechanisms[12].

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CAS Registry numbers:
1, 68-19-9; **5a**, 94110-41-5; **5b**, 94110-42-6.

[1] C. S. Foote in W. A. Pryor: *Free Radicals in Biology, Vol. 2*, Academic Press, New York 1976, 85, and references cited therein.

[2] See e.g. H. H. Wasserman, R. W. Murray: *Singlet Oxygen*, Academic Press, New York 1979.

[3] H. H. Wasserman, *Tetrahedron 37* (1981) 1825.

[4] L. Werthemann, Dissertation ETH Nr. 4097, Juris Druck + Verlag, Zürich 1968.

[5] B. Kräutler, *Helv. Chim. Acta 65* (1982) 1941.

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[7] The inertness of **1** is lifted by addition of $CN^{\ominus}$ (**1**→**4**) and is attributable to the lack of reactivity of its "cationic" *Coβ*-CN-Co^{III} corrin center in the photooxygenolysis (cf. footnote 14 in [5]) and perhaps, in addition, to geometrical restraints on the reaction by the intramolecularly coordinated nucleotide.

[8] Solvent-H/D isotope effects characteristic of $^1O_2$ reactions (cf. [5]).

[9] Procedure (for details of the photolysis experiment see [5]): **1** (90 mg), KCN (4.5 mg), and methylene blue (0.10 mg) in 2.5 mL CD_3OD, −70 °C (bath temperature) O_2 (1 atm): 45 min irradiation; warmed to RT, then concentrated; separation (HPLC: silica gel RP-8, 7 μm; $H_2O/CH_3CN/CH_3OH$ (9:2:1); detection at 510 nm; retention: **1**/**5b**/**5a** = 6.4/14.0/16.9 min); dried (RT, high vacuum, 3 d): 9.3 mg **5a**; 22.2 mg **5b**; in addition 28 mg **1** (crystallized from H_2O/acetone).

[10] CH_3OH/H_2SO_4 (4:1); 6 d, reflux, N_2 (for the esterification **1**→**2**, cf. [4]): **5a**→**3a** (15%); **5b**→**3b** (53%).

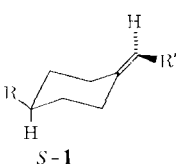
[11] N. J. Lewis, R. Nussberger, B. Kräutler, A. Eschenmoser, *Angew. Chem. 95* (1983) 744; *Angew. Chem. Int. Ed. Engl. 22* (1983) 736.

[12] See e.g. E. J. Corey, N. J. Copper, M. L. H. Green, *Proc. Natl. Acad. Sci. USA 74* (1977) 811.

Axial Chirality can lead to Chiral Smectic and Cholesteric Liquid Crystals**

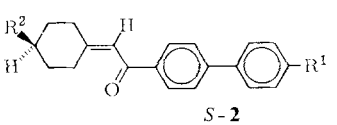
By *Guy Solladié** and *Richard G. Zimmermann*

Although the fact that optically active compounds can form mainly cholesteric liquid crystals has been known for some time[1], the chirality has always been introduced by way of one or more asymmetric centers, generally located in a terminal chain. In contrast, there are no reports of any attempts to synthesize optically active liquid crystal materials having molecular asymmetry[2], although such molecules could be of interest as dopants for nematic displays.



S-**1**

R′ = CO−R″



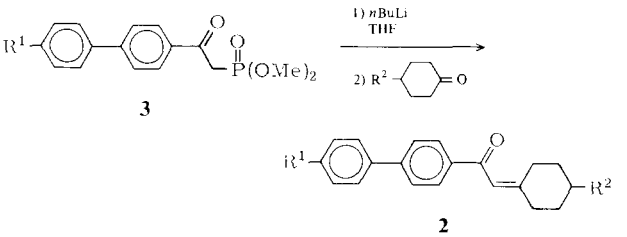
S-**2**

Here we report our results on the synthesis of optically active compounds with axial chirality. The axial chirality arises from the presence of the chiral cyclohexylidene ethanone unit **1** (R′ = CO−R″); the plane defined by C4, R, and H is perpendicular to the plane of the double bond substituents. Compounds **2** with suitable substituents R^1 and R^2 were shown to be chiral smectic or cholesteric liquid crystals (in some cases at room temperature).

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Racemic **2** was synthesized by Wittig-Horner condensation of β-oxophosphonates **3** with 4-substituted cyclohexanones (Scheme 1, Table 1).



3

2

Scheme 1. THF = tetrahydrofuran.

Table 1. Mesomorphic properties of racemic, substituted 1-biphenylyl-2-cyclohexylidene ethanones **2**.

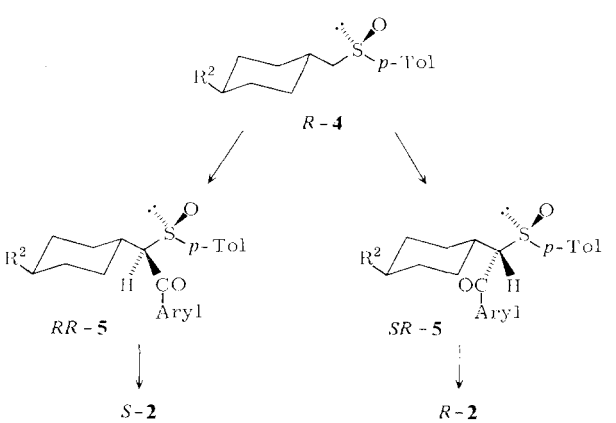
	R^1	R^2	Transition temp. [°C] [a]
2a	H	O−CO−*p*-C_6H_4−CN	c 131−133 i
2b	*n*-C_5H_{11}	H	c 67 i (56 a)
2c	*n*-C_5H_{11}	CH_3	c 53 s 71 i
2d	*n*-C_5H_{11}	*t*-Bu	c 118−120 i (80 a)
2e	*n*-C_5H_{11}	OCH_3	s_A 95 i
2f	*n*-C_5H_{11}	O-*n*-C_5H_{11}	s 80 i
2g	*n*-C_5H_{11}	CO_2Et	c 64 s_1 66 i (19 s_2)
2h	*n*-C_5H_{11}	O−CO−*p*-C_6H_4−CN	c 128 i (110 n)
2i	*n*-C_5H_{11}	O−CO−*p*-C_6H_4−Cl	c 125 i (97 n 77 s_A)

[a] c = crystalline, i = isotropic, n = nematic, s, s_1, s_2 = unidentified phases, s_A = smectic A, a = unidentified anisotropic phase.

As shown in Table 1, most of these compounds exhibit monotropic mesophases which are generally smectic. Compounds **2e** and **2f** are notable because they do not crystallize but occur as smectic mesophases at room temperature and below. **2a** is the only compound which does not exhibit mesomorphic properties, probably because it has no pentyl chain (R^1) at the "aromatic end". In contrast, **2b**, which has no substituents R^2 at the "cyclohexyl end", has a monotropic mesophase.

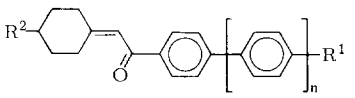
The optically active, substituted cyclohexylidene ethanones *R*-**2** and *S*-**2** were obtained by stereoselective acylation[3] of the sulfoxides *R*-**4**, followed by stereospecific elimination of the sulfoxide[4] (Scheme 2, Table 2).

From the results listed in Table 2 it can be concluded that the presence of a biphenyl moiety is necessary for formation of liquid crystals (compounds **6a** and **6b** are iso-



Scheme 2. *p*-Tol = *p*-Tolyl.

Table 2. Mesomorphic properties of optically active, substituted 1-phenyl- **6** and 1-biphenylyl-2-cyclohexylidene ethanones **2**.



6, n = 0
2, n = 1

	R^1	R^2	$[\alpha]_D^{20}$ [a]	Transition temp. [°C] [b]
(−)-*S*-**6a**	Cl	CH_2OEt	−3.0 (0.9)	oil
(+)-*R*-**6b**	CN	CH_2OEt	+4.8 (5)	c 46 i
(+)-*R*-**2j**	n-C_5H_{11}	n-C_5H_{11}	+1.0 (0.6)	c 44 s_A 105 i
(−)-*S*-**2k**	n-C_5H_{11}	CH_2OEt	−0.6 (0.6)	c 43 s 63 ch 67 i
(−)-*S*-**2l**	OCH_3	n-C_5H_{11}	−3.9 (0.2)	c 65 ch 124 i
(+)-*R*-**2m**	n-$C_8H_{17}O$	CH_2OEt	+2.5 (0.2)	c 102 s_A 123 i
(−)-*S*-**2n**	NC	n-C_5H_{11}	−4.4 (0.6)	c 102 s 113 ch 135 i

[a] In parentheses: conc. in acetone. [b] See Table 1, footnote [a]; ch = cholesteric.

tropic). Most of the compounds in Table 2 exhibit smectic phases. However, **2k** and **2n** also display a cholesteric phase, while **2l** shows only cholesteric properties. **2l** is also the first example of a cholesteric liquid crystal having axial chirality.

Although these substituted cyclohexylidene ethanones showed low light stability, which prevents their practical application, this study has demonstrated that molecules having axial chirality and in this case a 90° dihedral angle between the two parts of the molecule, can exhibit liquid crystalline properties.

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2a, 94110-63-1; **2b**, 94110-64-2; **2c**, 94110-65-3; **2d**, 94110-66-4; **2e**, 94110-67-5; **2f**, 94110-68-6; **2g**, 94136-09-1; **2h**, 94110-69-7; **2i**, 94110-70-0; (+)-*R*-**2j**, 94110-73-3; (−)-*S*-**2k**, 94110-74-4; (−)-*S*-**2l**, 94110-75-5; (+)-*R*-**2m**, 94136-15-9; (−)-*S*-**2n**, 94110-76-6; **3** (R′ = H), 51638-45-0; **3** (R′ = C_5H_{11}), 94110-77-7; *R*-**4** (R^2 = C_5H_{11}), 94110-80-2; *R*-**4** (R^2 = CH_2OEt), 94110-81-3; (−)-*S*-**6a**, 94110-71-1; (+)-*R*-**6b**, 94110-72-2; 4-(4-cyanobenzoyl)cyclohexanone, 94110-78-8; cyclohexanone, 108-94-1; 4-methylcyclohexanone, 589-92-4; 4-(1,1-dimethylethyl)cyclohexanone, 98-53-3; 4-methoxycyclohexanone, 13482-23-0; 4-pentyloxycyclohexanone, 82492-51-1; 4-ethoxycarbonylcyclohexanone, 17159-79-4; 4-(4-chlorobenzoyl)cyclohexanone, 94110-79-9.

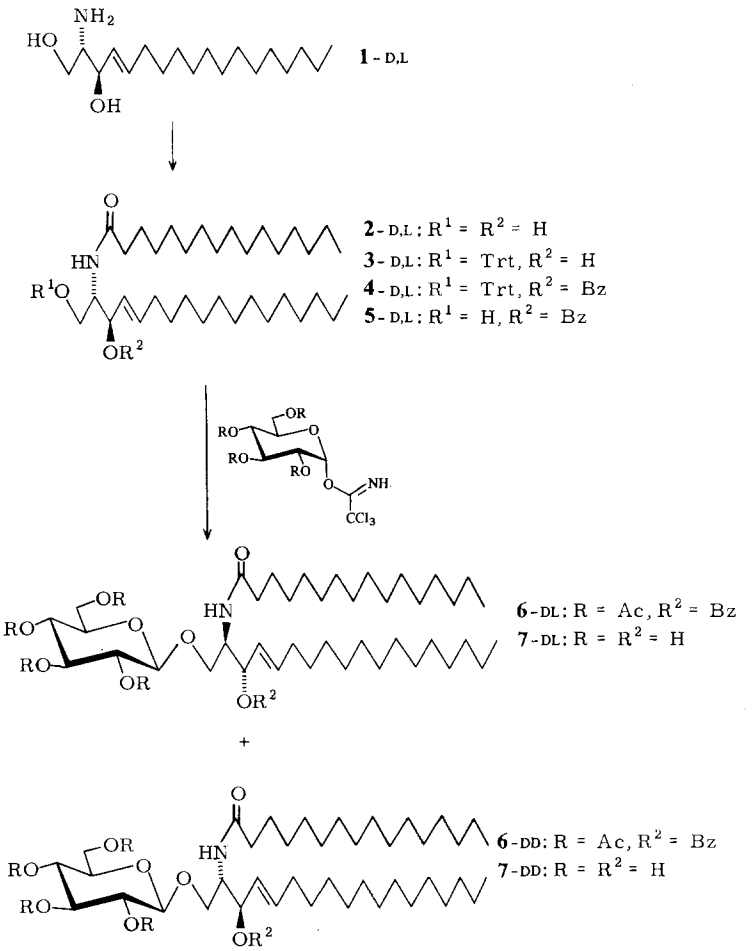
[1] H. Kelker, R. Katz: *Handbook of Liquid Crystals*, Verlag Chemie, 1980; G. Gray, P. A. Winsor: *Liquid Crystals and Plastic Crystals*, J. Wiley, New York 1974; G. Solladié, R. Zimmermann, *Angew. Chem.* 96 (1984) 335; *Angew. Chem. Int. Ed.* 23 (1984) 348.
[2] L. A. Karamysheva, T. A. Geivandova, K. V. Roitman, N. F. Ljukmanov, E. I. Kovshev, *Mol. Cryst. Liq. Cryst.* 99 (1983) 169. These authors described one example of a liquid crystalline compound containing a cyclohexylidene fragment, which, however, was only prepared as a racemic mixture.
[3] G. Solladié, *Synthesis 1981*, 185; G. Solladié, R. Zimmermann, R. Bartsch, *Tetrahedron Lett.* 24 (1983) 755.
[4] G. Solladié, R. Zimmermann, R. Bartsch, H. M. Walborsky, *Synthesis*, in press.

Short Synthesis of Cerebrosides**

By *Richard R. Schmidt** and *Rudolf Kläger*

Cerebrosides are major constituents of the membranes of brain cells. They are the simplest glycosphingolipids and serve as model substances for more complex lipids of this kind. Furthermore, they are credited with important properties as receptors for hormones, interferons, and toxins[1]. Herein we describe a short synthesis of natural D-*erythro*-configurated D-glucosylcerebroside[2].

We prepared D,L-C_{18}-sphingosine **1**-D,L using a method developed by us for the two-step synthesis of *erythro*-sphingosine[3]. In analogy to previously described methods[4], on reaction of **1** with palmitoyl chloride we obtained the D,L-ceramide **2**-D,L[5] (77%) and, on subsequent tritylation, the 1-*O*-tritylated compound **3**-D,L (60%). 3-*O*-Benzoylation with benzoyl chloride/pyridine (to **4**-D,L, 92%) and detritylation with $BF_3 \cdot OEt_2$ then afforded the 1-*O*-unprotected ceramide **5**-D,L (69%)[4,6].



Scheme 1. In the case of **1**-D,L, **2**-D,L, **3**-D,L, **4**-D,L, and **5**-D,L only the D-isomers are depicted. For catalysts for the reaction of **5**-D,L see text. Bz = benzoyl, Trt = trityl.

The best method for the glycosylation of **5**-D,L proved to be that developed by us, namely the trichloroacetimidate method[7], which, without optimization, afforded better yields than the cerebroside synthesis according to the Koenigs-Knorr method or the Helferich-Weis method[1,4,8]. Thus, with *O*-(2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl) trichloroacetimidate in dichloromethane at room temperature, using $BF_3 \cdot OEt_2$ or trimethylsilyl trifluoromethanesulfonate as catalyst, the diastereomeric D-glucocerebrosides **6**-D,D[6] and **6**-D,L[6] were obtained in 50—70% yield. Despite only small differences in elution behavior[9], the separation of the diastereomers could be realized by column chromatography. On treatment of **6**-DD and **6**-DL with so-

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dium methoxide/methanol, the *O*-unprotected cerebrosides **7**-D,D[6] and **7**-D,L[6] were formed quantitatively; both compounds are of interest for biological investigations[2].

For verification of the structure and for the direct synthesis of the natural cerebroside **7**-DD the racemate **3**-D,L was acylated at the 3-hydroxy group with L-*O*-acetylmandelic acid chloride in the presence of pyridine. The diastereomers thus obtained were separated chromatographically and converted into the enantiomeric ceramides **3**-D and **3**-L (total yield 70%) by treatment with sodium methoxide/methanol. These compounds afforded, as described above, the well-known ceramides **5**-D and **5**-L, respectively, which could be identified by comparison of their rotations[10]. Moreover, the natural isomer **5**-D was converted, via compound **6**-DD, into the cerebroside **7**-DD.

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CAS Registry numbers:
1-D,L, 2733-29-1; **2**-D,L, 52019-77-9; **3**-D,L, 94069-97-3; **3**-D, 94198-71-7; **3**-D (*L*-*O*-mandeloyl ester), 94070-00-5; **3**-L, 94132-55-5; **3**-L (*L*-*O*-mandeloyl ester), 94198-88-6; **4**-D,L, 94069-98-4; **5**-D,L, 71806-70-7; **5**-D, 4201-55-2; **5**-L, 4201-57-4; **6**-DD, 94069-99-5; **6**-DL, 94132-56-6; **7**-DD, 74365-77-8; **7**-DL, 94132-57-7; palmitoyl chloride, 112-67-4; *O*-(2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl)trichloroacetimidate, 74808-10-9; *L*-*O*-acetylmandeloyl chloride, 51019-44-4.

[1] P. Tkaczuk, R. Thornton, *J. Org. Chem. 46* (1981) 4393, and references cited therein.

[2] Syntheses of D-glucocerebroside with C_{18}-sphingosine from natural substances, still containing other sphingosines as impurities, or with D,L-*erythro*-C_{18}-sphingosine have been reported: E. Freire, *Biochemistry 19* (1980) 3662; T. Ariga, T. Murata, M. Oshima, M. Maezawa, T. Miyatake, *J. Lipid Res. 21* (1980) 879; R. Skarjune, E. Oldfield, *Biochemistry 21* (1982) 3154; A. E. Gal, P. G. Pentchov, J. M. Massey, R. O. Brady, *Proc. Natl. Acad. Sci. USA 76* (1979) 3083.

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[6] ^{1}H-NMR data (250 MHz, $CDCl_3$, TMS int.): **5**-D,L: 8.04 (m, 2H, benzoyl); 7.6 (m, 1H, benzoyl), 7.47 (m, 2H, benzoyl), 6.05 (d, 1H, NH, J=8.8 Hz), 5.86 (td, 1H, $-CH_2-CH=C$, J=14.7, J=6.7 Hz), 5.61 (dd, 1H, $-C=CH-CH$, J=14.7, J=7.6 Hz), 5.53 (m, 1H, $-CH-OBz$), 4.29 (m, 1H, $-CH-N$), 3.72 (m, 2H, $-CH_2-O$), 2.9 (br. s, 1H, OH), 2.2 (m, 2H, $CO-CH_2-$), 2.05 (m, 2H, $-CH_2-$), 1.7—1.15 (m, 48H, $-CH_2-$), 0.88 (m, 6H, $-CH_3$).—**6**-DD: 8.0 (m, 2H, benzoyl), 7.57 (m, 1H, benzoyl), 7.44 (m, 2H, benzoyl), 5.81 (m, 2H, NH, $CH_2-CH=C$), 5.42 (m, 2H, $C=CH-CH-OBz$), 5.15 (dd, 1H, H-4, J=7.5, J=7.5 Hz), 5.01 (m, 2H, H-3, H-2), 4.47 (m, 1H, $CH-N$), 3.39 (d, 1H, H-1, J=7.9 Hz), 4.23 (dd, 1H, H-6, J=12.2, J=4.9 Hz), 4.04 (dd, 1H, H-6′, J=12.2, J=2.1 Hz), 3.9 (dd, 1H, $-CH_2-O-$, J=9.8, J=3.05 Hz), 3.68 (m, 2H, $-CH_2-O$, H-5); 2.2—1.9 (m, 16H, $-CO-CH_3$, $-CO-CH_2-$; $-CH_2-$), 1.7—1.1 (m, 48H, $-CH_2-$), 0.86 (m, 6H, $-CH_3$).—**6**-DL: 8.04 (m, 2H, benzoyl), 7.57 (m, 1H, benzoyl), 7.46 (m, 2H, benzoyl), 5.85 (m, 1H, $CH_2-CH=C$), 5.75 (d, 1H, NH, J=8.2 Hz), 5.6—5.4 (m, 2H, $C=CH-CH-O-Bz$), 5.19 (dd, 1H, H-4, J=9.5, J=9.5 Hz), 5.05 (dd, 1H, H-3, J=9.5, J=9.5 Hz), 4.97 (dd, 1H, H-2, J=9, J=9 Hz), 4.47 (m, 2H, $-CH-N$, H-1, J=7.3 Hz), 4.2—3.9 (m, 3H), 3.65 (m, 2H), 2.2—1.95 (m, 16H, $CO-CH_3$, $CO-CH_2-$, $-CH_2-$), 1.7—1.2 (m, 48H, $-CH_2-$), 0.88 (m, 6H, $-CH_3$).—**7**-DD: 7.51 (d, 1H, NH, J=8.7 Hz), 5.52 (m, 1H, $-CH_2-CH=C$), 5.35 (dd, 1H, C=CH–, J=15.2, J=6.5 Hz), 5.03 (d, 1H, OH, J=4.3 Hz), 4.92 (m, 3H, OH), 4.5 (t, 1H, OH, J=4.9 Hz), 4.09 (d, 1H, H-1, J=8.2 Hz), 4.0—3.55 (m, 4H), 3.45 (m, 2H); 3.15—2.9 (m, 4H), 2.1—1.9 (m, 4H), 1.45 (m, 2H), 1.22 (m, 46H, $-CH_2-$), 0.85 (m, 6H, CH_3).—**7**-DL: 7.49 (d, 1H, NH, J=7.9 Hz), 5.51 (td, 1H, $-CH_2-CH=C$, J=13.4, J=6.1 Hz), 5.34 (dd, 1H, C=CH–, J=13.4, J=6.1 Hz), 4.93 (m, 4H, OH), 4.6 (m, 1H, OH), 4.13 (d, 1H, H-1, J=7.3 Hz), 3.98—3.29 (m, 6H), 3.2—2.88 (m, 4H), 2.12—1.88 (m, 4H, $CO-CH_2-$, $-CH_2-$), 1.44 (m, 2H, $-CH_2-$), 1.24 (m, 46H, $-CH_2-$), 0.88 (m, 6H, $-CH_3$).

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[8] D. Shapiro, A. J. Acher, *Chem. Phys. Lipids 22* (1978) 197; R. Gigg, *ibid. 26* (1980) 287, and references cited therein.

[9] Thin-layer chromatography (silica gel, toluene/acetone = 4 : 1) R_F, **6**-DD: 0.55, **6**-DL: 0.54; column chromatographic separation was achieved with silica gel "LiChroprep" Si 60, particle size 40—60 μm (Merck), eluent toluene/acetone 9 : 1.

[10] D. Shapiro, H. M. Flowers, *J. Am. Chem. Soc. 84* (1962) 1047.

Synthesis and Structure of $[(C_5H_5)_3M_3(CO)_6(\mu_3\text{-As})]$ (M = Mo, W), Transition-Metal-Stabilized Arsanetriyl Compounds**

By *Klaus Blechschmitt, Heike Pfisterer, Thomas Zahn,* and *Manfred L. Ziegler**

Reaction of the molybdenum complex **1** with As_4S_4 in toluene leads to formation of the compound **2** and the species **3a** and **4** containing Mo_2As_2 and $MoAs_3$ clusters, respectively[1]. The Mo_2As_2 moiety has also been detected in the cyclopentadienyl complex **3b**, R = H, by X-ray crystallography[2]. Hence, in the homologous series As_nMo_{4-n} (n = 0—4), the only member missing is $AsMo_3$. Compounds containing μ_3-As bridging atoms in transition-metal clusters have hitherto only been found in the iron- and cobalt-complexes **5**[3] and **6**[4], respectively. In these complexes the arsenic atom is in a trigonal-pyramidal environment[5].

$$[(C_5Me_5)_2Mo_2(CO)_4] \xrightarrow[\text{toluene}]{As_4S_4} [(C_5Me_5)_2Mo_2(\mu\text{-}As_2S)(\mu\text{-}S_2)] +$$

1 **2**

$$[(C_5R_5)_2Mo_2(CO)_4(\mu\text{-}As_2)] + [(C_5Me_5)Mo(CO)_2As_3]$$

3a R = Me **4**

$$[\{Fe(CO)_3\}_3(\mu_3\text{-}As)(\mu_3\text{-}As)] \quad [\{Co(CO)_3\}_3(\mu_3\text{-}As)]$$

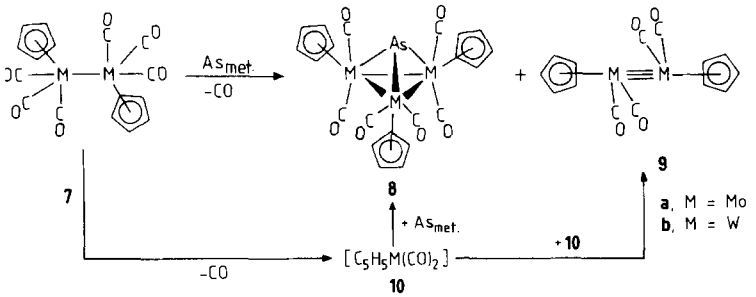
5 **6**

We have now been able to prepare the clusters **8a**, **b** from the binuclear complexes **7a**, **b** and metallic arsenic in a surprisingly simple reaction[6], and to unequivocally characterize them by elemental analysis, spectroscopic data[7], and, in the case of **8a**, by an X-ray structure analysis[8]. The simplicity of the method of preparation of these clusters containing Mo_3As and W_3As units is surprising, in particular since the arsanetriyl derivatives **5** and **6** are only accessible via the AsX_3 compounds (**5**: X = F, **6**: X = Cl, Br, I). On heating **7a**, **b** and As under reflux in *p*-xylene, **8a** and **8b** are formed in 65% and 40% yield, respectively (referred to **7a**, **b**), together with **9a**, **b** (≈15%). It can therefore be concluded that homolytic dissociation of **7** and elimination of CO leads to intermediate formation of **10a**, **b**, which then react further with arsenic to give the compounds **8** or dimerize to the species **9**[9].

According to the X-ray structure analysis, **8a** has a tetrahedrane structure (trigonal pyramidal). Since the absorption pattern in the ν_{CO} region of the IR spectrum of **8a** is identical with that of **8b**, it can be assumed that **8b** has an analogous structure. The Mo—As—Mo bond angles have a

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mean value of 75.87°, and are therefore distinctly larger than in As_4 and in **5** (67.87°)[3]. The Mo–As bonds have a mean length of 253.4 pm and are thus shorter than in **4** (266.1 pm) and in **3b** (262.0 pm).

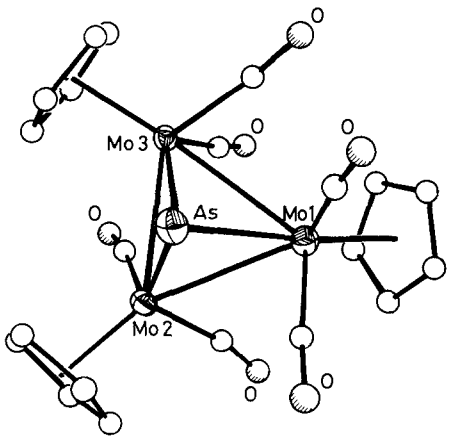
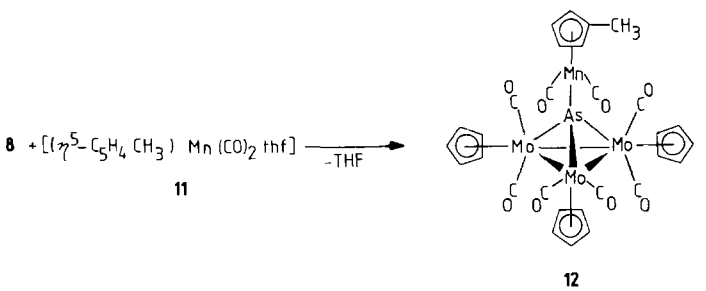


Fig. 1. Structure of **8a** in the crystal.

In compounds **8**, arsenic utilizes only three of its five valence electrons; therefore, electrophilic reactions at the arsenic atoms are to be expected. Accordingly, **8a** reacts with the substitution-labile THF-complex **11** (THF = tetrahydrofuran) with formation of the cluster **12**[10].



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7a, 12091-64-4; **7b**, 12091-65-5; **8a**, 93923-00-3; **8b**, 93923-01-4; **9a**, 56200-27-2; **9b**, 62853-03-6; **11**, 51922-84-0; **12**, 93923-02-5; **As**, 7440-38-2.

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[6] A solution of **7a** (1.5 g, 3.3 mmol) in *p*-xylene (50 mL) was treated with 2.6 g (34.6 mmol) metallic arsenic and the mixture stirred under reflux in a nitrogen atmosphere for 12 h. The green reaction solution was filtered, concentrated to 10 mL, and transferred onto a column (silica gel 0.05–0.2, length 40 cm, diameter 2 cm). A red zone (unreacted **7a**) and then a brown zone (**9a**) were eluted from the column with hexane/toluene (2:1). On subsequent elution with toluene/ether a green solution of **8a** was obtained, which, after removal of solvent and recrystallization from toluene/ether (1:1) at −18°C, furnished analytically pure, dark-green crystals (65% yield referred to **7a**). **8b** could be prepared analogously (yield 40% referred to **7b**). In the analogous reaction of $[(C_5H_5)_2Cr_2(CO)_6]$ with metallic arsenic, no identifiable products were formed.

[7] Spectroscopic data of **8a** and **8b**: IR (ν(CO) [cm^{-1}]): **8a**: 1972 st, 1933 vst, 1894 vst, 1878 w, 1864 st, 1847 st, 1804 w, 1784 st; **8b**: 1970 st, 1930 vst, 1897 vst, 1875 w, 1855 st, 1842 st, 1805 w, 1786 st. FD-MS (toluene): **8a**: *m/z* 726 ($M^{\oplus}$); EJ-MS (70 eV): *m/z* 726 ($M^{\oplus}$), 670 ($Mo_3As(CO)_4(C_5H_5)_3^{\oplus}$), 614 ($Mo_3As(CO)_3(C_5H_5)_3^{\oplus}$), 586 ($Mo_3As(CO)(C_5H_5)_3^{\oplus}$), 558 ($Mo_3As(C_5H_5)_3^{\oplus}$). ^{1}H-NMR (300 MHz, $CDCl_3$, 25°C, TMS): **8a**: $\delta = 5.07$ (s, 15H, C_5H_5), **8b**: $\delta = 5.12$ (s, 15H, C_5H_5). **8a**, and **8b**, which gave correct elemental analyses, are air-stable; recrystallization from toluene/ether (1:1) at −18°C, dark green (**8a**) and greenish yellow (**8b**) crystals; **8a**: m.p. 238–240°C; **8b**: m.p. 256–258°C; soluble in all common organic solvents except *n*-hexane.

[8] X-ray structure analysis of **8a**: $P2_1/c$, $a = 1402.8(3)$, $b = 751.3(2)$, $c = 2084.9(3)$ pm, $\beta = 91.76(2)°$. $R_{iso} = 0.082$, $R_w = 0.0405$. Most important bond lengths [pm] and angles [°]: As–Mo1 255.3(1), As–Mo2 254.0(1), As–Mo3 250.9(1), Mo1–Mo2 312.2(1), Mo1–Mo3 312.5(1), Mo2–Mo3 310.1(1); Mo1–As–Mo2 75.6(0), Mo1–As–Mo3 76.2(0), Mo2–As–Mo3 75.8(0). Further details of the crystal structure investigation are available on request from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2, on quoting the depository number CSD 51067, the names of the authors, and the journal citation.

[9] A comparable reaction is assumed to take place in the formation of **9a**, **b** and the heterodinuclear species $[(C_5H_5)_2MM'(CO)_4]$ (M = Mo, M' = W) from **7a**, **b**: M. D. Curtis, N. A. Fotinos, L. Messerle, A. P. Sattelberger, *Inorg. Chem. 22* (1983) 1559.

[10] **12**: Reddish brown crystals, soluble in ether, CH_2Cl_2; IR: ν(CO) [cm^{-1}] = 1980 vst, 1948 vst, 1925 vst, 1910 w, 1900 vst, 1890 st, 1872 vst, 1857 w, 1850 w; H-NMR (300 MHz, $CDCl_3$, 25°C, TMS): $\delta = 5.14$ (s, 15H, Mo–C_5H_5), 4.89, 4.47 (2s, 4H, Mn–$C_5H_4CH_3$), 1.96 (s, 3H, Mn–$C_5H_4CH_3$); m.p. 205°C.

c-TiS_2, a New Modification of Titanium Disulfide with Cubic Structure

By *Robert Schöllhorn** and *Andreas Payer*

Hexagonal titanium disulfide belongs to the group of transition-metal chalcogenides with layer structure and has been extensively studied with respect to correlations between structural anisotropy, physical properties, and chemical reactivity[1]. Moreover, the compound has found technical application as an electrode material for high energy-density secondary batteries[2]. We report here on the formation and basic properties of a new metastable modification of this compound with cubic structure.

Ternary thermal phases $A_xM_yX_z$ (A = alkali metal, Cu, Ag, Tl; M = transition metal; X = nonmetal) having appropriate structural and electronic properties and an ionic constituent A selectively mobile in the lattice at low temperatures can undergo topotactic redox reactions via electron/ion transfer to yield new binary phases M_yX_z[3]. The reactions described below are based on this mechanistic concept.

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The starting compound chosen was the copper thiospinel $CuTi_2S_4$ (cubic lattice parameter $a = 999.8$ pm), prepared at 1100 K from the elements[4]. We found that the $Cu^{\oplus}$ ions are mobile at ambient temperature and that the electronic properties of the system are consistent with the following redox reaction:

$$CuTi_2S_4 \rightleftharpoons Cu_xTi_2S_4 + (1-x)Cu^{\oplus} + (1-x)e^{\ominus}$$

The oxidation can be performed chemically in aqueous suspension with strong oxidants, e.g. $FeCl_3$; however, it was not possible to avoid contamination of the products by titanium hydroxide oxide formed at the surface of the crystallites under these conditions. Pure phases were obtained electrochemically on anodic galvanostatic or potentiostatic oxidation of pressed polycrystalline $CuTi_2S_4$ working electrodes in aprotic $Cu^{\oplus}$ electrolytes. The oxidation products belong to a nonstoichiometric series $Cu_xTi_2S_4$ and exhibit an almost linear correlation between the change in copper content x and the lattice parameter a (Fig. 1). The chemical diffusion coefficients $\tilde{D}$ for copper ions measured by the electrochemical potential step technique lie in the range 10^{-11} to 10^{-12} cm^2 s^{-1} at 300 K.

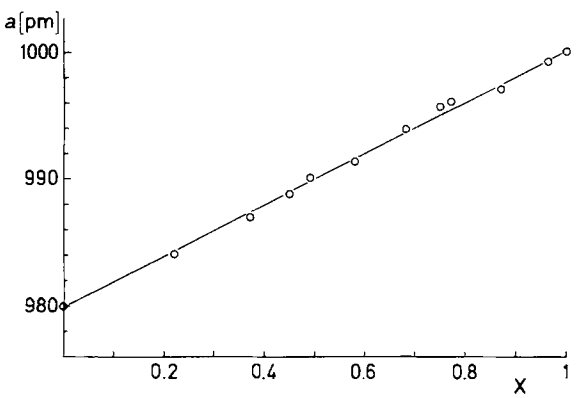


Fig. 1. Variation of the cubic lattice parameter a with the copper level x in $Cu_xTi_2S_4$ phases prepared by anodic oxidation of the thiospinel $CuTi_2S_4$ in $Cu^{\oplus}$ electrolytes at 300 K.

The phase range observed corresponds to $1 \geq x \geq 0$, and the pure cubic binary phase Ti_2S_4 or c-TiS_2 can thus be obtained. Analytical studies confirm this composition and the quantitative removal of copper. The lattice parameter is $a = 980.1$ pm, and the space group is Fm3m (Fd3m). The structure can be derived from a sodium chloride lattice in which half of the octahedral cation positions are vacant, i.e. $\square_{1/2}Ti_{1/2}S$. So far no single crystals of appropriate quality could be prepared, but the intensity calculation from the X-ray powder data ($R = 0.09$) confirms the structural model, which is also supported by the reversibility of the above reaction. The AB_2 structural type to which cubic titanium disulfide belongs has been observed so far only for a modification of MnO_2, prepared similarly via a ternary phase[5].

At temperatures above ca. 700 K, c-TiS_2 undergoes a phase transition to hexagonal TiS_2 with the lattice parameters $a = 339.2$, $c = 569.1$ pm. Both the change in symmetry and the decrease in unit cell volume (3%) suggest that c-TiS_2 is a metastable phase. Differential thermal analysis (DTA) studies indicate a rather small exothermic effect with a sluggish transformation over a large temperature range; this is most probably due to the kinetics of $Ti^{4\oplus}$ diffusion.

The thiospinel $CuTi_2S_4$ can formally be described as $Cu^{\oplus}[Ti^{3\oplus}Ti^{4\oplus}(S^{2\ominus})_4]$ and is a metal in terms of its electronic structure and transport properties[6]. Since c-TiS_2 is a d^0-system, it is expected to exhibit semiconductor properties. The data for polycrystalline samples show, however, that the electronic conductivity between 80—295 K is almost constant with a relatively high value of 60 Ω^{-1} cm^{-1}. Conclusions on the electronic nature of c-TiS_2 cannot therefore be derived from the present data; we draw attention to hexagonal TiS_2, which exhibits metallic properties, although the origin of the carriers is still under discussion[7].

At ambient temperature c-TiS_2 behaves as a framework host lattice for the intercalation of small atomic guest ions ($H^{\oplus}$, $Li^{\oplus}$, $Cu^{\oplus}$) via electron/ion transfer. Cathodic reduction of c-TiS_2 in $Cu^{\oplus}$ electrolytes, the reverse of the above reaction, affords the spinel $CuTi_2S_4$ with lattice parameters identical to those of the thermal phase. A maximum charge transfer of $3e^{\ominus}$/c-TiS_2 is observed upon electrochemical intercalation of lithium from a $LiClO_4$/propylene carbonate electrolyte. The partial molar free energy of reaction for the uptake of one equivalent of lithium ($Li + Ti_2S_4 \rightarrow LiTi_2S_4$) estimated from the potential/charge transfer is $\Delta G_R = -205$ kJ mol^{-1}. This is comparable to that for the formation of the corresponding phase $Li_{0.5}TiS_2$ from hexagonal TiS_2. Cubic titanium disulfide is thus of interest with respect to its use as an electrode material for secondary batteries; compared to layered hexagonal TiS_2 it offers the advantage that solvent co-intercalation on extended cycling is precluded by the framework structure.

A considerable number of other copper transition-metal chalcogenides CuM_2X_4 with the spinel structure have been described in the literature[8], and further studies are required to establish whether additional metastable binary compounds with the c-TiS_2 structure (e.g. cubic ZrS_2, VS_2, $CrSe_2$) can be obtained by this type of reaction. We also expect that the corresponding lithium chalcogenospinels will exhibit similar reactivity.

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Novel Aspects of the Coordination Chemistry of Phosphane**

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Phosphane, PH_3, is not generally regarded as a good ligand. It is a poor σ-donor, and the absence of electronega-

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tive ligands appears likely to make it a weak π-acceptor. Most of the known PH_3-complexes of transition metals are of the elements of the chromium triad[1]. Phosphane does not add oxidatively to $PtClH(PEt_3)_2$; instead, it displaces chloride ion at low temperatures[2], forming the cationic complex $[PtH(PEt_3)_2(P'H_3)]^{\oplus}$, which loses PH_3 and gives the starting material when warmed. We have recently discovered a richer coordination-chemistry of phosphane, involving both donor-acceptor complex formation and oxidative addition, in reactions with Ir^I substrates.

Phosphane adds oxidatively to *trans*-$[Ir(CO)X(PEt_3)_2]$ (X = Br or Cl) in toluene, forming a PH_2-complex of Ir^{III} with H *trans* to X.

$$[Ir(CO)X(PEt_3)_2] + PH_3 \longrightarrow [Ir(CO)XH(PEt_3)_2(P_c'H_2)]$$
1, X = Cl; **2**, X = Br

We have isolated **2** and the arsenic analogues of **1** and **2** (**1a** and **2a**, respectively) and characterized them by NMR spectroscopy (Table 1), their reactions, and the crystal

Table 1. Selected NMR parameters.

	δ(P)	δ(P_c')	δ(P_t')	δ(H_c)	$^1J(P_c'H)$ [Hz]	$^1J(P_t'H)$ [Hz]	T [K]
1 [a]	−13.5	−217.9	—	−18.4	172.4	—	298
1a [a]	−13.7	—	—	−18.4	—	—	298
2 [a]	−16.7	−219.3	—	−17.5	172.8	—	298
2a [a]	−17.5	—	—	−17.5	—	—	298
3 [b, c]	− 8.7	−190.3	—	—	ca. 350	—	183
4 [b]	−15.5	−224.6	−168.3	−10.6	177.2	374.0	233
5 [b]	−15.7	−159.0	−173.6	−10.8	431	405	200
6 [a]	−21.3	−218.2	−239.4	−11.1	176	164	298

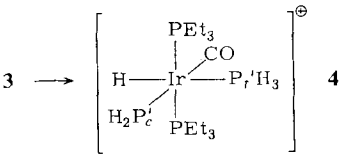
Standards: ^{1}H-NMR: Me_4Si; ^{31}P-NMR: 85% H_3PO_4. [a] toluene. [b] CD_2Cl_2. [c] $^2J(PP') = 36.9$, $^2J(P'P') = 80.3$ Hz.

structures of **1a** and of the $RuCl_2$(*p*-cymene) complex of **2**[3]. The reaction between $[Ir(CO)X(PEt_3)_2]$ and PH_3 in dichloromethane takes a different course. At 180 K the ^{31}P-{^{1}H} spectrum shows that the reaction is rapid, and the first product is a bis-PH_3 complex of pentacoordinated Ir.

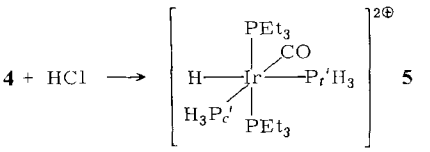
$$[Ir(CO)X(PEt_3)_2] + 2\,PH_3 \longrightarrow [Ir(CO)(PEt_3)_2(P'H_3)_2]^{\oplus}\ \mathbf{3}$$

This product is formed even in equimolar solutions, leaving excess of the Ir^I starting-material. **3** was characterized by NMR spectroscopy. The ^{31}P-{^{1}H} spectrum shows the presence of two equivalent PEt_3-groups and two equivalent $P'H_3$-groups; the presence of three hydrogen atoms bound to P′ is established from the proton non-decoupled spectrum, when a complex pattern is observed arising from the magnetic nonequivalence of the $P'H_3$-groups. Analysis of the second-order P′*H*-NMR spectrum gives $^2J(P'P') = 80.3$ Hz, a value much too large for a complex of hexacoordinated Ir^{III}, but appropriate for pentacoordinated Ir^I[4]. The same product is obtained when X = Cl and X = Br, showing that there is no halogen bound to Ir in **3**, and no noncondensible gas is evolved. **3** is unstable at temperatures above 230 K and undergoes internal oxidative addition to give an Ir^{III} complex cation **4** containing a $P'H_2$ and a $P'H_3$ ligand; the PH_3-phosphorus atom has $^2J(P'IrH) = 140.7$ Hz and is therefore *trans* to the H atom.

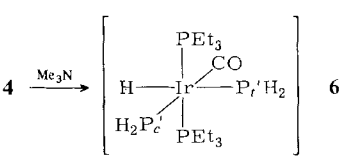
Cation **4** has been isolated as the chloride and characterized by its NMR spectra (which are particularly characteristic) and by its reactions with electron pair acceptors.



The ^{31}P- and ^{1}H-NMR spectra show clearly that there is no fast exchange of protons between $P_c'H_2$ and $P_t'H_3$; $^1J(P'H)$ is retained for both groups up to 273 K, and the two P′ resonances remain sharp and widely separated. **4** reacts with an excess of HCl to give the bis-(PH_3) dication **5**:



This reaction is reversible, and in the presence of an equimolar proportion of HCl the equilibrium shifts markedly with temperature. At 180 K ca. 90% of the iridium is present as the dication **5**; resonances in the ^{31}P-{^{1}H} spectrum arising from both **4** and **5** are sharp, and proton coupling can be observed in all P′ resonances. As the temperature is raised, the relative intensities of the resonances from **4** increase, and all the P′ resonances broaden and shift. Peaks arising from $P_c'H_2$ of **4** and $P_c'H_3$ of **5** move towards each other, as do those from $P_t'H_3$ of **4** and $P_t'H_3$ of **5**. When proton coupling is restored, $^1J(P'H)$ can be observed in the resonances from $P_t'H_3$ of **4** and $P_t'H_3$ of **5**, but not in the resonances from $P_c'H_2$ of **4** and $P_c'H_3$ of **5**. This shows that the broadening is due to proton exchange between $P_c'H_2$ of **4** and $P_c'H_3$ of **5**; there is no fast exchange of protons involving $P_t'H_3$ of **4** or $P_t'H_3$ of **5**. Exchange of P′ cannot be involved, since $^2J(PP')$ is retained for both **4** and **5** in the mixture. Free PH_3 cannot be involved either, since some is present in solution and its resonance remains sharp. As the temperature is raised still further, the resonances from $P_c'H_2$ of **4** and $P_c'H_3$ of **5** coalesce; with increasing temperature the coalesced peak then moves towards the position of the resonance from $P_c'H_2$ of **4**, showing that the position of equilibrium shifts to the left as the temperature rises, possibly because of the change in solubility of HCl with temperature. Above ca. 260 K, the complexes decompose, giving $[Ir(CO)ClH(PEt_3)_2(P'H_3)]^{\oplus}$ with H *trans* to the $P'H_3$ group.



We have also deprotonated **4** with Me_3N, and characterized the complex **6** formed, which contains two PH_2 ligands, from its NMR spectra and chemical reactions.

The ease with which Cl or Br is expelled from $[Ir(CO)X(PEt_3)_2]$ (X = Cl, Br) to form the bis-PH_3 cation of pentacoordinated Ir^I is surprising, as is also the marked dependance of the basicity of the coordinated PH_2-group upon the ligand *trans* to it. A coordinated PH_3-group is normally acidic; the absence of proton exchange between $P'H_2$ and $P'H_3$ in **4** is unexpected and clearly reflects a re-

duction in electron-donor properties of $P'H_2$ *trans* to CO as opposed to $P'H_2$ *trans* to H.

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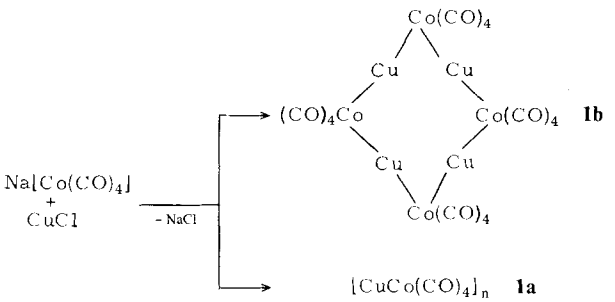
CAS Registry numbers:
1, 94090-24-1; **1a**, 94090-25-2; **2**, 94090-26-3; **2a**, 94090-27-4; **3**, 94090-28-5; **4** · Cl, 94090-29-6; **5**, 94090-30-9; **6**, 94090-31-0; $[Ir(CO)ClH(PEt_3)_2(P'H_3)]^{\oplus}$, 94090-32-1; $[Ir(CO)Cl(PEt_3)_2]$, 21209-85-8; $[Ir(CO)Br(PEt_3)_2]$, 78548-99-9.

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$[CuCo(CO)_4]_n$—Crystal Structure of a Polymer with a One-Dimensional, Infinite Copper-Cobalt Bonding System**

By *Peter Klüfers**

$CuCo(CO)_4$ crystallizes dimorphically. The tetrameric molecules **1b** with a Cu_4Co_4 eight-membered ring are the building blocks of one modification which forms orange-red crystals[1]. These are frequently accompanied by strongly distorted yellow platelets or needles of the same composition, which, according to an X-ray structure analysis, consist of the polymeric modification **1a**.



The existence of an infinite metal atom chain in a carbonylheterometal, established here for the first time by a single crystal investigation, has frequently been the subject of controversy for compounds of the type $MFe(CO)_4$ (M = Zn, Cd, Hg). Based on the results of the structure analysis on $[CdFe(CO)_4]_4[(CH_3)_2CO]_2$, oligomeric building units are assumed for this class of compounds[3].

The Cu–Co chains in **1a** are constructed from a slightly bent backbone of copper atoms, in which every two Cu atoms are bridged by a $Co(CO)_4$ group to form Cu–Co bonds. This results in a [010] wavy zig-zag chain of metal atoms along [001] (Figs. 1 and 2). The center of gravity of each of the pairs of copper atoms lies approximately on a twofold axis of a $Co(CO)_4$-tetrahedron. The edge of the tetrahedron which is directed towards the Cu_2-fragment is markedly lengthened (Table 1, Fig. 2).

Apart from an almost linear environment of the Cu atoms in **1a**, the geometry of the $Cu_{2/2}Co(CO)_4$ building blocks is almost the same as in **1b**; furthermore, both modifications have approximately the same spatial requirements (Table 1).

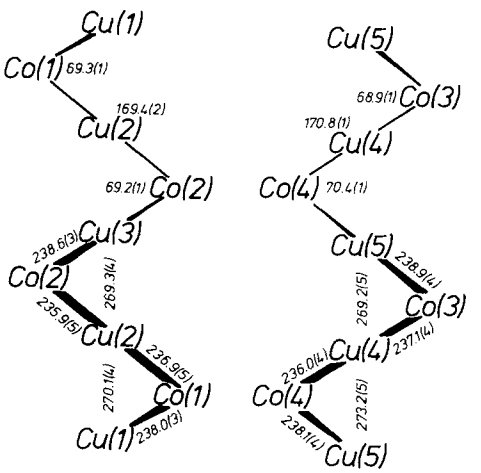


Fig. 1. Distances [pm] (below) and angles [°] (above) in the two symmetrically independent metal atom chains in **1a**. Projection along [010]. Left: chain at $y \approx 0$; Cu1 and Cu3 in the centrosymmetric position. Right: $y \approx 1/4$, all atoms in the general position. Cu–Cu–Cu angle at Cu2 147.6(1), Cu4 145.7(1), Cu5 176.1(1).

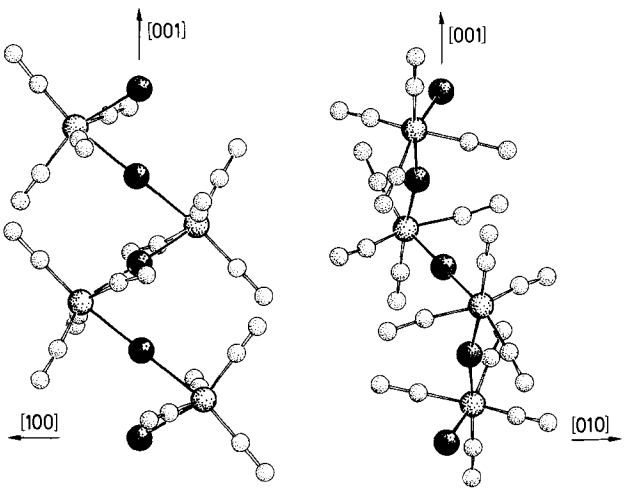


Fig. 2. Structure of the carbonylmetal chain at $y \approx 0$ in the crystal. The geometry of the chain at $y \approx 1/4$ is only slightly different. Left: Projection along [010] as in Figure 1—zig-zag chain along [001]. Right: chain rotated counterclockwise—waves of the zig-zag chain in [010].

Table 1. Mean atomic distances [pm] and bond angles [°] in **1a** and **1b**; V/Z = volume of a $CuCo(CO)_4$ moiety [10^6 pm^3].

	1a	**1b**
V/Z	168.4	169.3
Cu–Co	237.4	236.5
Cu···Cu	270.5	271.7
$(C–Co–C)_{max}$	138.0	136.7
Cu–Co–Cu	69.5	70.1
Co–Cu–Co	174.9	162.8

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The mechanical properties of **1a** are dominated by the orientation of the metal atom chains: the strongly distorted crystals—the needles are often bent—do not cleave perpendicular to [001], but rather separate into fibers. The appearance of the lemon-yellow, water-clear crystals gives no indication of charge delocalization along the metal atom chains. Here, the usefulness of the simplifying concept which regards carbonylmetalate (1−) ions as large, nucleophilic pseudohalide ions becomes apparent[4].

After $[AgCo(CO)_4]_4$[5] (isotypic with WOF_4[6a]), **1a** is a further example of a structural relationship between carbonylmetal compounds and fluorides: polymeric structures with similar geometry have been described for $MoOF_4$ **2**[6b] ($a_{1a}=c_2$, $b_{1a}=b_2$, $c_{1a}=2a_2$).

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[2] **1a**: $P2_1/c$, $Z=16$ $CuCo(CO)_4$, $a=936.9(3)$, $b=2775.2(7)$, $c=1036.0(5)$ pm; $\beta=90.40\ (5)°$, $\rho_{calc.}=2.313\ g\cdot cm^{-3}$; crystalline platelets from toluene/pentane, $Mo_{K\alpha}(\omega-2/3\vartheta)$ scan (Enraf-Nonius CAD4), $\pm h+k\pm l$, $1°\le\vartheta\le27°$, 11563 reflections, 5861 symmetry-independent, $R_i=0.033$ after absorption correction (crystal described by 8 faces); 2139 reflections with $|F|\ge6\sigma(F)$, SHELX, heavy atoms anisotropically, C and O isotropically, 205 parameters, $R=0.099$, $R_w=0.050$; maximal residual electron density $1.18\,e/10^6\,pm^3$. Further details on the crystal structure investigation can be obtained from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2, by quoting the depository number CSD 51111, the name of the author, and the journal citation.

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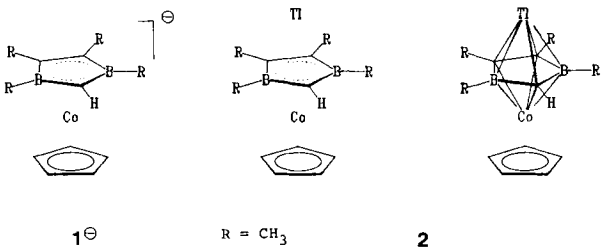
Synthesis and Structure of a Thallium Complex with an Anionic Sandwich Complex Ligand**

By *Klaus Stumpf, Hans Pritzkow,* and *Walter Siebert**

Dedicated to Professor Gerhard Fritz on the occasion of his 65th birthday

In the solid state, cyclopentadienylthallium is ionic and occurs as a zig-zag chain, but in solution and in the gas phase is a mononuclear molecular unit[1]. SCF-MO calculations[2] support the proposed predominantly covalent Tl–C bond[3]. From the isolobal analogy between $C_5H_5^\ominus$ and the heterocycle side of the sandwich complex ion $\mathbf{1}^\ominus$, a thallium compound [**1**·Tl] is expected, whose structure should, however, differ from that of $[Tl(C_5H_5)]$. We report here the first sandwich complex with an apical thallium atom **2**, which can also be described as a hepta-atomic *closo*-structure.

Reaction of the neutral complex (η^5-cyclopentadienyl)(η^5-1,3,4,5-tetramethyl-2,3-dihydro-1*H*-1,3-diborolyl)-cobalt [**1**·H][4] with $[Tl(C_5H_5)]$ in refluxing tetrahydrofuran (THF) affords orange-brown, crystalline **2** in 61% yield[5]. In solution the complex, which is readily soluble in nonpolar solvents, is rapidly decomposed by air, but in the solid



$\mathbf{1}^\ominus$ R = CH_3 **2**

state is stable for some time. Upon sublimation **2** partially decomposes to form $[Tl(C_5H_5)]$. In the mass spectrum (EI) the $M^\oplus$ ion appears in low relative intensity (m/z 448; 13%), and $(M-Tl)^\oplus$ forms the base peak. The ^{1}H-NMR spectrum[5], like that of $[Tl(C_5H_5)]$[6], exhibits no ^{205}Tl-^1H coupling. In the ^{11}B-NMR spectrum (C_6D_6, $\delta=20.4$) the boron atoms are strongly shielded, as in triple-decker sandwich complexes[7].

The X-ray structure analysis[8] indicates that in the crystal **2** occurs as discrete molecules and differs from the polymeric zig-zag chain structure of $[Tl(C_5H_5)]$. The distances between thallium and the atoms of neighboring molecules (>3.6 Å) preclude further interactions. The molecule lies on a mirror plane through Co, Tl, C2, and C6, and the distances of the metal atoms to the plane through the almost planar rings (deviations $\le\pm0.02$ Å) are (C_5H_5)–Co 1.67 Å, (C_2B_2C)–Co 1.60 Å, and (C_2B_2C)–Tl 2.47 Å [(C_2B_2C): heterocycle]. The geometry of the $[(C_5H_5)Co(C_2B_2C)]$ moiety hardly differs from that of the triple-decker sandwich complexes $[(C_5H_5)Co(C_2B_2C)M(C_5H_5)]$ (M = Fe, Ni)[7] (Figs. 1 and 2).

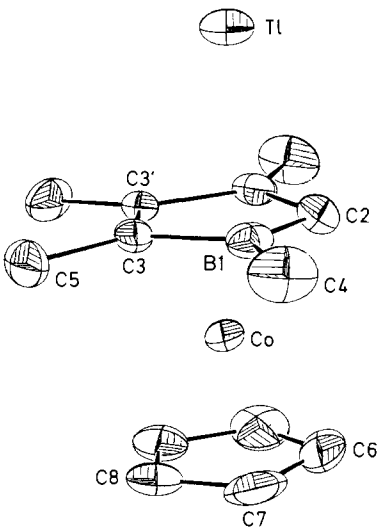


Fig. 1. Structure of **2** in the crystal. Selected bond lengths [Å]: Tl–B1 2.771(8), Tl–C2 2.700(11), Tl–C3 2.892(6), Co–B1 2.101(8), Co–C2 2.035(9), Co–C3 2.034(7), B1–C2 1.527(10), B1–C3 1.574(10), C3–C3' 1.450(13).

The thallium atom does not lie exactly over the centroid of the C_2B_2C ring, but is displaced by 0.24 Å in the direction of C2, the site of highest charge density in $\mathbf{1}^\ominus$. Thallium assumes a similar position over the C_2B_3-opening in the complex $[(C_6H_5)_3P{-}CH_3]^\oplus[3,1,2\text{-}TlC_2B_9H_{11}]^\ominus$[9] (Tl–($C_2B_3$) 2.39 Å; Tl shifted towards B8 by 0.34 Å). The

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borinato derivatives $[Tl(C_5H_5BR)]$ ($R=CH_3$, C_6H_5) have similar properties to $[Tl(C_5H_5)]$. One therefore expects that they should have similar structures[10]. Compared to the 6e-ligands $C_5H_5^{\ominus}$ and $C_5H_5BR^{\ominus}$, the heterocyclic anion in **1** exhibits stronger acceptor functions which in the solid state prevent dissociation into ions.

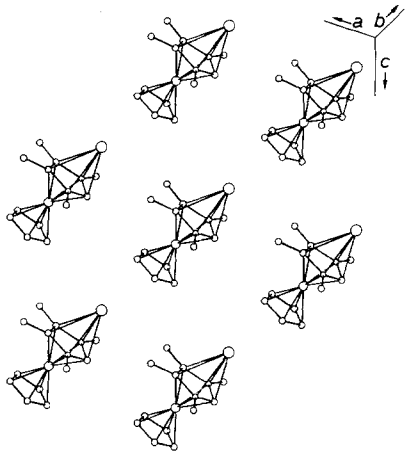


Fig. 2. Section of the crystal structure.

We view **2** as a cluster with the 16 skeletal electrons necessary for the stabilization of the hepta-atomic *closo*-structure[11] being provided by the framework atoms carbon ($3\times 3e$), boron ($2\times 2e$), cobalt (2e), and thallium (1e).

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CAS Registry numbers:
1·H, 93842-61-6; **2**, 93842-62-7; $Tl(C_5H_5)$, 34822-90-7.

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[5] Procedure for **2**: $[Tl(C_5H_5)]$ (300 mg, 1.10 mmol) and 1·H (180 mg, 0.73 mmol) are refluxed in 30 mL THF for 1 h. Excess $[Tl(C_5H_5)]$ is decanted off, the THF removed, and the residue taken up in hexane and filtered through a G3 frit. After removal of hexane, the residue is sublimed at $80-90\,^{\circ}C/10^{-2}$ torr. 240 mg of crude product is obtained, which after recrystallization from hexane affords orange-brown crystals (200 mg, 61%; m.p. = 145 °C, C,H-analysis); ^{1}H-NMR (300 MHz, C_6D_6): $\delta=4.21$ (s, 5H), 3.01 (s, 1H), 1.93 (s, 6H), 0.92 (s, 6H).
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$(C_6H_5Sb)_6\cdot$(1,4-Dioxane), the First Cyclohexastibane**

By *Hans Joachim Breunig**, *Karl Häberle*, *Martin Dräger*, and *Tevfik Severengiz*

Monocyclic organostibanes $(RSb)_n$ have previously been prepared as three-, four-, and five-membered ring compounds with bulky organic substituents $R=t$-C_4H_9, $(Me_3Si)_2CH$[1]. In contrast, various attempts to synthesize a phenylstibane $(C_6H_5Sb)_n$ have led to formation of high-polymer black solids[2,3]. Only one yellow crystalline compound whose properties are consistent with those of a cyclostibane has been reported. The proposed structure, $(C_6H_5Sb)_6\cdot C_6H_6$, could, however, only be substantiated by elemental analysis[4].

We now report the synthesis and X-ray structure analysis of hexaphenylcyclohexastibane·(1,4-dioxane) **1**, which crystallizes directly as yellow needles when the reaction solution produced by mixing $C_6H_5Sb(SiMe_3)_2$ and 1,4-dioxane is slowly oxidized in air[5]. As easily detectable by its ^{1}H-NMR signal at $\delta=0.1$, hexamethyldisiloxane also readily forms in the reaction mixture, and hence the overall reaction can be described by the following equation

$$6\,C_6H_5Sb(SiMe_3)_2 + 3\,O_2 + 1,4\text{-}C_4H_8O_2 \longrightarrow (C_6H_5Sb)_6\cdot(1,4\text{-}C_4H_8O_2) + 6\,(Me_3Si)_2O$$
1

The novel cyclostibane has several unusual properties. As indicated by its synthesis in the solid state, the compound is remarkably inert towards O_2. In contrast, solutions of **1**, which is slightly soluble in $CHCl_3$ and toluene, react very rapidly with air to afford colorless solids. Conversion into a black-brown solid—presumably the polymeric "phenylantimony"—occurs upon warming and subsequent cooling of solutions of **1** in toluene. Both for this reason and because of the low solubility of **1** at room temperature, the size of the ring could not be determined by M_r-determinations in solution. EI mass spectroscopy[6] was also unable to provide identifying evidence, since the significant signals that appear at oven temperatures of ca. 200 °C and above originate from fragment ions such as $(C_6H_5Sb)_4^{\oplus}$ and $(C_6H_5Sb)_3^{\oplus}$ and from rearrangement products such as $(C_6H_5)_5Sb_3^{\oplus}$. Signals from dioxane occur at 100 °C. In the FD mass spectrum only oxidation products could be observed. Above 200 cm^{-1} the IR spectrum of **1** exhibits absorptions typical of C_6H_5Sb moieties and dioxane. Signals from dioxane can also be detected in the ^{1}H-NMR spectrum ($CDCl_3$), where their position is not influenced by the $(C_6H_5Sb)_6$ ring. In solution, therefore, a strong interaction is not expected. Broad multiplet signals from the phenyl protons appear in the region expected.

In order to obtain unequivocal evidence for the molecular structure and to clarify the role played by the dioxane in stabilizing the $(C_6H_5Sb)_6$ ring against oxidation and chain formation, a crystal structure analysis of **1**[7] was performed. This indicates the presence of isolated centrosymmetric $(C_6H_5Sb)_6$ molecules (Fig. 1) in which the Sb_6 rings adopt a chair conformation and the phenyl groups are equato-

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rial (overall symmetry, approximately D_{3d}). The Sb_6-chair is considerably steeper than in the analogous $[(C_6H_5)_2Sn]_6$[8] and the Sb–Sb distances (284 pm) are in accord with those in distibanes (283–287 pm[9]). No specific interactions occur between the dioxane molecules and Sb atoms; in the crystal, dioxane is present with van der Waals contacts to the phenyl groups and a mutual 8:8-coordination between $(C_6H_5Sb)_6$ and dioxane.

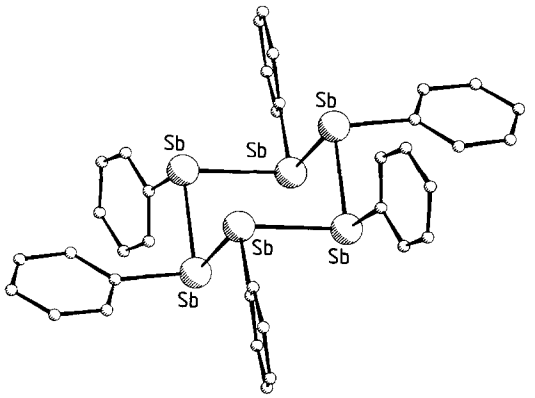


Fig. 1. Structure of the centrosymmetric $(C_6H_5Sb)_6$ molecule in crystals of **1**. Distances: Sb–Sb 283.6–283.9(1), Sb–C 216–217(1) pm. Bond angles: Sb–Sb–Sb 86.8–93.6(1), Sb–Sb–C 92.8–99.7(3)°. Torsion angles: SbSb–SbSb 86.4–93.2(1), SbSb–C_6H_5 166.9–179.7(3)° [7].

At first sight, the mode of formation of **1** is surprising since Sb–Sb bonds are usually reductively coupled. Similar behavior has recently been observed for $(Me_3Sn)_3Sb$, which is oxidized in air to $(Me_3Sn)_2O$ and $(Me_3Sn)_2Sb–Sb(SnMe_3)_2$[10].

If the oxidation of $C_6H_5Sb(SiMe_3)_2$ is conducted in benzene instead of dioxane, orange-yellow crystals of composition $(C_6H_5Sb)_6 \cdot C_6H_6$ **2** are formed, the structure of which has also been corroborated by full elemental analysis[11].

C_6H_5Sb moieties and crystal benzene can also be detected in **2** by IR and ^{1}H-NMR spectroscopy: In its properties **2** is similar to the "phenylantimony" described by *Issleib* and *Balszuweit*[4]. We therefore presume that they are one and the same compound.

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[5] Procedure: $C_6H_5Sb(SiMe_3)_2$ (200 mg) is dissolved in 1,4-dioxane filled to half the depth of a glass tube (length 180 mm, diam. 5 mm). The tube is sealed with a plug so that it is not quite airtight and stored for 7 d at room temperature. The reaction solution initially becomes colored, and after a few days needles form in the tube; these are first outwardly black-brown and then become yellow. These crystals of **1** are filtered off, washed with dioxane, and dried in vacuo. Yield 20 mg (16%), correct elemental analysis.

[6] MS (30 eV, 230°C) relative to ^{121}Sb, observed isotopic pattern corresponds to the calculated: *m/z* (relative intensity) 792 (1, $(C_6H_5)_4Sb_4^{\oplus}$), 748 (2, $(C_6H_5)_5Sb_3^{\oplus}$), 715 (2, $(C_6H_5)_3Sb_4^{\oplus}$), 594 (10, $(C_6H_5)_3Sb_3^{\oplus}$), 550 (10, $(C_6H_5)_4Sb_4^{\oplus}$), 484 (8, $Sb_4^{\oplus}$), 319 (1, $C_6H_5Sb_2^{\oplus}$), 275 (30), 198 (60), 154 (100). 30 eV, 100°C: 88 (70, $C_4H_8O_2^{\oplus}$), 58 (80), 28 (100).

[7] Crystal structure analysis of **1**: $P2_1/c$, $a = 576.2(1)$, $b = 2189.9(4)$, $c = 1661.3(2)$ pm, $\beta = 99.45(2)°$, $V = 2068 \times 10^6$ pm^3, $Z = 2$, $\rho_{calc} = 2.06$, $\rho_{exp} = 2.04$ g cm^{-3}, $\mu(Mo_{K\alpha}) = 39.0$ cm^{-1}. CAD4-diffractometer: 5120 reflections, 2795 of which with $I > 2\sigma(I)$, 207 variables, $R = 0.042$, $R_w = 0.058$, no H atoms. In part, dioxane disordered: two different positions for the O. Further details of the crystal structure analysis can be obtained from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2, by quoting the depository number CSD 51148, the names of the authors, and the journal citation.

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[11] Procedure: $C_6H_5Sb(SiMe_3)_2$ (500 mg) is allowed to react with air as described above. After 10 d the crystals formed are filtered off, washed with C_6H_6, and dried in vacuo. Yield of **2**: 60 mg (20%). Correct C, H, Sb elemental analysis.

A Novel Rearrangement in $(R_2S\cdot\cdot SR_2)^{\oplus}$-Radical Cations with a 3e-Bond

By *Roland Goslich, Joachim Weiss, Hermann J. Möckel, Jörg Mönig,* and *Klaus-Dieter Asmus**

Dedicated to Professor Dietrich Schulte-Frohlinde on the occasion of his 60th birthday

Radical cations derived from aliphatic sulfides $R_2S^{\odot\oplus}$ show a marked tendency to stabilize themselves by reacting with a second sulfide molecule R_2S[1,2] via the equilibrium

$$R_2S^{\odot\oplus} + R_2S \rightleftharpoons (R_2S\cdot\cdot SR_2)^{\oplus}$$

The "dimeric" radical cation thus formed is characterized by a 3e-bond (two σ-electrons and one σ*-electron)[3]. Pulse radiolytic[1–5] and ESR-spectroscopic studies[6,7] have provided some information about the reactivity of these radical cations and some radicals derived from them. The development of sensitive methods for determination of organic sulfur compounds[8,9] has now enabled us to undertake qualitative and quantitative product analysis. In the course of investigations on the radical-induced oxidative degradation of some aliphatic sulfides, we have discovered a remarkable rearrangement, which we report here.

The 1e-oxidation of aliphatic sulfides in aqueous solution was carried out using $^{\odot}OH$ radicals, generated by γ-irradiation of N_2O-saturated aqueous solutions. End products were identified and determined by capillary GC-MS.

The main products of the oxidation of dimethyl sulfide (Me_2S) are found to be 1,2-bis(methylthio)ethane (1,2-BMTE) and diethyl disulfide (EtSSEt). The yields are independent of pH between pH 3 and pH 10, but exhibit a marked inverse dependence on the Me_2S concentration (Fig. 1). 1,2-BMTE is the main product at low Me_2S concentrations and its yield decreases with increasing Me_2S concentration. The yield of EtSSEt, however, increases drastically only at concentrations above 0.01 mol dm^{-3} Me_2S. The formation of 1,2-BMTE is attributed to the reaction

$$2\,\overset{\odot}{C}H_2SCH_3 \longrightarrow CH_3SCH_2CH_2SCH_3$$

i.e. combination of two radicals formed from deprotonation of molecular radical cations. Addition of phosphate

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ions to the system doubles the yield of 1,2-BMTE, since deprotonation of the radical cation is favored at the expense of competing reactions. Oxygen (2.8×10^{-4} mol dm^{-3}, corresponding to air saturation), which scavenges $^{\ominus}CH_2SCH_3$ in a fast reaction, completely suppresses formation of 1,2-BMTE.

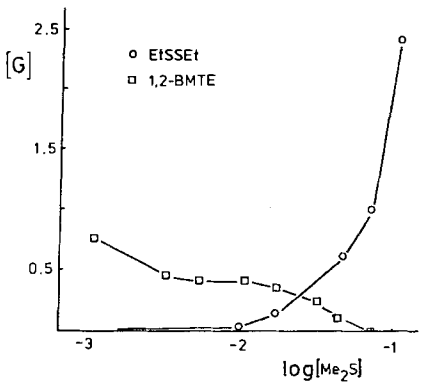


Fig. 1. Yields of 1,2-BMTE and EtSSEt vs. Me_2S concentration in N_2O-saturated solutions at pH 7. (Yields [G] = molecules formed per 100 eV absorbed radiation energy, highest EtSSEt yield corresponds to ca. 40% of the $(Me_2S.\cdot.SMe_2)^{\oplus}$ yield).

Doubtless more interesting than the formation of 1,2-BMTE is that of EtSSEt. Since the latter compound is only observed at high Me_2S concentrations, the participation of a second Me_2S molecule is indicated. Remarkably, the yield of EtSSEt is not affected by the presence of oxygen (2.8×10^{-4} mol dm^{-3}). Free $EtS^{\odot}$ radicals cannot therefore be responsible for formation of EtSSEt, since oxygen reacts rapidly with $EtS^{\odot}$[10]. The inverse behavior of 1,2-BMTE and EtSSEt yields at increasing Me_2S concentration clearly shows that new reactions occur when $(Me_2S.\cdot.SMe_2)^{\oplus}$ is increasingly stabilized at higher Me_2S concentrations. These new reactions compete with deprotonation of the molecular radical cation, $R_2S^{\oplus\odot}$, which is in equilibrium with $(Me_2S.\cdot.SMe_2)^{\oplus}$. The formation of EtSSEt is therefore not only fundamentally connected with the existence of $(Me_2S.\cdot.SMe_2)^{\ominus}$, but derives from the 3e-system itself. Mechanistically this can only be explained by a rearrangement, i.e. migration of a methyl group across the sulfur bridge in every contributing Me_2S molecule. The yield of EtSSEt in 0.1 mol dm^{-3} Me_2S solutions corresponds to ca. 40% of that of $(Me_2S.\cdot.SMe_2)^{\oplus}$.

For formation of the rearrangement product we suggest the following mechanism: The first step involves deprotonation of the 3e-species **1** at a C-atom in the α-position to one of the sulfur atoms, the rest of the stabilized electronic structure being preserved. The first rearrangement step occurs in carbanion **2**. The neutral radical **3** also possesses a 3e-bond and is expected to exist in the equilibrium

$$\mathbf{3} \rightleftharpoons Me_2S + {}^{\odot}SCH_2CH_3$$

in analogy to all σ^2/σ^* bonded systems. Dimerization of $^{\odot}SCH_2CH_3$ radicals could represent a route to EtSSEt. However, this overlooks the fact that EtSSEt is formed even in the presence of oxygen. The formation of EtSSEt can therefore only be understood in terms of a fast, second rearrangement within the 3e-species **3**, which is likely to be unreactive towards oxygen[10]. The simplest mechanism involves either homolytic fission of a C–H bond or electron transfer associated with deprotonation [reaction (c)]. Rearrangement to afford EtSSEt can be expected to occur from **4**, particularly from its equivalent ionic form **4a**.

Isotope-effect experiments corroborate the proposed mechanism. Both for reaction (a), and particularly for reaction (c), a marked difference between H- and D-substituted compounds should be observed. In fact, in the oxidation of $(CD_3)_2S$ even at a concentration of 0.16 mol dm^{-3} no diethyl disulfide is found. Instead, however, a large yield of sulfoxide is observed. Formation of sulfoxide therefore seems to be an important process competing with the rearrangement.

Comparable results were also obtained for the oxidation of other sulfides. Thus, the rearrangement product di-*sec*-butyl disulfide is formed from diethyl sulfide, Et_2S, via the 3e-bonded radical cation $(Et_2S.\cdot.SEt_2)^{\oplus}$.

The present results unequivocally identify radical cations with 3e-bonds between two sulfur atoms as the source of a rearrangement. The two steps of this rearrangement are reminiscent of the well-known Wittig and Stevens rearrangements.

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Me_2S, 75-18-3; 1,2-BMTE, 6628-18-8; EtSSEt, 110-81-6.

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The Chemistry of the Metal-Carbon Bond. Vol. 1: The Structure, Preparation, Thermochemistry and Characterization of Organometallic Compounds. Edited by *F. R. Hartley* and *S. Patai*. John Wiley, Chichester 1982. xii, 1071 pp., bound, £ 125.00.

According to the editors' foreword this book is the first volume of a series covering the highly topical field of the chemistry of organometallic compounds and should (again according to the foreword) be of particular interest to organic chemists. Whether it achieves this aim is, however, questionable. The subtitle itself is confusing; even though *without* index there are 969 pages available *nothing* is said about the preparation and almost nothing is said about the structure of the organometallic compounds of the main group elements; in other words not a word about Grignard reagents, nothing about organolithium compounds (apart from the structure of CH_3Li and the enthalpies of formation of C_2H_5Li and n-C_4H_9Li), nothing about organoaluminum, organozinc, organocadmium, organomercury compounds (apart from some thermodynamic data) and all that for the princely sum of £ 125 (!!). It is stated in the foreword that the editors had other ideas concerning the arrangement of this and the succeeding volumes, but that is not consolation to the reader. What a pity—particularly when one considers the contents of some of the chapters (there is a total of 22).

Chapter 1 of the book *(A. D. Redhouse)* deals in very concentrated form with the structures of organometallic compounds (more precisely organotransition metal compounds) but unfortunately omits any reference to their bonding relationships. Anyone wishing to know *why* a compound like $C_6(CH_3)_6RuC_8H_8$ possesses the structure given on p. 26 has to wait for the following volumes and hope to find an answer there. Have the editors not heard of "Structure *and* Bonding"? Chapter 2 *(G. Pilcher* and *H. A. Skinner)* covering thermodynamic aspects is significantly more informative. Here one learns where details concerning enthalpies of formation and bonding energies are to be found and where the difficulties lie in such investigations. The next 4 chapters—Synthesis of ylide-metal complexes *(L. Weber)*, Carbenemetal complexes *(H. Fischer)*, Carbyne-metal complexes *(U. Schubert)* and Alkyl and aryl transition metal complexes *(R. J. Puddephatt)* are similarly competently produced. Here it can be seen that the authors are themselves active in their respective fields and understand their metiers. This also applies to Chapter 12 (Synthesis of organolanthanide and organoactinide complexes by *W. J. Evans*) and 13 (Metal atoms in organometallic synthesis by *M. J. McGlinchey*), in which, pleasingly—as the interested reader would expect—also the most recent literature (1980 and 1981) is taken into account. This ought to be automatic—at least in a book that the editors wish to present as a standard work.

Chapters 7 and 9—11 on the synthesis of η^3-allyl complexes *(P. Powell)* and complexes with η^4, η^5, η^6, η^7 and η^8 coordinated ligands *(G. Marr* and *B. W. Rockett)* are somewhat less up-to-date than those mentioned above and only provide a limited view of the "state of the art"; they lack references later than 1979 and the sovereignty of choice, which is featured in Chapters 12 and 13 for example. Chapters 14—19 (by *T. R. Crompton* 180 pp.) are largely superfluous. Anyone wishing to know how to determine $Pb(C_2H_5)_4$ in gasoline, how to ascertain the carboxyhemoglobin content of blood and how to measure small quantities of H_2Se in air (where is the metal carbon bond?) will probably inform himself from the standard analytical literature. One seeks in vain, here, for any connection with the reality of the practical preparative organometallic chemist, who characterizes his compounds by elementary analysis (which he does not usually perform himself) and by spectroscopy.

These spectroscopic methods are discussed in Chapters 20 (IR and Raman by *M. J. Taylor*), 21 (NMR by *J. A. Davies*) and 22 (MS by *T. R. Spalding*). The treatment of the application of NMR spectroscopy deserves unstinting praise; it its exceedingly informative and takes account of both theoretical and practical problems. There is no doubt that an engaged author was at work here, who did not shy at the effort of including the latest publications (from 1981 and 1982) in an appendix. This is missing in the chapter concerned with mass spectroscopy, in which the treatment of such currently important areas as field ionization and field desorption techniques is crammed into half a page.

Finally the question—who is going to buy it? And above all—who can pay for it? Are the editors of such series and the publishers not aware of the situation in the universities today (not only in the Federal Republic of Germany)? In view of just this situation, should one not consider more critically and scrupulously how best to serve the reader—and here this means the organometallic (and organic) chemist—at his place of work? The present work does not exhibit signs of such considerations and that has to be laid, above all, at the door of the editors. It is scarcely possible to recommend purchase under present conditions.

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Organic Chemistry in Colour. By *P. F. Gordon* and *P. Gregory*. Springer-Verlag, Berlin 1983, xi, 322 pp., bound, DM 178.00.

Dyestuffs chemistry is applied organic chemistry. Since it is mainly practised in the laboratories and finishing shops of the dyestuff manufacturers, this review, written by employees of one of these companies (ICI), deserves particular attention.

The book, which is almost exclusively devoted to textile dyes, begins in Chapter 1 with a retrospect, which covers the period before *Perkin* through the structural assignment of the natural dyestuffs up to the most recent areas of dyestuff application.

Two sections of Chapter 2 with cleverly chosen and generalizable examples of the synthesis of dyestuffs and intermediates will meet with approval. Probably these sections would have been enriched if Chapters 3 to 5 had followed this pattern and emphasized market and environmentally oriented synthesis strategies more markedly. The normal classification method, whereby textile dyes are divided into a maximum of seven main structural classes, has been effectively adopted. A second classification principle and its influence on the C.I. (Color Index) dyestuff names, which are frequently quoted in this work, ought to have been explained in more detail in view of the heterogeneous readership. However, to devote a section to classification principles is not very helpful if the care has not been taken which is necessary for the coordination of individual struc-

tural features or even if both principles are combined. The headings to 2.2.3 and 2.4.3 (vat dyestuffs) and most of subsection 2.2.9 (miscellaneous) in particular can be criticized on these grounds.

Phenylogue polymethine dyestuffs, alongside the cyanines the most important class with delocalized charge, are grouped under the heading arylcarbenium. Inconsistently, however, it is left to the reader to place the charge sign in the correct place in the formulas or to search (in vain) for a carbenium center. May be because of the (apparent) dilemma with mono and pentamethinecyanines, the authors exclusively employ inapplicable resonance formulas with the charge on one of the heteroatoms, which cannot be said to be acceptable nowadays for anything other than to illustrate a symmetry-hostile nomenclature (Chemical Abstracts, cyanines).

The main concern of the authors is obviously the interaction between structure, chemical and physical properties, on the one hand, and marked value, on the other, which may to some extent justify the size of Chapters 3—5. Chapter 3, azo dyes, is introduced by a short section concerning the structure of the basic chromogen. The section on tautomerism emphasizes the relationship between substitution, equilibrium position and extinction. A further section is concerned with metal complexes including some aspects of complex isomerism. The section on constitution and color gives the same weight to a review as to the results of MO treatment. Chapter 4, anthraquinone dyes, is similarly constructed, while the remaining structural classes are treated somewhat more briefly in Chapter 5.

The discussion of textile fibers is reduced to a minimum and included in Chapter 6. The section on application and wet fastness is very clearly laid out with a classification according to bonding principles; there is no mention of a competing concept which views the binding of direct dyestuffs to cellulose in terms of the demonstrable—to be sure only in solution and on films—aggregate formation. Light fastness is also discussed in detail; key words are test methods, photochemical principles, attempts to clarify the bleaching mechanisms, catalytic processes, photochemical fiber damage. Short sections concerning fastness to sublimation, solvolysis in the dyeing vat, fastness to bleaching, solvatochromism, photochromism and metamerism round off the chapter. Extensive reference lists are included at the end of each chapter and (concerning MO theory, colorimetrics and the often neglected facet of color perception) in the appendix.

This book is primarily intended for readers practising the subject. Students of chemistry and possibly of textiles will find a wealth of useful information, which will not replace lectures on dyestuffs but can usefully complement them. A book that deliberately sets its accent differently and (the criticisms mentioned above excepted) a book that can be recommended.

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New Books

The following books have been received by the editor. All the publications listed are available through W & P Buchversand für Wissenschaft und Praxis, Boschstrasse 12, D-6940 Weinheim (Federal Republic of Germany). Tel. (06201) 606-0, Telex 465516 vchwh d, Telefax (06201) 602328.

Reihe Hochschultexte. Chemische Aspekte der Festkörper-Physik. By *H. Endres*. Springer-Verlag, Heidelberg 1984. iv. 160 pp., stitched, DM 42.00.—ISBN 3-540-13604-5

Methods of Enzymatic Analysis. By *H. U. Bergmeyer*. **Vol. V: Peptidases, Proteinases and Their Inhibitors.** Verlag Chemie, Weinheim 1984. xxvii, 558 pp., bound, subscription price: DM 235.00; later, price per volume: DM 270.00.—ISBN 3-527-26045-5

Biotransformation von Arzneimitteln. Vol. 5. By *S. Pfeifer* and *H.-H. Borchert*. Verlag Chemie, Weinheim 1984. 468 pp., bound, DM 168.00.—ISBN 3-527-26075-7

Corrigendum

The following correction should be made to the communication entitled "Synthesis and Structure of the 7-Trifluoromethyl-1,3,5,2,4,6,8-trithiatetrazocine Cation" by *H.-U. Höfs, G. Hartmann, R. Mews,* and *G. M. Sheldrick,* Angew. Chem. Int. Ed. Engl. 23 (1984) 988:
In Formula 1 the chlorine substituents should be attached to the *sulfur* atoms and not to the *nitrogen* atoms.

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Synthesis of Cyclosporine and Analogues: Structural Requirements for Immunosuppressive Activity**

By Roland Maurice Wenger*

Cyclosporine is a new immunosuppressive drug which was first marketed in 1983 under the trade name Sandimmune®. This compound, an innovation in selective immune modulation, was isolated from a fungal culture and characterized as a cyclic undecapeptide containing a novel amino acid together with several *N*-methylated amino acids. The new amino acid (4*R*)-4-[(*E*)-2-butenyl]-4,*N*-dimethyl-L-threonine (MeBmt) was the only unknown amino acid of cyclosporine and there had previously been no means for its isolation. For this reason and because it seemed possible that MeBmt could play a significant role in determining the pharmacological activity of cyclosporine, its synthesis in enantiomerically pure form was undertaken. The next step was the development of a total synthesis of cyclosporine, which appeared attractive, not only for its intrinsic worth, but also as an important tool for investigating the relationships between structure and immunosuppressive activity. Essential for the immunosuppression are the amino acids MeBmt, Abu, Sar, and MeVal in the positions 1, 2, 3 and 11, but probably also still larger parts of the molecule. Such information could be valuable for finding new chemical leads or drugs with a new activity profile.

1. Introduction

1.1. Pharmacological Activity and Clinical Application of Cyclosporine

As reported by *Borel* et al.[2–6], cyclosporine is a selective immunosuppressive drug with antifungal and antiinflammatory properties. It has been shown to strongly suppress the production of haemagglutinating antibodies against sheep erythrocytes in mice and to be effective in inhibiting both humoral and cell-mediated immune responses. Its effect is reversible, and for T-lymphocytes specific; the hemopoietic tissues in immunosuppressed animals are not affected. More recently *Bueding* et al.[7] demonstrated an antischistosomal activity and *Thommen-Scott*[8] an antimalarial effect of cyclosporine, both antiparasitic activities being independent of immunosuppression.

The first transplantations in humans with the aid of cyclosporine were reported in 1978 by *Calne* et al.[9] for kidney and by *Powles* et al.[10] for bone marrow. Today, cyclosporine is used successfully to prevent graft rejection following bone-marrow and organ transplantations. Other possible applications, such as in the treatment of autoimmune and other diseases, are currently under investigation.

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Sandoz AG, CH-4002 Basel (Switzerland)

[**] Presented in part at the International Symposium on Cyclosporine held in Houston, TX (USA), May 16—20, 1983; see reference [1].

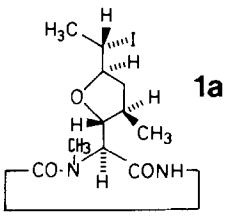
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1.2. Production of Cyclosporine

Cyclosporine[*], originally named "cyclosporin A" by *Rüegger* et al.[13], was shown by *Dreyfuss* et al.[14][**] to be produced by fungi of the genus *Tolypocladium* in submerged cultures. In normal fermentation broths it is the main component of a group of cyclic peptides, each comprising 11 amino acids. These naturally occurring cyclosporine analogues have been partly reported by *Traber* et al.[17–19]. They usually differ in their chemical structure only at one amino acid and their biosynthesis can be directed by externally supplying the corresponding precursor. For example, *Kobel* et al.[20] reported the more selective production of (norvaline^2)cyclosporine by adding L-norvaline to the fermentation broths. Addition of D,L-α-aminobutyric acid almost completely suppresses the formation of undesired cyclosporine analogues and leads to a higher percentage of cyclosporine in the crude product.

1.3. Elucidation of the Structure of Cyclosporine

The structure of cyclosporine **1** (Fig. 1) was determined by chemical degradation[13] together with an X-ray crystallographic analysis of the iodo derivative **1a**.



1a

As described by *Petcher* et al.[21], this analysis not only established the sequence of the native peptide, but also gave an insight into its shape. Later, *Loosli* et al.[22] were able to confirm the structural and conformational assignments by an X-ray crystallographic analysis and by two-dimensional nuclear magnetic resonance (NMR) studies of cyclosporine itself. Cyclosporine (Fig. 1) is a neutral, hydrophobic, cyclic peptide composed of eleven amino acid residues, all having the L-configuration of the natural amino acids, except for the D-alanine (D-Ala) in position 8 and the non-chiral sarcosine (*N*-methylglycine) in position 3. Seven amino acids—in positions 1, 3, 4, 6, 9, 10 and 11—are *N*-methylated. Ten of the eleven ring members are derivatives of known aliphatic amino acids: they are α-aminobutyric acid (Abu) in position 2, sarcosine (Sar) in position 3, *N*-methylleucine (MeLeu) in positions 4, 6, 9 and 10, valine (Val) in position 5, alanine (Ala) in position 7, D-alanine (D-Ala) in position 8, and *N*-methylvaline (MeVal) in position 11. These amino acids were readily characterized following acid hydrolysis of cyclosporine. One amino acid, namely that in position 1, was hitherto unknown. Being composed of 9 carbon atoms this amino acid was reported on under the name "C-9 amino acid"[13]. It was found to have the composition (2*S*,3*R*,4*R*,6*E*)-3-hydroxy-4-methyl-2-(methylamino)-6-octenoic acid, and, in accord with amino acid nomenclature, is now designated as (4*R*)-4-[(*E*)-2-butenyl]-4,*N*-dimethyl-L-threonine and abbreviated MeBmt. Thus, the novel amino acid has the polar features of an *N*-methyl-L-threonine which is substituted at the end of the carbon chain by butenyl and methyl groups. This amino acid was hitherto not known in the free form, since only artifacts and derivatives were obtained from degradation experiments on cyclosporine[13]. Hydrolysis of cyclosporine followed by ion-exchange chromatography afforded a cyclic derivative **1b** of the MeBmt amino acid as the only isolable MeBmt-derivative, while acidic treatment of cyclosporine **1** in the absence of water effects an *N*,*O*-acyl migration of the methylvalyl moiety and furnishes isocyclosporine **1c**. A modified Edman degradation of isocyclosporine **1c** using methyl isothiocyanate produced an anhydrothiohydantoin-derivative **1d** as the only isolable MeBmt derivative and thus established MeBmt as the first amino acid in the peptide sequence. The complete sequence was established by repetitive Edman degradation.

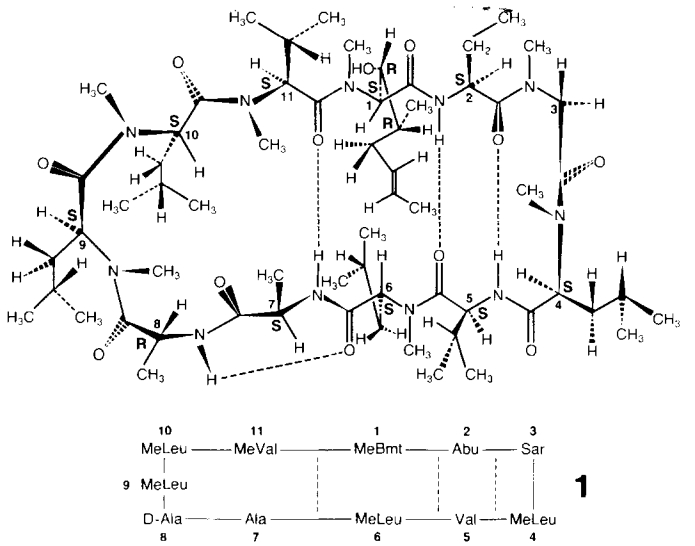
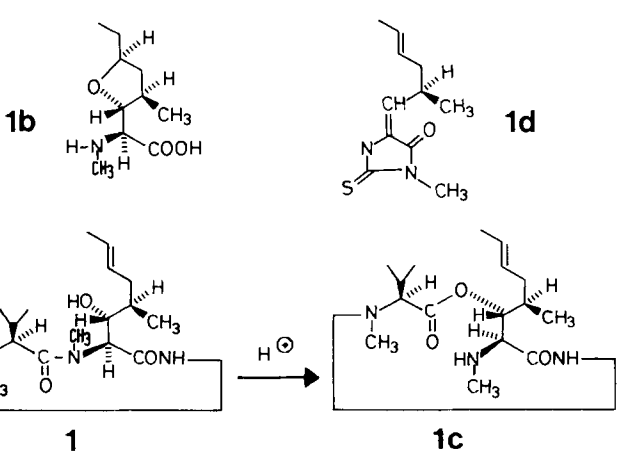


Fig. 1. Structure of cyclosporine **1** (schematic). MeBmt = (4*R*)-4-[(*E*)-2-butenyl]-4,*N*-dimethyl-L-threonine (see text).



[*] For practical reasons, it was previously proposed to define "cyclosporin" as the cyclic undecapeptide with the structure of "cyclosporin A" [11, 12]. Now that the USAN name "cyclosporine" has been accepted in the USA, this name will be adopted for the basic structure. Meanwhile the following names have been accepted in other countries: England, cyclosporin (BAN name); France, ciclosporine; Switzerland and others ciclosporin (INN name, WHO).

[**] The cyclosporine-producing organism which was initially identified as *Trichoderma polysporum* [14] is now classified under the genus *Tolypocladium* established by *Gams* [15] and is called *Tolypocladium inflatum* Gams [16].

From the X-ray structure and NMR data it follows that cyclosporine assumes a rather rigid conformation, both in the crystalline state and in solution (Fig. 2). A large portion

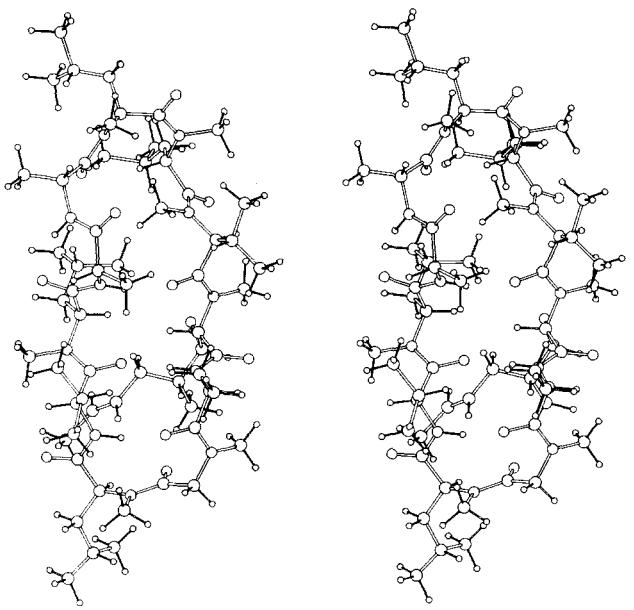


Fig. 2. Conformation of cyclosporine **1** in the crystal (stereograph).

of the backbone (residues 1—6) adopts an antiparallel β-pleated sheet conformation which contains three transannular H-bonds and is markedly twisted. The sarcosine in position 3 and *N*-methylleucine in position 4 participate in a type II′ β-turn[23-25]. This means that, in the orientations chosen in Figures 1 and 2, the CO group of Abu-2 and the *N*-CH_3 group of MeLeu-4 are up and the CO group of Sar-3 and NH group of Val-5 are down. The *pro-S* proton of the methylene group of Sar-3 is axial, and the side chain of MeLeu-4 equatorial. The remaining residues 7—11 form an open loop. This loop contains the only *cis*-amide linkage in the molecule between the two adjacent *N*-methylleucine residues 9 and 10. The remaining H-bond is of a γ-type and serves to hold the backbone in a folded L shape.

As a consequence of this rather rigid conformation of the cyclosporine skeleton, six amino acids have their side chains directed quasi-perpendicular to the plane of the peptide ring: In Abu-2, Val-5, Ala-7 and MeVal-11 they are pointing upwards, in MeBmt-1 and MeLeu-6 they are pointing downwards. The side chains of the remaining five amino acids lie more or less in the plane of the peptide ring.

1.4. Biosynthesis of Cyclosporine

In the initial biosynthetic studies of *Kobel* et al.[26], ^{3}H- and ^{13}C-labeled precursors were fed to the culture and the position of incorporation of the label in cyclosporine was determined by NMR spectroscopy. It was demonstrated that the *N*-methyl groups of the molecule and the methyl group in the γ-position of the unsaturated amino acid MeBmt are introduced as intact methyl groups from methionine and that the remaining carbons of the MeBmt moiety are derived from the head-to-tail condensation of four acetate units. The ^{13}C-NMR spectrum of the enriched cyclosporine derived from [1-^{13}C]acetate showed four enhanced signals corresponding to the carbon atoms 1, 3, 5 and 7 of the MeBmt unit and no ^{13}C incorporation into any other amino acid.

In enniatin, an analogous example of non-ribosomal cyclic peptide synthesis by fungi, *Zocher* and *Kleinkauf*[27] demonstrated that a multifunctional enzyme carries out the *N*-methylation of the constituent amino acids following an activation step when the acids are bound to the enzyme as thioesters. Supporting evidence for a similar mechanism in cyclosporine biosynthesis was provided by the observation of *Zocher* et al.[28] that [^{14}C]sarcosine was not incorporated and that the radioactivity from [Me-^{14}C]methionine incorporated into each *N*-methylated amino acid was directly proportional to the number of the corresponding amino acid residues in cyclosporine, thus indicating that *N*-methylation of the amino acids occurred simultaneously.

From the results of *Kobel* et al.[26] the site of biosynthesis of the Bmt unit remains unclear. However, the results obtained by the *Kleinkauf* group[28] with short-term feeding experiments using labeled acetate and methionine, in which probably only incorporation of label in the *N*-methyl group occurred, suggest that the amino acid Bmt is not biosynthesized on the enzyme matrix but at some other site before incorporation into cyclosporine.

2. Enantioselective Synthesis of the Amino Acid MeBmt from (*R*,*R*)-Tartaric Acid[*]

In the amino acid (4*R*)-4-[(*E*)-2-butenyl]-4,*N*-dimethyl-L-threonine (MeBmt) the MeNH- and OH-groups are in a *threo*-configuration and the OH- and CH_3-groups in an *erythro*-configuration; the double bond has the *trans*-(or *E*-)configuration. The systematic name (see Ref.[30]) for MeBmt is (2*S*,3*R*,4*R*,6*E*)-3-hydroxy-4-methyl-2-(methylamino)-6-octenoic acid.

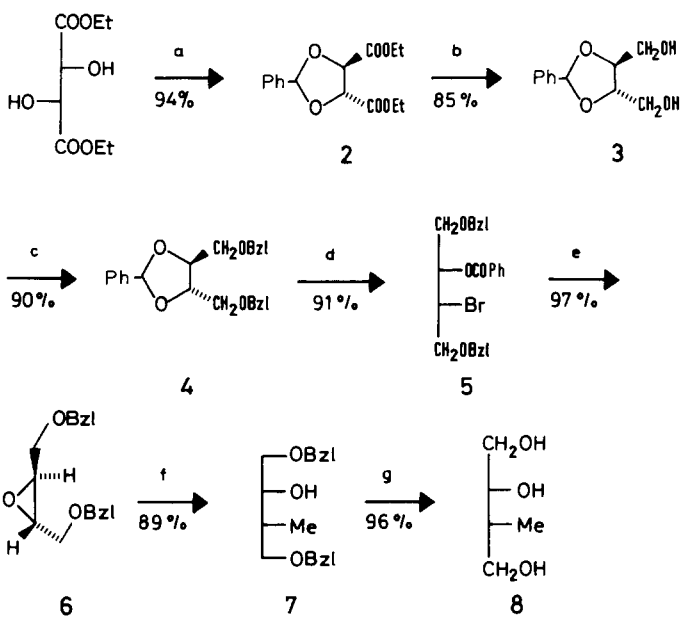
(*R*,*R*)-(+)-Tartaric acid was used as the basic chiral building block—for the use of tartaric acid as a practical source of chiral building blocks for syntheses, see the recently published review by *Seebach* and *Hungerbühler*[31]. It was modified in three major operations to introduce the features of the target amino acid. In the first operation, summarized in Scheme 1, one OH-group of the (*R*,*R*)-(+)-tartaric acid molecule was incorporated with the correct configuration, and the other OH-group was replaced by a CH_3-group accompanied by inversion of configuration. This provided the asymmetric centers C3 and C4 of the amino acid MeBmt. The second operation consisted of introducing the (*E*)-butenyl moiety (Scheme 2) after having elongated the carbon chain by formation of an aldehyde which was the starting material for a Wittig reaction under Schlosser and Christmann conditions[32]. The third operation consisted of oxidizing the diol **14** to the hydroxy aldehyde **19** (Scheme 3) and of introducing the MeNH- and the COOH-groups via a cyclic intermediate permitting ste-

[*] For details of the synthesis of MeBmt see reference [29].

reochemical control during the formation of the asymmetric center at C2 (Scheme 4).

2.1. Synthesis of (2*R*,3*R*)-3-Methyl-1,2,4-butanetriol 8; Formation of the Asymmetric Centers C3 and C4

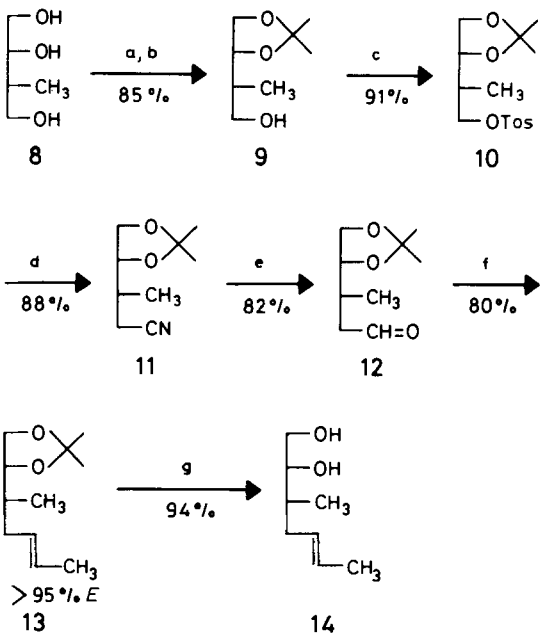
As shown in Scheme 1, the OH-groups of (*R*,*R*)-diethyl tartrate are first converted with benzaldehyde into the acetal **2**. Reduction with $LiAlH_4$ to give the diol **3** and subsequent benzylation then furnishes the dioxolane **4**. For the replacement of one of the OH-groups of tartaric acid by a CH_3-group with inversion of configuration, the epoxide **6** is first prepared from **4** according to the procedure described by *Seeley* and *McElwee*[33]; because of the symmetry of **4** it is immaterial on which of the two secondary C-atoms the displacement occurs. Thus, treatment of **4** with *N*-bromosuccinimide yields the bromo ester **5**, which upon alkaline hydrolysis is directly converted into the optically active and therefore *trans*-disubstituted oxirane **6**. Methylation of the epoxide (C_2-symmetry) using the method of *Johnson* et al.[34] affords the single product **7**. Hydrogenolysis of the benzyl-protecting groups leads to formation of the triol **8** in an overall yield of 56% from diethyl tartrate (seven steps).



Scheme 1. Synthesis of **8**. a: $PhCHO/HC(OEt)_3/TosOH \cdot H_2O$. b: $LiAlH_4$/tetrahydrofuran (THF). c: BzlBr/toluene/KOH. d: *N*-bromosuccinimide (NBS)/CCl_4. e: KOH/EtOH. f: 2 MeLi (CuI)/Et_2O, −15 °C. g: Pd/H_2.— Bzl = benzyl.

2.2. Synthesis of (2*R*,3*R*,5*E*)-3-Methyl-5-heptene-1,2-diol 14; Chain Elongation with Introduction of the *trans*-Double Bond

The two vicinal OH-groups of the triol **8** are, as shown in Scheme 2, selectively protected by preparation of the ketal **9**. The formation of 10—15% of the isomeric 1,3-dioxane besides the desired dioxolane **9** could not be avoided. The dioxolane **9** is converted into the tosylate **10**. Subsequent carbon chain elongation with potassium cyanide furnishes the nitrile **11**, which is converted into the aldehyde **12**. The aldehyde is then subjected to a *Wittig* reaction to give **13**[32]. After removal of the isopropylidene-protecting group the diol **14** is obtained in 42% overall yield from the triol **8** (six steps).



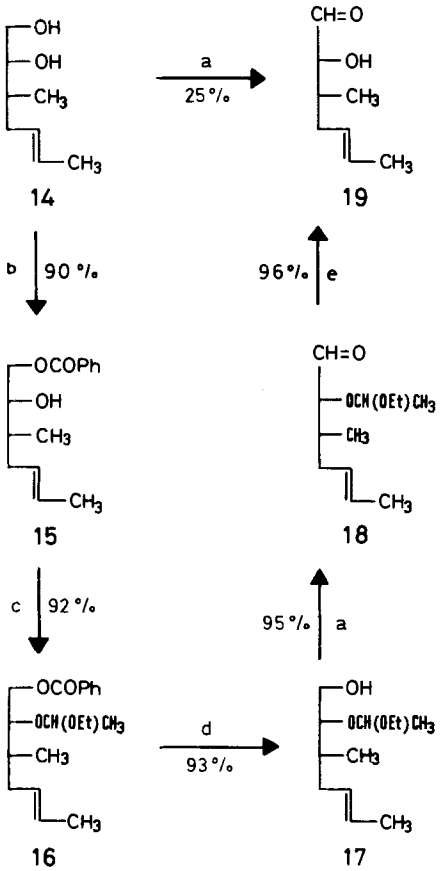
Scheme 2. Synthesis of **14**. a: $Me_2C(OMe)_2/TosOH \cdot H_2O/C_6H_6$, 2 h reflux. b: $Me_2CO/TosOH \cdot H_2O$, 15 h reflux. c: TosCl/pyridine, 35 °C, 4 h. d: KCN/dimethyl sulfoxide (DMSO), 20 °C, 3 d. e: Diisobutylaluminum hydride/hexane, −75 °C, 2 h. f: $Ph_3EtPBr/BuLi$, Schlosser-conditions [32]. g: 1.1 equiv. 1 N HCl/(THF/H_2O 4:1), 20 °C, 2 d.

2.3. Synthesis of (2*R*,3*R*,5*E*)-2-Hydroxy-3-methyl-5-heptenal 19; Oxidation of 14 to 19

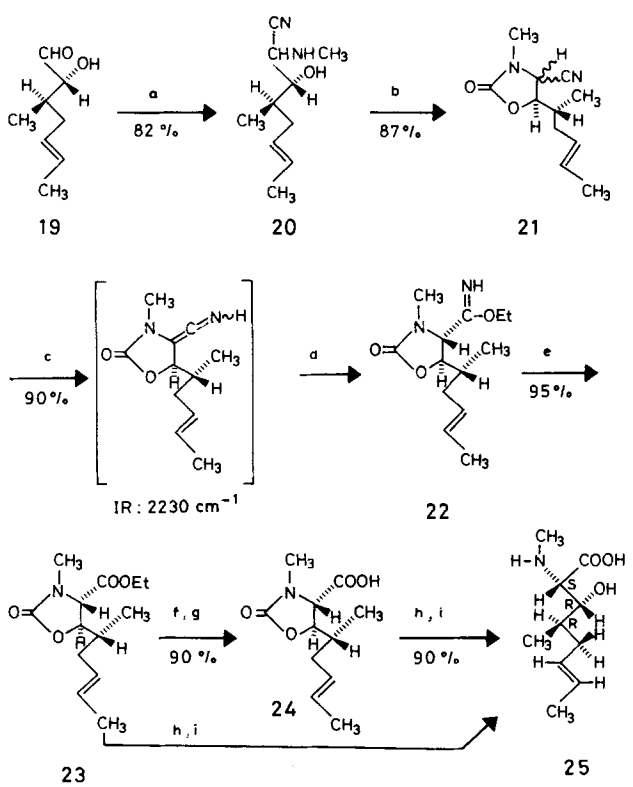
The oxidation of the diol **14** (Scheme 3) can be effected by the Pfitzner-Moffatt method[35] in one step, but only in low yield (25%). To obtain the hydroxyaldehyde **19** in high yield, it is necessary to protect the secondary OH-group of **14**. This is done by monobenzoylation (→ **15**), followed by protection of the secondary OH-group as the ethoxyethyl derivative **16**, and alkaline hydrolysis of the benzoate to give the primary alcohol **17**. Using the Pfitzner-Moffatt method, **17** can now be oxidized to the aldehyde **18** in 95% yield. Removal of the ethoxyethyl-protecting group furnishes the hydroxyaldehyde **19** in a total yield of 70% (five steps).

2.4. Synthesis of (2*S*,3*R*,4*R*,6*E*)-3-Hydroxy-4-methyl-2-(methylamino)-6-octenoic acid (MeBmt) 25; Introduction of the Methylamino-Group and the Carboxy-Group

Scheme 4 outlines the last steps of the MeBmt synthesis. Reaction of freshly prepared hydroxyaldehyde **19** with potassium cyanide and methylammonium chloride affords the cyanohydrin **20** as a mixture of diastereomers. The mixture **20** is converted into the 2-oxazolidinone **21** (6:1/*cis*:*trans* relative to the ring). **21** can be converted in high yield into the imidate **22** by treatment with potassium car-



Scheme 3. Synthesis of **19**. a: Dicyclohexylcarbodiimide (DCCI)/DMSO/C_6H_6/pyridine/trifluoroacetic acid (TFA), 20°C, 2 h. b: PhCOCl/pyridine, 20°C, 1 h. c: CH_2=CHOEt/TFA, 20°C, 1—3 d. d: 10 N KOH/EtOH, 20°C. e: 1 N HCl/THF, 20°C, 2 h.



Scheme 4. Synthesis of MeBmt **25**. a: KCN/$MeNH_2$·HCl/MeOH/H_2O, 20°C, 2 h. b: 1,1'-Carbonyldiimidazole/CH_2Cl_2, 20°C, 16 h. c: K_2CO_3/EtOH, 20°C, 6 h. d: EtOH. e: 1 equiv. 1 N HCl/EtOH, 20°C, 1.5 h. f: 0.1 N KOH/dioxane, 20°C, 1 h. g: HCl (pH 2). h: 2 N KOH/H_2O, 80°C, 3 h. i: HCl (pH 5).

bonate in ethanol. The intermediate iminomethylene derivative (IR band at 2230 cm^{-1} in ethanol) reacts stereospecifically to give the thermodynamically more stable *trans*-imidate **22**. Hydrolysis of **22** furnishes the enantiomerically pure *N*-methylamino acid derivative **23** with the *O*- and *N*-functional groups in the desired *threo*-configuration. Both protecting groups of **23** can be removed in one step, or stepwise via **24**. The desired *N*-methylamino acid **25** crystallizes from the reaction mixture following acidification to pH 5 with 1 N HCl. The yield of **25** is 48% after six steps from the aldehyde **19** or 7.8% after 24 steps from (*R,R*)-diethyl tartrate. This corresponds to an average yield of 90% per step.

The stereospecific synthesis described here allowed the characterization of the new amino acid MeBmt **25** for the first time, and thus opened the way for a total synthesis of cyclosporine.

3. Total Synthesis of Cyclosporine[*]

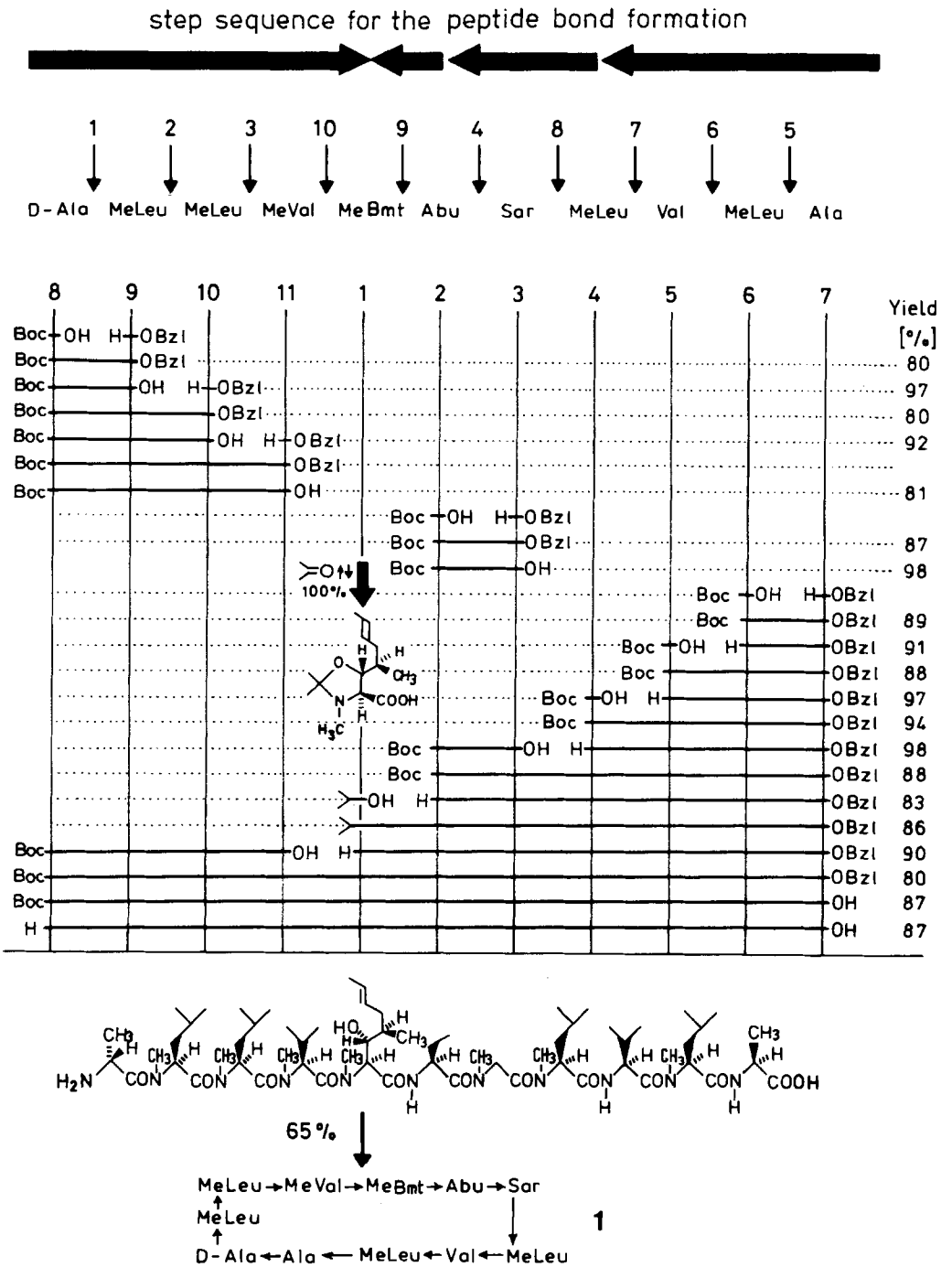
3.1. Strategy Used for the Synthesis of Cyclosporine

For the synthesis of cyclosporine **1** (Fig. 1), the peptide bond between the L-alanine in position 7 and the D-alanine in position 8 was chosen for the cyclization step. There were two main reasons for choosing this strategy: 1. The intramolecular hydrogen bonds between the amide groups of this linear peptide could operate so as to stabilize the open chain in folded conformations approximating the cyclic structure of cyclosporine and thus assist cyclization. 2. The bond formation between *N*-methylated amino acids is more difficult than between non-methylated amino acids (for further details see [36, 37]); therefore, bond formation between the only consecutive pair of non-methylated amino acids in cyclosporine appeared the logical choice for the cyclization step.

For the synthesis of the undecapeptide, a fragment-condensation technique introducing the amino acid MeBmt at the end of the synthesis was used. In this way, the number of steps after the introduction of this amino acid was minimized. Scheme 5 shows the step sequence used for joining the (protected) peptide fragments.The carboxy groups were generally activated using a variation of the mixed pivalic anhydride method reported by *Zaoral*[38] and adapted by us for *N*-methylamino acid derivatives[36]. This strategy allowed slow anhydride formation in chloroform at −20°C with pivaloyl chloride in the presence of 2 equivalents of a tertiary base such as *N*-methylmorpholine before adding the amino acid or peptide esters to be coupled in the form of their free bases. The free bases were obtained by removal of the Boc-protecting groups with trifluoroacetic acid at −20°C and subsequent neutralization with $NaHCO_3$; the benzyloxy-protecting groups of the peptide intermediates were removed hydrogenolytically with palladium/carbon in ethanol.

The tetrapeptide Boc-D-Ala-MeLeu-MeLeu-MeVal-OBzl was synthesized from the left to the right by forming

[*] For details of the synthesis of cyclosporine see references [12, 36].



Scheme 5. Synthesis of cyclosporine **1**. Bold arrows: strategy for the synthesis of the peptides. For details see text. Boc = *tert*-butoxycarbonyl, Bzl = benzyl, >—OH = isopropylidene-protected MeBmt.

bonds 1, 2 and 3 (Scheme 5). Bond 4 was formed on synthesis of the dipeptide Boc-Abu-Sar-OBzl. The tetrapeptide Boc-MeLeu-Val-MeLeu-Ala-OBzl was synthesized from the right to the left by forming bonds 5, 6 and 7 in that order. Subsequent coupling (bond 8) with the previously synthesized dipeptide then furnished the hexapeptide Boc-Abu-Sar-MeLeu-Val-MeLeu-Ala-OBzl. During incorporation of the amino acid MeBmt, the hydroxy- and *N*-methylamino functions were protected in the form of a dimethyloxazolidine derivative. This isopropylidene-protecting group was readily introduced by refluxing the amino acid in acetone and has the advantage of avoiding epimerization of the amino acid MeBmt during peptide-bond formation. This means that the oxazolidine ring retains the thermodynamically more stable *trans*-configuration of substituents during carboxy activation and peptide formation. On preparation, but before activation, the protected MeBmt amino acid was stabilized by addition of *N*-methylmorpholine (1 equiv.). To prepare the protected heptapeptide from the protected MeBmt amino acid and the hexapeptide, the dicyclohexylcarbodiimide (DCCI) coupling method was used in presence of *N*-hydroxybenzotriazole[39]. After removal of the isopropylidene-protecting group (1 equiv. of 1 N HCl/MeOH), the final amide linkage 10 was made by coupling Boc-D-Ala-MeLeu-MeLeu-MeVal-OH with the heptapeptide in presence of *N*-me-

thylmorpholine in CH_2Cl_2 at room temperature using the reagent (1*H*-1,2,3-benzotriazol-1-yloxy)tris(dimethylamino)-phosphonium hexafluorophosphate ($BtOP(NMe_2)_3^{\oplus}PF_6^{\ominus}$) developed by *Castro* et al.[40]. After hydrolysis of the ester group (NaOH at 0°C) and removal of the Boc group (CF_3COOH at −20°C), the unprotected undecapeptide was cyclized at room temperature to cyclosporine **1** (0.0002 M CH_2Cl_2, 1 equiv. $BtOP(NMe)_3^{\oplus}PF_6^{\ominus}$[40], *N*-methylmorpholine). The yield of crystalline cyclosporine was 62%. By using the mixed phosphonic anhydride method described by *Wissmann* and *Kleiner*[41] or the pentafluorophenol-DCCI complex of *Kovacs*[42] to effect cyclization of the unprotected undecapeptide, the yield of cyclosporine could be increased to 65%. Using the fragment-condensation technique described here it is now possible to synthesize cyclosporine very efficiently in 27.5% yield with respect to the amino acid MeBmt. Thus, 1.6 g of cyclosporine can be produced starting from 1 g of the amino acid MeBmt. This synthesis of cyclosporine also opens the way for the preparation of analogs with which the many unanswered problems concerning the structure-activity relationships of this drug can be investigated.

4. Cyclosporine Analogues

4.1. Choice of Variations

Some naturally occurring modifications of the cyclosporine peptide structure have been described by *Rüegger* et al.[13] and *Traber* et al.[17–19] and their contribution to our understanding of structure-activity relationships will be described below (see Section 5). In principle, the new synthetic approach enables any amino acid of the peptide chain of cyclosporine to be modified and thus allows successive examination of specific aspects of the structure-activity relationships. The first aspect to be studied was the importance of the near environment of the MeBmt amino acid in position 1 of cyclosporine; for this purpose variations at positions 1, 2, 3 and 11 were undertaken. Seven such variations will be described here together with the synthesis of (*N*-methyl-D-valine[11])cyclosporine, a naturally occurring isomer of cyclosporine.

In order to study the importance of the unusual side chain of MeBmt in position 1 of cyclosporine, this amino acid was replaced by *N*-methylthreonine (MeThr); thereby, the polar features of MeBmt are retained, but not the pronounced lipophilic character of the side chain.

(Threonine[2])cyclosporine [(Thr[2])CS], a naturally occurring isomer of cyclosporine, is a potent immunosuppressant. However, in contrast to other natural analogues with variations of the amino acid in position 2, (Thr[2])CS contains a hydroxy group. To examine whether or not this hydroxy group is involved in some special receptor interaction, a modified cyclosporine with a serine in position 2 (replacing Abu in cyclosporine and threonine in (Thr[2])CS) was prepared.

The X-ray structure analysis of cyclosporine indicates that the sarcosine in position 3 participates in a type II′ β-turn (see Section 1.3). Replacement of sarcosine by D-proline would be expected to stabilize this structural feature and make it more rigid. The proline ring would be expected to take an equatorial position relative to the peptide ring and should not alter the conformation of the peptide backbone relative to that of cyclosporine.

To relieve steric crowding and to allow more flexibility at position 11, of the peptide ring, MeVal was replaced by MeLeu, i.e. by an amino acid having one additional methylene group on its carbon chain.

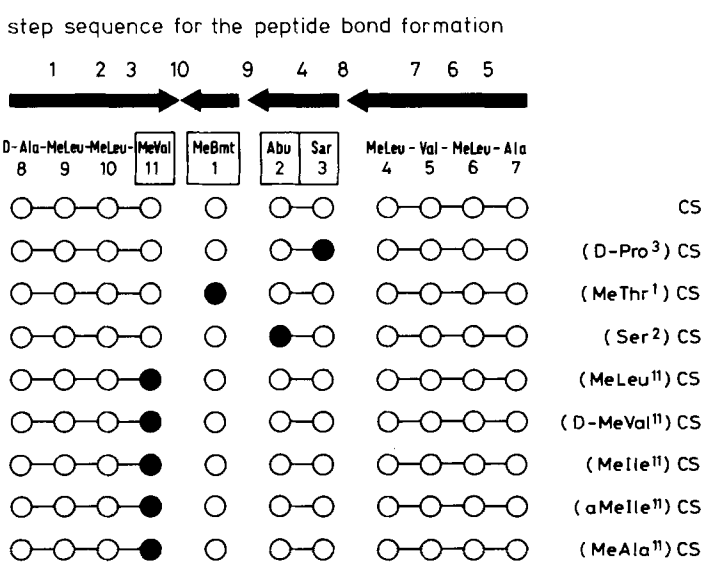
The replacement of MeVal by MeIle (*N*-methyl-L-isoleucine) or aMeIle (*N*-methyl-L-alloisoleucine), two amino acids containing a *sec*-butyl instead of an isopropyl side chain, afforded models resembling more closely the natural cyclosporine. In the case of MeIle a hydrogen atom of the *pro-S* methyl of MeVal is replaced by a methyl group, while in aMeIle a hydrogen atom of the *pro-R* methyl of MeVal is replaced by a methyl group.

A further variation was the introduction in position 11 of a less hindered and smaller amino acid, namely MeAla (*N*-methylalanine), instead of MeVal, thus replacing the two methyl groups of MeVal by two hydrogen atoms.

The above modifications of cyclosporine would also be expected to provide information on the sensitivity of the biological activity of cyclosporine toward minor changes at each position and to indicate whether or not these amino acids are likely to be involved in interactions with the receptor.

4.2. Synthesis of Cyclosporine Analogues

Following the same strategy as used for the synthesis of cyclosporine (Scheme 5), the new peptide fragments were synthesized as shown in Scheme 6. The new peptide fragments were built up in the direction shown by the arrows using the step sequence indicated; the black circles show the positions of the modified amino acids. The undecapeptides with a free amino group and a free carboxy group were cyclized with $(PrPO_2)_3$[41] in the presence of 4-dimethylaminopyridine in CH_2Cl_2.



Scheme 6. Concept for the synthesis of cyclosporine analogues (see also Scheme 5). Black circles: modified amino acids. CS = cyclosporine.

4.3. Determination of the Structure of the Cyclosporine Analogues

The structural assignments for these cyclosporine analogues (Scheme 6) have been supported by NMR data. All analogues excepting (D-MeVal[11])cyclosporine, whose complicated NMR-spectrum indicates at least 7 peptide ring conformations, have NMR-spectra similar to that of natural cyclosporine, with essentially only one conformation in $CDCl_3$. Hence, it could be predicted that the new cyclosporine analogues have a conformation similar to that of cyclosporine. In the case of (MeLeu[11])cyclosporine, the structure predicted on the basis of its synthesis and physical data has been confirmed by an X-ray crystallographic analysis. This also showed that the backbone of (MeLeu[11])cyclosporine has practically the same conformation as cyclosporine itself in the solid state. The geometric arrangement of the β-carbons of *N*-methylvaline and *N*-methylleucine in position 11 are identical.

5. Biological Activity and Structure-Activity Relationships of Cyclosporine Analogues

The relative potencies of some synthetic and naturally occurring analogues of cyclosporine are shown in Table 1. The compounds were characterized using pharmacologic models previously used for testing cyclosporine[2-6]. The suppression of *the humoral immune response* was determined by measuring the antibody-forming cells in the spleens of mice immunized against sheep erythrocytes (Jerne plaque forming test). The suppression of *the cell-mediated immune response* was quantified in an immune reaction of a delayed-type hypersensitivity (DTH) by measuring the suppression of the oxazolone-induced skin reaction in mice. The *suppressive index* in vitro could be determined by quantifying the suppression of the proliferative response of lymphoid cells which are activated by mitogens or alloantigens.

From the results presented in Table 1 it is evident that the side chain of amino acid 1 (MeBmt) is important for biological activity. Removal of the nonpolar part of the side chain, as in (MeThr[1])cyclosporine, dramatically reduces the immunosuppressive activity; this is also the case on modification of the hydroxy group, as seen in *O*-acetyl- and deoxy-cyclosporine. Even the double bond makes a contribution to the biological activity: dihydro compounds are generally less potent immunosuppressants. MeBmt alone, however, has no immunosuppressive activity.

Amino acid 2 (Abu) permits some variation with alkyl chains of 2–3 carbons, resulting in good activity. Although (Thr[2])cyclosporine is a potent immunosuppressant, (Ser[2])cyclosporine is significantly less active. This would suggest that hydrophobic interactions are more important for the interaction of the aliphatic chain of amino acid 2 with the receptor.

Although (D-Pro[3])cyclosporine and (MeLeu[11])cyclosporine should have almost the same conformation as cyclosporine itself (similar NMR spectra of both analogues and similar structure of cyclosporine and (MeLeu[11]) in the solid state) they are negative variants, suggesting that in this case the steric bulk of the peptide side chains, in position 3 and 11 respectively, probably prevents efficient binding of these derivatives to the cyclosporine receptor. The loss of activity observed with (D-MeVal[11])cyclosporine, a derivative in which the conformation of the peptide ring at this position is certainly different (NMR) from that of cyclosporine, also confirms that the carbon chain of amino acid 11 is important for biological activity.

Minor variations of the structure of amino acid 11 can reduce the immunosuppressive activity of cyclosporine analogues. According to X-ray structure analyses on cyclosporine the *pro-R* methyl group of *N*-methylvaline would appear to be closer to the *N*-methyl group of MeBmt than the *pro-S* methyl group and is somewhat more sensitive to variation. The lower activity of the MeAla analogue could be due to the failure to fill a critical hydrophobic cavity on the receptor or to reduce conformational rigidity of the molecule.

Table 1. Immunosuppressive activity of some cyclosporine analogues and derivatives. Irrespective of its source, the cyclosporine (CS) has strong immunosuppressive activity (***); H-MeBmt-OH has no activity (*).

CS contains	Position	Analogue/Derivative contains	Source [a]	Activity [b]
MeBmt	1	(*O*Ac)MeBmt	ss	*
MeBmt	1	(3′-Deoxy)MeBmt	ss	*
MeBmt	1	(Dihydro)MeBmt	ss	**
MeBmt	1	MeThr	s	*
Abu	2	Ser	s	**
Abu	2	Ala	n	**
Abu	2	Thr	n	***
Abu	2	Val	n	**
Abu	2	NorVal	n	***
Sar	3	D-Pro	s	*
MeVal	11	MeLeu	s	*
MeVal	11	D-MeVal	n, s	*
MeVal	11	aMeIle	s	*
MeVal	11	MeIle	s	(*)*
MeVal	11	MeAla	s	*

[a] n = natural, ss = semisynthetic, s = synthetic. [b] *** = strong immunosuppressive activity in pharmacological models previously used to test cyclosporine [2-6]; ** = average activity; * = little or no activity.

6. Conclusion

Some structure-activity relationships (SAR) for cyclosporine are now emerging from the study of specifically modified derivatives. However, in order to obtain a more exact picture of SAR for cyclosporine, and then to synthesize derivatives with an improved activity profile, much remains to be done.

It is nevertheless already clear that the unusual MeBmt chain is intimately involved in the biological actions of the cyclosporine molecule but that it alone is not sufficient for immunosuppressive activity. The biological activity is associated with a larger portion of the cyclosporine structure and the results presented above (Section 5) indicate that this probably includes amino acids 1, 2, 3 and 11.

The synthesis of further derivatives should help answer many of the remaining questions concerning the structure-activity relationships of this drug.

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Basic Principles of Protease-Catalyzed Peptide Bond Formation

By Hans-Dieter Jakubke*, Peter Kuhl, and Andreas Könnecke

The stereospecific formation of peptide bonds under mild conditions and without side reactions is still a formidable task in peptide synthesis. One approach that springs to mind, namely the use of the naturally occurring catalyst involved in the biosynthesis of proteins, the ribosomal peptidyl transferase, cannot be realized in practice. The fact, however, that the natural cleavage of proteins is carried out by other enzymes, namely the proteases, together with the reversibility of these cleavage reactions in principle, has led to an interesting synthetic concept. Proteases normally catalyze the enzymatic degradation of proteins and peptides by hydrolytic cleavage of the peptide bond in an exergonic reaction. The use of physicochemical principles in order to influence the equilibrium, the concentration of products, and the kinetic parameters of the reaction results in the successful application of the catalytic properties of proteases to peptide synthesis. The purpose of this review is to describe and summarize the methods used in such approaches and to attempt a systematic categorization. The principles are applied to the synthesis of such practically relevant products as aspartame and human insulin.

1. Introduction

Peptide synthesis has made a significant contribution over the last 30 years to progress in peptide research[1-3]. Besides the total synthesis of native active peptides and their analogues, which play an important role in the elucidation of structure-activity relationships, the semisynthesis of proteins[4] as well as the chemical modification of peptides and proteins, in order to modulate physiological or pharmacological effects, have been the focus of attention.

Ideally, the formation of the peptide bond should proceed fast and without racemization or other side reactions and, using equimolar amounts of carboxy and amino components, should result in quantitative yields. This goal, however, is not reached by any of the more than 130 variations of chemical peptide bond formation. Even the use of pro-

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ven synthetic concepts in combination with well-tested coupling methods, which in model systems do not result in any racemization, does not guarantee the absolute avoidance of racemization when applied to the condensation of peptide segments. Accordingly, in order to improve peptide synthesis, the avoidance of undesired side reactions plays an important role. Based on such considerations, the use of appropriate enzymes to form the peptide bond springs to mind, since most enzymatic reactions are highly stereospecific. Unfortunately, one cannot use the ribosomal peptidyl transferase to such an end, since it can only act as an integral component of the ribosome in coordination with further factors that are involved in elongation of the peptide chain[5].

Based on considerations concerning chemical equilibria, *van't Hoff* already discussed in 1898 the possibility of using proteases, which normally catalyze the hydrolysis of peptide bonds, to catalyze their formation[6]. About 40 years later *Bergmann* and *Fraenkel-Conrat* presented experimental proof that the reversibility of protease-catalyzed reactions can be used to form peptide bonds[7,8]. *Bergmann* and his students, in particular *Fruton,* came to the right conclusions about enzymatic peptide synthesis, based on results on the hydrolytic action of proteases as well as their substrate specificity and stereospecificity. Enzymatic peptide synthesis, however, lost its importance with the elucidation of the central principles of protein synthesis in vivo. Apart from subsequent basic research, it was only unambiguously shown in the mid-seventies that proteases could be used successfully as biocatalysts in the synthesis of peptides on a preparative scale. The use of biocatalysts in peptide synthesis lies within the general trend to employ enzymes for organic synthesis[9], and the numerous reviews dealing with this subject[10-19] reflect the wide interest in protease-catalyzed peptide synthesis over the last 10 years.

It is in principle possible to influence the enzymatic formation of peptide bonds either thermodynamically or kinetically. Based on energetic considerations, significant differences emerge. Taking the basic principles of peptide bond formation using proteases as catalysts into account, an attempt will be made to illustrate systematically the present possibilities and limitations of this novel synthetic approach.

2. Thermodynamically Controlled Peptide Synthesis

The thermodynamically controlled formation of peptide bonds represents the direct reversal of the catalytic cleavage of peptides by proteases[10-13]. Since, however, concentrations are used in the description below instead of activities, this is not an exact thermodynamic treatment. In contrast to the hydrolysis, the synthesis of a peptide bond is an endergonic process, i.e. proceeds with loss of entropy and is energetically so unfavorable that the equilibrium constant K_{syn} for the coupling of two unprotected amino acids is $<10^{-5}$. Since the ionic forms of the two substrates are unreactive, for the thermodynamic approach two equilibria have to be taken into account:

$$R{-}COO^{\ominus} + H_3\overset{\oplus}{N}{-}R' \overset{K_{ion}}{\rightleftharpoons} R{-}COOH + H_2N{-}R' \overset{K_{inv}}{\rightleftharpoons} R{-}CO{-}NH{-}R' + H_2O$$

Preceding the "inversion equilibrium" K_{inv} between the uncharged substrates and the product is an "ionization equilibrium" K_{ion}. Taking the concentration of water into the equilibrium constant, the total process is given by

$$K_{syn} = K_{ion} \cdot K_{inv} = [R{-}CO{-}NH{-}R'] \cdot ([R{-}COO^{\ominus}] \cdot [H_3\overset{\oplus}{N}{-}R'])^{-1}$$

For any given pair of substrates and known pH, K_{ion} and K_{inv} are fixed. Therefore, the peptide concentration for the inversion equilibrium is dependent on the concentrations of the uncharged substrates that are formed in the preceding ionization equilibrium. These concentrations in turn are determined by their pK values. pK values of *N*- and *C*-protected amino acids as well as those for longer segments are substantially different from those of free amino acids; therefore, sufficiently high concentrations of uncharged substrates are present in the ionization equilibrium to give measurable concentrations of peptide in the inversion equilibrium.

The only function of the protease is to accelerate the attainment of the equilibrium for formation of the peptide. Its effectiveness is greater the more specific the protease is for the substrates. Therefore, reaction conditions should be chosen that ensure a high catalytic activity of the protease. The pH optimum of the synthesis lies—apart from pepsin-catalyzed couplings—in the pH range between the pK of the α-carboxyl group and that of the amino group of the substrates, i.e. normally between pH 6 and 7. The time necessary to finally attain the inversion equilibrium is determined by the concentration and the catalytic activity of the protease as well as the affinity of the protease for the substrates; this can be several minutes up to several days.

Thermodynamically controlled peptide synthesis can be employed for all proteases in conjunction with carboxy components unprotected at the *C*-terminus. However, if nonspecific proteases are used to condense segments, undesired peptide cleavages may occur. Even for highly specific proteases, such side reactions can take place if the sequence of one segment contains any amino acids that correspond to the substrate specificity of the protease.

There are two principal ways by which one can further influence thermodynamically controlled peptide formation:

- —increasing K_{ion} by alteration of the pK values of the substrates, and
- —increasing the concentration of the peptide product via manipulations based on the law of mass action.

Both possibilities can be achieved in quite different ways; in practice, however, one generally prefers to influence the equilibria in favor of synthesis by a combination of both factors. For didactic reasons the different possibilities of control are discussed separately below.

2.1. Increase in K_{ion}

For a given set of reaction conditions there are two ways to decrease the difference in pK values between amino and

carboxy components in order to increase K_{ion}. This leads, in turn, to an increase in $K_{syn} = K_{ion} \cdot K_{inv}$.

2.1.1. Use of Water-Miscible Organic Solvents[20]

Water-miscible organic solvents decrease the acidity of the α-carboxy group of the carboxy component, whereas they only marginally influence the pK value of the amino group of the nucleophile. For example, the pK value of acetylglycine (Ac-Gly) in water is 3.60, while in 80% (v/v) dimethylsulfoxide it is 6.93; the pK values of Gly-NH_2, 8.20 and 8.10, respectively, remain almost constant. Since pK_{app} values measured in organic solvents have no great relevance, pK values determined under the same conditions should bear greater significance. In water ΔpK for acetylglycine/Gly-NH_2 is 4.60, while in 80% (v/v) DMSO it is only 1.11. A variety of other cosolvents can be used to change the pK value by one to two units, resulting in a significant increase in K_{syn}. For the coupling of 1 mM Z-Trp with 100 mM Gly-NH_2 at pH 6.7 using chymotrypsin, K_{syn} is 0.45 M^{-1} in water, 2.12 M^{-1} in 60% (v/v) glycerol and 38 M^{-1} in 85% (v/v) 1,4-butanediol.

This approach, however, is problematic insofar as the catalytic activity of proteases decreases with increasing concentration of the cosolvent; thus, the time required to reach the inversion equilibrium increases. Using 50% (v/v) ethanol, dimethylformamide (DMF), DMSO, dioxane, acetone, or acetonitrile results in inactivation of chymotrypsin, and no synthesis occurs. Only polyalcohols, which act as enzyme stabilizers, may be used at higher concentrations without inactivation of the enzyme[21], but even in these cases one finds a negative effect on the catalytic activity[22-25]. It was shown that no significant alteration of the substrate specificity occurs[20].

2.1.2. Use of Biphasic Systems

In systems consisting of an aqueous phase and a nonmiscible phase (nonpolar organic solvent), pK values are influenced in such a way that K_{ion} increases[23]. Depending on the volume ratio α of organic and aqueous phase and the partition coefficient P, an increase in the pK values of the carboxy components and a decrease in the pK values of the amino components by $\lg(1+\alpha \cdot P)$ is observed.

Since the enzyme is localized in the aqueous phase, the activity can be influenced only by the saturation concentration of the organic solvent in water, and the enzyme is therefore inhibited far less than by solvents miscible with water[24,25]. This advantage, however, is counteracted by the prolonged time required to reach equilibrium, and additional partition equilibria are most likely the rate-determining steps. Solubility of the substrates in the nonpolar organic phase limits the general use of biphasic systems for the enzymatic peptide synthesis.

2.2. Influence on Product Formation Based on the Law of Mass Action

The first positive experimental results for the potential use of a reversal of protease-catalyzed peptide hydrolysis were based on the limited solubility of the products, which thus are removed from the inversion equilibrium and accumulate[11]. The product can also be removed from the equilibrium by extraction or specific complexation.

2.2.1. Formation of Insoluble Products

If sufficiently high concentrations of substrates are employed, such that in the equilibrium K_{inv} it is possible to have a peptide concentration that lies above the maximal saturation concentration, precipitation occurs and thus the product of the synthesis accumulates. This can be explained using the law of mass action (see also [23]). If two substrates A and B of equal concentration react to form a product C, the equilibrium $A + B \rightleftharpoons C$ exists in solution, the equilibrium constant of which is given by Equation (1).

$$K = [C]([A] \cdot [B])^{-1} = [C] \cdot [A]^{-2} \tag{1}$$

If part of the product C forms a precipitate, Equation (2) holds.

$$K_{app} = ([C]_l + [C]_s) \cdot [A]^{-2} \tag{2}$$

where $[C]_l$ is the maximal concentration of the product in solution and $[C]_s$ the concentration of the insoluble product with respect to the total volume.

Using the starting concentration $[A]_0$, the mass balance results in Equation (3)

$$[A]_0 - [A] = [C]_l + [C]_s \tag{3}$$

with [A] as the equilibrium concentration of the substrate A in solution. Insertion of Equation (3) into Equation (2) results in

$$K_{app} = ([A]_0 - [A]) \cdot [A]^{-2} \tag{4}$$

Substitution of $[A] = \left(\frac{[C]_l}{K}\right)^{1/2}$ from Equation (1) with $[C] = [C]_l$ into the above equation gives, after rearrangement, Equation (5).

$$K_{app} = \frac{K}{[C]_l}[A]_0 - \left(\frac{K}{[C]_l}\right)^{1/2} \tag{5}$$

Thus, the apparent equilibrium constant for a reaction in which some of the product precipitates due to its limited solubility in the system is greater the higher the starting concentration of substrates and the lower the solubility of the product in this system.

Using one component in excess may result in almost quantitative reaction of the other substrate. This method is very popular in practice since the condition of low solubility of the product compared to that of the substrates frequently holds.

2.2.2. Extraction of Products

In biphasic systems the product is removed from the equilibrium if, due to a favorable position of the partition

equilibrium, it is extracted and thus accumulates in a nonpolar phase that is not miscible with water. *Martinek* et al.[23] derived the following equation for a reaction A + B ⇌ C + D [Eq. (6)].

$$K_{\text{biphas}} = K_{\text{aq}} \frac{(1+\alpha P_{\text{C}})\cdot(1+\alpha P_{\text{D}})}{(1+\alpha P_{\text{A}})\cdot(1+\alpha P_{\text{B}})} \qquad (6)$$

where $\alpha = V_{\text{org}}/V_{\text{aq}}$ and P is the partition coefficient. They showed that $K_{\text{biphas}}(\alpha)$ shows a maximum for a defined ratio of partition coefficients. This means that the effective equilibrium constant may be smaller or larger than that in either of the two phases alone.

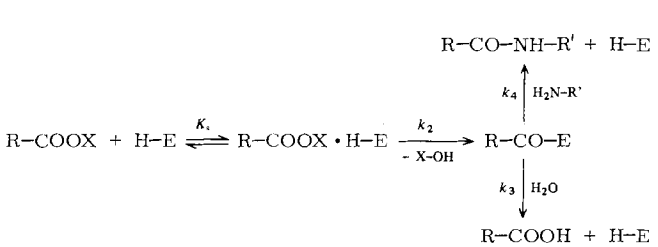
In most cases, however, the product is only marginally soluble in the organic phase; it precipitates and is thus removed from the equilibrium[24-28]. This can also be achieved by the use of particular solvent combinations which allow the adjustment of the saturation concentration of one substrate, so that the product with the longer peptide chain is less soluble in that particular system[24].

2.2.3. *Specific Complexation of the Product*

If compounds are available that can form specific complexes with the product, the latter can be removed from the equilibrium by adding such a complex-forming material and the complex can be accumulated[29] (see also Section 4.7).

3. Kinetically Controlled Syntheses

Investigation of the catalytic mechanism of serine and cysteine proteases using chymotrypsin and papain as examples revealed that, in the presence of nucleophiles, acyl-enzyme intermediates R–CO–E are deacylated competitively by water and the nucleophile H_2N-R'[30-32]. If the nucleophile is an amino acid or peptide derivative, then a new peptide bond is formed during the aminolytic deacylation (Scheme 1). If $k_2 \gg k_3 + k_4$ and $k_4[H_2N-R'] > k_3[H_2O] = k_3'$, then a kinetically controlled accumulation of the peptide product occurs, with a concentration greater than the thermodynamic equilibrium concentration. Especially suitable carboxy components for this type of enzymatically catalyzed peptide synthesis are acylamino acid alkyl esters if they match the substrate specificity of the particular protease, since in general they fulfill the condition $k_2 \gg k_3 + k_4$. Furthermore, k_2 of the ester substrate is substantially greater than k_2 of the peptide formed[33-35], which results in a maximum for product formation (Fig. 1) before the slower hydrolysis of the product starts to become important.



Scheme 1. Peptide synthesis catalyzed by serine and cysteine proteases (H–E) with R–COOX as the acyl donor (carboxy component) and H_2N-R' as *C*-protected amino acid or peptide (amino component); X = alkyl.

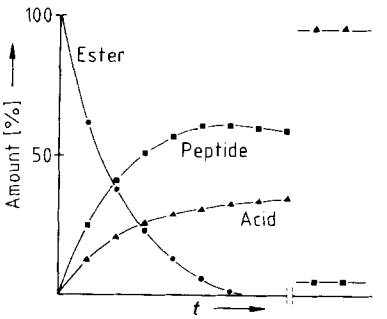


Fig. 1. Characteristic reaction pathway of a kinetically controlled peptide synthesis using an *N*-protected amino acid ester or peptide alkyl ester as acyl donor.

The area in which kinetically controlled synthesis can be used in practice is limited to serine and cysteine proteases with preferably acylamino acid esters as the carboxy component. The reactions are characterized by short reaction times and low enzyme requirements. In contrast to the thermodynamically controlled equilibration, here the ester substrate only occurs once as the acyl-enzyme intermediate, which is the decisive step for the ratio of peptide formation to hydrolytical cleavage.

3.1. Nucleophile Specificity of Proteases

Substrate binding sites in the active centers of proteases exhibit differentiated specificity towards nucleophiles such as amino acid and peptide derivatives. This influences primarily k_4 and thus the success of kinetically controlled peptide synthesis[13,32,36-41]. An acyl-enzyme breaks down via hydrolysis and aminolysis with reaction velocities v_3 and v_4, respectively. From Scheme 1, Equation (7) is obtained.

$$\frac{v_3}{v_4} = \frac{\dfrac{\text{d[R–COOH]}}{\text{d}t}}{\dfrac{\text{d[R–CO–NH–R']}}{\text{d}t}} = \frac{k_3'[\text{R–CO–E}]}{k_4[H_2NR'][\text{R–CO–E}]} \qquad (7)$$

This simplifies to Equation (8)

$$\frac{\text{d[R–COOH]}}{\text{d[R–CO–NH–R']}} = \frac{k_3'}{k_4[H_2N-R']} = \frac{p}{[H_2N-R']} \qquad (8)$$

with $p = k_3'/k_4'$. The partition constant p corresponds to the necessary concentration of nucleophile for d[R–COOH] = d[R–CO–NH–R'][40]; i.e., partition of the acyl-enzyme into peptide and acylamino acid occurs to 50% each. Table 1 contains some partition constants. These values indicate the possible use of p as an efficiency parameter for various nucleophiles. They also show that p is not a universal constant, since it is influenced by the acyl part of the acyl-enzyme. Nevertheless, it is possible to deduce the order of magnitude of the concentration of nucleophile required for a particular peptide synthesis directly from the value of p. Equation (8) is strictly valid only

Table 1. Partition constants p of some acylchymotrypsins [a].

Nucleophile	p [mol·L^{-1}·10^{-3}] Ac-Phe-CT [b]	Ac-Tyr-CT [c]	Mal-Phe-CT [40]
Gly-NH_2	90.0	104.7	95.0
Ala-NH_2	22.7	23.0	35.5
Val-NH_2		21.4	73.3
Leu-NH_2		19.3	20.2
Arg-NH_2			0.15

[a] CT = chymotrypsin; Mal = maleyl-(3-carboxyacryloyl-). [b] δ-CT; calculated according to [32]. [c] α-CT; calculated according to [39].

for the case where one finds a linear relationship between the concentration of nucleophile and the partition in the range of interest. This is true in the majority of cases investigated. However, deviations from linearity have been found[39]. The mathematical treatment of these cases is rather complicated since p becomes a function of the concentration of nucleophile.

3.2. Influence of the Reaction Medium

Since only the non-protonated form of the nucleophile reacts in the aminolytical deacylation of the acyl-enzyme, it is necessary to take the effective concentration of nucleophile instead of the total concentration into account. This can be calculated from the pK value of the nucleophile and the pH of the medium. Since pK values of α-amino groups of amino acid and peptide derivatives lie around 8, it is advisable to carry out kinetically controlled peptide synthesis at pH ≥ 8. The partition constant p is also dependent on pH. For the proteases trypsin and chymotrypsin p is reduced in alkaline medium, which results in increased synthesis[37]. Organic solvents and ionic substances as well as the reaction temperature can influence the partition constant p.

4. Selected Examples

Compared to the well-established chemical coupling reactions, a synthetic strategy based on proteases as catalysts is naturally still in its infancy. The majority of studies with respect to the usefulness of proteolytic enzymes for the formation of peptide bonds were initially model studies. In general, therefore, the methodological aspects were more important than any practical applications and substrates were chosen in such a way as to correspond to the specificity of the proteases employed. Recently, however, examples of the syntheses of biologically active peptides using coupling steps exclusively or partially catalyzed by proteases have increased. The area of semisynthesis of proteins has seen considerable progress based on the use of proteases[4,42].

The following selected examples illustrate the strategy and tactics as well as the present possibilities for the use of proteolytic enzymes in the synthesis of biologically active peptides and proteins.

4.1. Aspartame

The precursor (Z-Asp-Phe-OMe) for the peptide sweetener aspartame (Asp-Phe-OMe) is obtained by a thermolysin-catalyzed coupling of Z-Asp with Phe-OMe in a thermodynamically controlled reaction. An insoluble salt is formed with the enantiomer of the amino component, Z-Asp-Phe-OMe · Phe-OMe, which results in an almost quantitative shift of the equilibrium towards the product[43]. In this reaction the strategy of minimal protection is fortuitously complemented by the salt formation. Enzymatic synthesis is thus superior to chemical methods since the latter require the use of β-protected aspartate derivatives.

4.2. Leucine-Enkephalin

The kinetically controlled synthesis of Leu-enkephalin, Tyr-Gly-Gly-Phe-Leu, was achieved by stepwise elongation of the C-terminal end of the peptide via catalysis with the serine exoprotease carboxypeptidase Y (CPD-Y)[44]. Amino acid amides were used as nucleophiles since free amino acids produce only low yields and amino acid esters give rise to side reactions which are difficult to control[45]. Thus, the seemingly complicated route of selectively removing the C-terminal amide group with CPD-Y followed by esterification of the peptide had to be resorted to before it was possible to use the peptide in the next coupling step as the substrate. The protecting group for the α-amino function was Bz-Arg, which can easily be removed by tryptic cleavage[17,46].

4.3. Dynorphin(1-8)

Dynorphin(1-8), Tyr-Gly-Gly-Phe-Leu-Arg-Arg-Ile, a Leu-enkephalin that is extended at the C-terminal end, was synthesized by a combination of thermodynamically and kinetically controlled couplings with papain, chymotrypsin, and trypsin as biocatalysts[47]. To this end, four dipeptides were synthesized enzymatically and subsequently condensed to yield two tetrapeptide segments. Coupling of the two tetrapeptides Boc-Tyr(Bzl)-Gly-Gly-Phe-OEt and Leu-Arg-Arg-Ile-NH-NH-C_6H_5 with chymotrypsin results in a partially protected octapeptide, which after deblocking yields the biologically active dynorphin(1-8) (Fig. 2). The protecting group for the carboxy function is in general phenylhydrazide, which can be introduced via papain catalysis into Boc-amino acids[48] and can easily be removed by oxidation or can be converted into an ester[49].

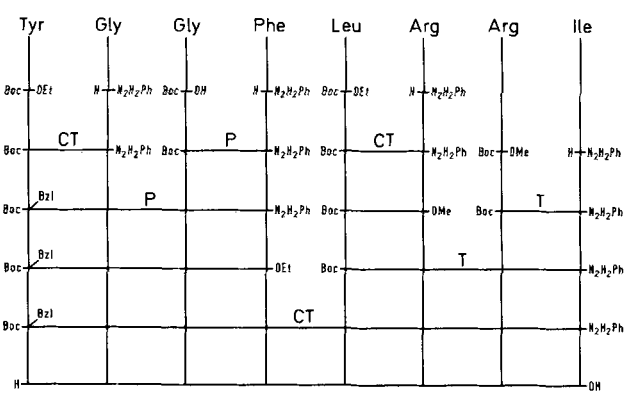


Fig. 2. Synthesis of dynorphin(1-8) catalyzed by proteases [47]; CT = chymotrypsin, P = papain; T = trypsin; Bzl = benzyl, Boc = tertbutoxycarbonyl.

This example demonstrates two major advantages of enzymatic peptide synthesis: condensation of segments containing a variety of amino acids can be achieved without the risk of racemization and it is not necessary to protect the guanidino group of arginine.

4.4. Bz[Gly^{21}(Acm)Cys^{31}] EGF(21—31)NHEt

The advantages of the combined use of chemical and enzymatic methods are illustrated by the synthesis of segments of the mouse epidermal growth factor (EGF)[50]. All couplings catalyzed by proteases were carried out under kinetic control (Fig. 3) since this ensures a short reaction time, even when low concentrations of enzyme are used. Enzyme-labile protecting groups were Bz-Arg and Bz-Phe[17,46], which were also used to regulate the hydrophobicity and hydrophilicity of the partial sequences.

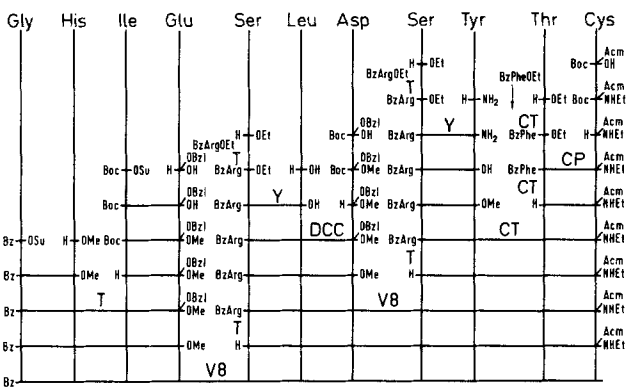


Fig. 3. Synthesis of Bz [Gly^{21}(Acm)Cys^{31}] EGF(21—31)NHEt [50]; CP = chymopapain, V8 = *Staphylococcus aureus* protease V8, Y = carboxypeptidase Y, DCC = dicyclohexylcarbodiimide; Bz = benzoyl, Su = succinimido, Acm = acetamidomethyl.

4.5. Eledoisin (6-11)-Hexapeptide

This hexapeptide was obtained by kinetically controlled couplings using papain and chymotrypsin in the biphasic system CCl_4/buffer[51] (Fig. 4). The biphasic system was employed not primarily to influence the equilibrium, but to insure a high catalytic activity of the protease dissolved in the buffer as well as excellent solubility of the substrates in the organic phase. Thus, the total reaction volume could be kept small, ensuring yields that are higher than can be achieved using water-miscible cosolvents[52].

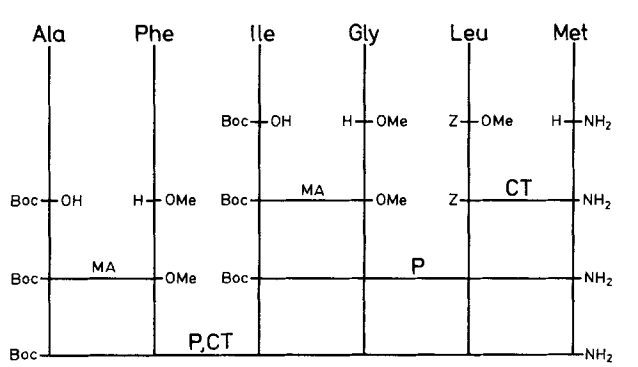


Fig. 4. Synthesis of eledoisin (6-11)-hexapeptide [51]; MA = mixed anhydride method; Z = benzyloxycarbonyl.

The *C*-terminal dipeptide could also be obtained by a thermolysin-catalyzed reaction in which the equilibrium of the thermodynamically controlled condensation was shifted in the direction of products by extraction of the product Z-Leu-Met-NH_2 into the organic phase.

4.6. Human Insulin

Using thermodynamically controlled reactions it is possible in a variety of ways to obtain semisynthetic human insulin and analogues from porcine insulin, which is available from natural sources (Fig. 5). The control of the thermodynamic equilibrium is always achieved by high concentrations of the appropriate nucleophilic amino component and frequently also by a large volume of water-miscible organic cosolvents. The simplest way to obtain the human insulin ester is in a one-step reaction involving an enzyme-catalyzed exchange of the *C*-terminal alanine-B30 of porcine insulin for a threonine ester[53-57]. Using the above reaction conditions prevents almost completely the possible cleavage of the Arg^{B22}-Gly^{B23} bond by trypsin. Such methods are now used commercially for the production of human insulin.

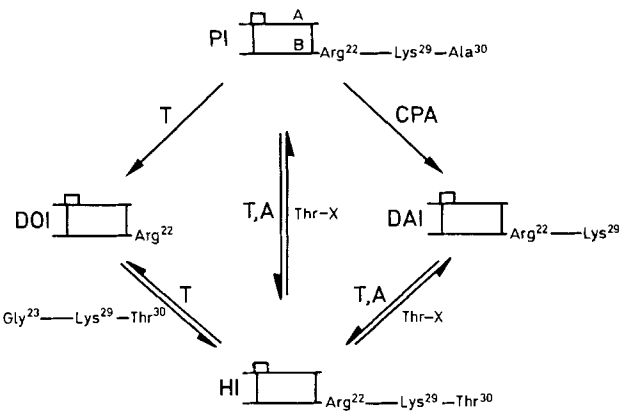


Fig. 5. Semisynthetic conversion of porcine insulin into human insulin; PI = porcine insulin, HI = human insulin; DAI = des-Ala^{30}-insulin, DOI = deoctapeptide$^{B23\text{-}B30}$-insulin, A = *Achromobacter* protease, CPA = carboxypeptidase A.

One can also use des-Ala^{B30}-[54,58,59] or deoctapeptide$^{B23\text{-}B30}$-insulin[21,60] as substrates which can be coupled to synthetic peptides and thus provide an easy approach to the synthesis of insulin analogues[61]. Apart from trypsin, a lysine-specific *Achromobacter* protease[54,58,59] and CPD-Y[55] have been used. The advantages of the enzymatic semisynthesis over chemical methods are obvious for the above mentioned examples since nearly all problems connected with blocking or deblocking are avoided using proteases.

4.7. Ribonuclease S-Peptide(1-15)

One example for the specific complexation of the peptide formed, which is thus removed from the synthesis equilibrium, is the coupling of the synthetic ribonuclease S-peptide segments 1—10 and 11—15 catalyzed by clostripain. The resulting peptide 1—15 is complexed by native ribonuclease(21-24) S-protein[29].

5. Use of Immobilized Proteases

For future applications of the enzymatic peptide synthesis, the use of immobilized proteases will probably be of technological and economical importance. Basic studies on the applicability of immobilized proteases have been carried out under kinetic as well as thermodynamic control using covalently bound chymotrypsin, trypsin, thermolysin, and papain[62–64]. It was shown that the immobilized biocatalysts have almost the same efficiency as the native enzymes. Contrary to earlier results[64], it could also be shown that immobilized papain is ideally suited for kinetically controlled synthesis at high pH values[37].

The effort involved in immobilizing an enzyme is compensated for by the possibility of its repeated use. Depending on the stability of the immobilized protease, this is guaranteed if short reaction times are employed, which is a characteristic of kinetically controlled reactions. In model experiments the possibility of repeated use under different reaction conditions could be demonstrated[37,62–64]. A further notable advantage of immobilized enzymes is the fact that the products are not contaminated with proteolytically active or denatured enzymes. Furthermore, the possibility of a continuous flow application may become a reality.

Of practical importance so far is the synthesis of the aspartame precursor using ionically bound thermolysin in a mixture of greater than 99% (v/v) ethyl acetate; this, however, requires rather long reaction times[65].

The thermodynamically controlled coupling of des-Ala^{B30}-insulin with Thr-O*t*Bu in the presence of high concentrations of water-miscible organic solvents is also effectively catalyzed by covalently bound *Achromobacter* protease[66] or trypsin[67].

6. Criteria for Synthesis Planning

In contrast to the synthesis of di- and tripeptides, it is necessary for the assembly of longer chains of peptide sequences to carry out an exact synthetic plan, the specific method of coupling being at first of little importance. The strategy of a peptide synthesis normally means the order in which the particular amino acid residues are coupled, namely either via stepwise addition from the *C*- or the *N*-terminal end or via condensations of presynthesized segments (segment condensation). A stepwise chemical synthesis starting from the *N*-terminal end, analogous to the ribosomal protein biosynthesis, is prohibited due to the permanent risk of racemization. Apart from the severe solubility problems in the synthesis of polypeptides with complete side-chain protection, it is mainly the risk of racemization that leads to the enormous variety of synthetic strategies for the chemical synthesis of peptides.

Although enzyme-catalyzed coupling reactions take place stereospecifically (free of racemization) and require only minimal side-chain protection, thereby solving the aforementioned problems, the substrate specificity is a limitation, which prevents this method from being universally applicable. A protease is much more limited in its area of use compared to chemical coupling methods, which are only influenced at most by the steric factors of the components to be coupled. This disadvantage, however, is compensated for completely by other advantages. These include not only the aforementioned factors (the stereospecific course of the reaction and the dispensing with the protection of side chains of trifunctional amino acids) but also mild and ecologically advantageous reaction conditions. If the potential of proteolytic enzymes that are to be used principally for the formation of peptide bonds is examined, it is seen that exopeptidases should find preferential application to the stepwise synthesis of short peptides and segments, while condensations to larger blocks should best be carried out by catalysis using endopeptidases of the required specificity. Exopeptidases have the great advantage that, in starting a stepwise synthesis either from the *C*-terminal end (aminopeptidases) or from the *N*-terminal end (carboxypeptidases), the internal peptide bonds within the growing chain can no longer be proteolytically cleaved by the enzyme employed as the biocatalyst. For preparative purposes aminopeptidases seem less well suited, since both substrate and product contain free α-amino functions which complicate the isolation of the product. Furthermore, since the substrate specificity is not strongly determined, there is a possibility of undesired coupling reactions. Carboxypeptidases exhibit superior properties as biocatalysts for stepwise coupling reactions, especially the serine protease carboxypeptidase Y (see also Section 4.2). Since, however, even the application of CPD-Y shows some preparative limitations, it is advantageous to have endopeptidases available for the synthesis of short peptides, especially since such enzymes can even be used for the synthesis of dipeptides if appropriate combinations of protecting groups are employed. Furthermore, one can use endopeptidases with broader specificity for stepwise synthesis as was shown for oligopeptide synthesis catalyzed by papain[68].

Problem-free coupling of segments require endopeptidases with high substrate specificity and the absence of the specific amino acids in the segments, except for the position where the peptide bond is to be formed. Apart from the lysine-specific *Achromobacter* protease, trypsin catalyzes the formation of a peptide bond after lysine and arginine residues. Thus, coupling of segments can only be carried out under the conditions described above for carboxy components that carry one of the mentioned basic amino acids in the *C*-terminal position. This restriction necessarily leads to the conclusion that one may employ less-specific proteases to catalyze coupling of segments. In order to avoid undesirable chain cleavage, manipulations that favor the synthesis have to be carried out, as described in Sections 2 and 3. From the literature, examples are known for the synthesis of biologically active oligopeptides using exclusively protease-catalyzed coupling steps (see also Sections 4.2 and 4.3). However, without intending to play down this ambitious synthetic concept, it seems unlikely that in the near future chemical coupling methods will be generally replaced by the enzymatic approach. Instead, the enzyme-catalyzed couplings will contribute significantly to the methods available to the peptide chemist.

In a given synthesis project it must first be determined if, for the separation into segments, favorable combinations

of amino acids can be found that permit protease-catalyzed coupling of segments. The synthesis of the segments should preferably be carried out in combination with proven chemical coupling reactions. Therefore, simple chemical coupling reactions without the risk of racemization are preferred by all means over enzymatic reactions, especially for segments containing a large number of amino acids that do not need further protecting groups. On the other hand, for segments with predominantly trifunctional amino acid residues where semipermanent side chain protection is not desired, enzyme-catalyzed reactions using proteases of the appropriate substrate specificity are preferable. In this way, segments are obtained with sufficient solubility to be used in protease-catalyzed block couplings.

For the use of serine and cysteine proteases a further point needs to be decided; namely, should the carboxy component be used as the acylamino acid or should a derivative (e.g. alkyl ester) that would favor acylation be used. Although the kinetically controlled reaction with little enzyme requirement and short reaction time should be preferable, the decision in each case will be determined by the overriding total synthetic concept. An unfavorable nucleophile specificity may be better taken care of in a thermodynamically controlled reaction with the appropriate manipulations of conditions than in a kinetically controlled coupling, where requirements are less flexible.

For the synthesis of biologically active peptides or segments with predominantly hydrophobic amino acid residues it is frequently necessary to overcome the poor solubility of the reactants through the introduction of solubilizing protecting groups[69]. The introduction of such solubilizing residues into the classical N^{α}- and C^{α}-protecting groups cannot be regarded as the solution to this problem; for enzyme-catalyzed peptide synthesis totally different protecting groups are required. Even polyethylene glycol esters, which have proved useful for chemical synthesis in aqueous solution[70], are less useful as carboxy components, whereas amino components blocked in this way can be reacted without any problems[71]. In general, protecting groups that can be removed under mild conditions are required, as is possible, for example, in the ease of Bz-Arg or Bz-Phe as α-amino protecting groups which can easily be cleaved off by trypsin or chymotrypsin[17,46,72]. Solubilizing ester groups attached to the carboxy component increase the solubility of the respective reactant in kinetically controlled reactions. After the coupling, however, this solubilizing effect is naturally lost. It is possibly preferable to use non-ionic solubilizing ester groups rather than charged residues.

The improvement of the solubility of reactants and products is of immediate importance for a continuous flow synthesis using immobilized proteases. Their application seems justified if the effort required for the immobilization is compensated for by the repeated use of the biocatalyst.

Finally, the question arises whether the use of proteases as catalysts can be of advantage for peptide bond formation via a polymer-based route. Simple model studies using a polymer-bound amino component show that polyethylene glycol is well suited as a soluble polymer[71]. Silica gel as the insoluble polymer matrix seems less promising since the fixed nucleophile is limited in its mobility and because of the possibility of steric hindrance between the enzyme and the polymer[73]. By the use of appropriate spacers as well as polymers with a high loading capacity for nucleophiles, these limitations should be successfully surmountable.

7. Summary and Prospects

Based on the classical studies of the reversibility of reactions catalyzed by proteases, it has been possible in the last ten years to show convincingly that proteolytic enzymes can in principle be used as biocatalysts. Thus, they can be employed in peptide bond formation on a preparative scale and are of practical use in the biotechnological synthesis of biologically active peptides and proteins. The stereospecificity of proteases guarantees the formation of stereochemically uniform products and requires only minimal semipermanent protection of side-chain functions in trifunctional amino acid residues. However, due to the substrate specificity, the universal applicability of proteases is limited. Therefore, it is of great importance to select proteases with modified substrate specificity based on strategic and tactical considerations with respect to the various product sequences. The advantages of both the thermodynamically and the kinetically controlled reactions have to be optimally exploited. Environmentally acceptable reaction conditions, which are characteristic of biotechnological processes, together with the potential for continuous flow application using immobilized proteases, should be an important stimulus to develop and perfect the methodology of enzyme-catalyzed peptide synthesis in order to improve and augment the armamentarium of the synthetic peptide chemist.

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Synthesis and Biological Activity of α-Methylene-γ-butyrolactones

By H. M. R. Hoffmann* and Jürgen Rabe

Dedicated to Dr. Wilhelm A. Schuler on the occasion of his 70th birthday

α-Methylene-γ-butyrolactones [dihydro-3-methylene-2(3*H*)furanones] constitute an important group of natural products and possess wide-ranging biological activities. Progress in the synthesis of the heterocycle and the classification of the synthetic methods are not only of practical interest, but also fundamentally important as a current example for the construction of an unusual 1,4-functionality distance and an α-substituted acrylic ester moiety which is susceptible to nucleophilic attack.

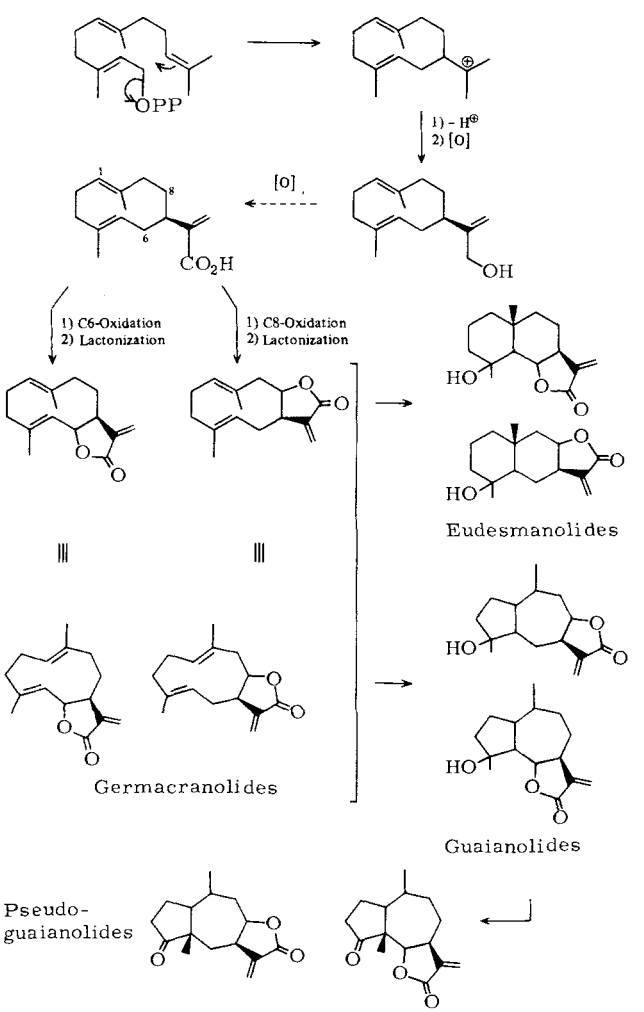
1. Introduction

The α-methylene-γ-butyrolactone ring is an integral building block of many natural products, especially the sesquiterpene lactones, which exhibit interesting biological properties. In a book[1a] published in 1973, ca. 200 representatives of this class of compounds together with their ^{1}H-NMR spectra and other physical data were listed; 6 years later there were already ca. 900[1b]. Since then the number of these compounds has risen further: a Chemical Abstracts Online Search with projection shows that at present at least 2000—3000 α-methylene-γ-butyrolactones, mainly of the sesquiterpene type, are known. Since the current number of structurally elucidated natural products has been estimated to be only between 25000 and 30000[2], α-methylenelactones represent (with approx. 10%) a major class of known natural products. α-Methylene-γ-butyrolactones have been dealt with in a series of articles[4a–d], which quickly appeared following the first review by *Grieco*[3] in 1975. After a description of the biological activities it is our purpose to present the various conceptions for the synthesis of the heterocycle and to describe recently developed syntheses.

2. Biosynthesis

The biosynthesis of the sesquiterpenoid α-methylene-γ-butyrolactones is fairly simple[1,5]. The compounds are derived from *trans,trans*-farnesyl pyrophosphate, which first cyclizes to give the strained cyclodecadiene skeleton of germacradiene (or germacra*triene*) and then reacts further intramolecularly to form a perhydroazulene system (e.g., guaiane and pseudoguaiane) or a decalin system (e.g., eudesmane). The sequence of oxidation steps is less well understood. In accord with Scheme 1, the lactone moiety, which is indicated by the suffix "olide", is *cis*- or *trans*-fused to a six-, seven-, or ten-membered ring. Further rearrangements and oxidative modifications give rise to the structural diversity of these compounds.

Many plants which belong to the large, species-rich family of the *Compositae*[1c] (composites) contain sesquiterpene lactones as characteristic constituents. These compounds are colorless, lipophilic, often bitter-tasting, and are mainly present in the leaf tissue, where they can constitute up to 5% of the dry weight. The closer two species are related to each other, the smaller is the difference between the distribution of these terpenes. In addition to morphology, i.e., the comparison of external plant form, chemotaxonomy, in which secondary plant metabolites are identified and compared, has established itself as a method for the botanical classification of plants and for the clarifica-



Scheme 1.

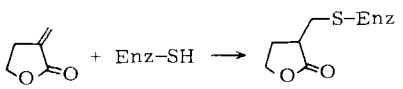
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tion of evolutionary problems (sesquiterpene lactones as chemotaxonomic markers)[1a,c].

3. Important Biological Activities

α-Methylene sesquiterpene lactones show cytotoxic, antitumoral, and bactericidal properties. Other representatives cause an allergenic contact dermatitis or affect plants by inhibition of growth. There are already several studies on the relationship between biological activity and structure[6-10]. As has been shown, α-methylene-γ-butyrolactones must be looked upon as alkylating agents which are biologically active because they undergo a Michael reaction with biological nucleophiles such as L-cysteine or thiol-containing enzymes (Enz-SH).

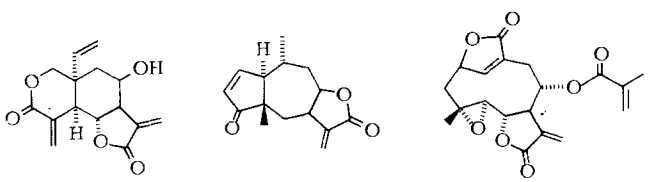


It is probable that these lactones inhibit the incorporation of selected amino acids into proteins, i.e., they inhibit the metabolism at the cellular level, but do not alkylate DNA[8,11-15].

Presumably, the residual molecule and its lipophilicity also determine the specificity and the site of the activity.

3.1. Antitumoral and Cytotoxic Activity

A large number of active sesquiterpene lactones, including vernolepin[18a], aromaticin[11], and elephantopin[18b], have been isolated from plant extracts which show tumor-inhibiting activity[16,17] (Scheme 2).

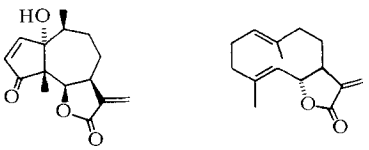


Scheme 2. From left to right: vernolepin, aromaticin, elephantopin.

It has been shown that almost all known cytotoxic sesquiterpene lactones possess an α,β-unsaturated lactone structure, and that the conjugated double bond must be exocyclic. A cyclopentenone or an additional α-methylene lactone moiety enhances the cytotoxic activity; hydroxy groups can also cause an enhancement. The high cytotoxicity of the sesquiterpene lactones is probably due to the inhibition of DNA synthesis and/or transcription[15]. However, protein synthesis, also, is partially impaired[13,14]. It should be mentioned, however, that at present there is no sesquiterpene cytostatic which is used clinically, apparently because of the relatively high toxicity of the compounds. Attempts to increase the activity by chemical modification have, so far, been unsuccessful.

3.2. Allergenic Activity

Many people suffer from an allergic contact dermatitis (ACD) which is caused by contact with plants or their chemical constituents[19]. Sesquiterpene lactones, which are sometimes present in the pollen, can cause this allergic contact dermatitis—even when carried by the wind. The presence of an α-methylene butyrolactone moiety is a sufficient requirement for the allergenic activity. For example, parthenin, present in *Parthenium hysterophoros,* is a primary allergen of this wide-spread and unusually aggressive pioneer plant. The allergy thus caused represents a serious dermatological problem in India and her neighboring countries[20].

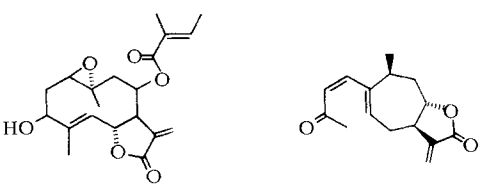


Scheme 3. Left: Parthenin; right: costunolide.

Perfume oils extracted from the costus root *(Saussurea lappa)*[21] or from the laurel *(Laurus nobilis)*[22], cultivated since antiquity, can also cause a dermatitis due to the germacranolide costunolide present in both mixtures. In order to obtain a perfume free from allergen, one passes the raw oil through a column containing a nucleophile on a solid support, e.g. β-aminoethyl-polystyrene. Thus, the allergen is bound to the nucleophile[19b]. Finally, even simple acrylic esters, such as those used in the printing trade and in other industries, can cause occupational dermatitis[19d]. With respect to the pathogenesis of ACD, it is assumed that the α-methylene lactone becomes bonded to a skin protein via a Michael reaction, thus forming an antigen which causes the sensitization of the lymphocytes[20b]. In view of the widespread occurrence of ACD, further research efforts can be expected in this area.

3.3. Phytotoxic and Antimicrobial Activities

In addition to the cytotoxic and allergenic activities described, phytotoxic activities are shown by a number of sesquiterpene lactones[6,7]. Thus, heliangin, a germacranolide of the tuberous sunflower *(Helianthus tuberosus L.,* also called topinambur or Jerusalem artichoke), and vernolepin, from *Vernonia hymenolepsis,* cause plant growth inhibition[6,23]. Xanthatin is also used in the regulation of plant growth[5] (Scheme 4).

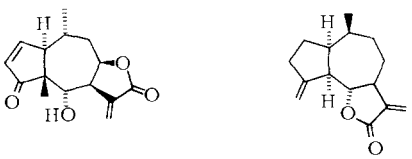


Scheme 4. Left: heliangin; right: xanthatin.

According to *Hager*[24a-c], α-methylene sesquiterpene lactones can attack an SH-group of the auxin-receptor complex; upon binding of the growth hormone auxin to its protein receptor the SH-group is set free. As a result of this

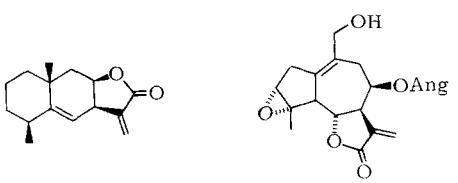
sulfur bond, the lactone effects the irreversible inhibition of plant growth. The α-methylene lactones present in the common sunflower *(Helianthus annuus L.)* appear to be *stress metabolites*, i.e. they are formed, e.g., during attack by pests, during periods of dryness or overexposure to sunlight and heat, and probably act mainly as chemical defenses against pests, especially microorganisms[24c]. This fascinating plant, originating in the USA and Mexico, is mainly cultivated at present in the USSR and in Eastern Europe. It is, after the soybean, the second most important oil-producing plant in the world (annual world production in 1982 more than 16 million metric tons of sunflower seeds)[24d].

Other α-methylene-γ-butyrolactones show bactericidal, fungicidal, and anthelminthic activities[25]. Helenalin[26a] and eremanthin[26b] are shown here as representatives of such compounds (Scheme 5).



Scheme 5. Left: helenalin; right: eremanthin.

Recently, *Picman* et al. were able to show that sesquiterpene lactones such as parthenin and alantolactone, which are present in the sunflower, also play a role in the defense of plants against insects[27a–c] and even against herbivorous mammals[27d]. Similarly, euponin, which has been isolated from the leaves of *Eupatorium japonicum*, inhibits the development of the fruit fly *(Drosophila melanogaster)* at the egg stage and thus protects the plant from insect attack[27e] (Scheme 6).



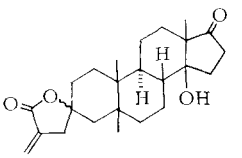
Scheme 6. Left: alantolactone; right: euponin.

Not only highly functionalized, complex sesquiterpene lactones but also simple representatives have been studied for their biological activity. Several years ago, two compounds with fungicidal properties were isolated from tulip bulbs and identified[28]. Tulipalin A is the simplest α-methylene-γ-butyrolactone possible (Chemical Abstracts Name: dihydro-3-methylene-2(3*H*)furanone). The 4-hydroxy derivative, i.e., tulipalin B, is present in nature as the (*S*)-enantiomer (Scheme 7). It appears certain that α-methylene-γ-butyrolactones, due to their high and selective antibiotic activities, afford important protection to plants. In the course of evolution, this fact, together with the outstanding adaptive and reproductive capabilities of the *Compositae*, has contributed to a selective advantage in the survival of this plant family and also to its broad distribution over all continents with the exception of Antarctica.

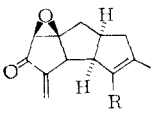


Scheme 7. Left: tulipalin A; right: tulipalin B.

In the future, the study of analogues[16] will become increasingly important. The steroidal spiro-α-methylene lactones[29], which are not found in nature, possess tumor-inhibiting activity (see also [10,66b]).

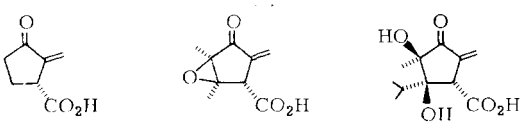


Thus, α-methylene-γ-butyrolactones can serve as a model in the search for biological activity. The structurally related five-membered-ring α-methylene ketones pleurotellol and pleurotellic acid have been found in fungi and show antibiotic activity[30] (Scheme 8).



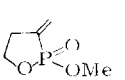
Scheme 8. R = CH_2OH: pleurotellol; R = CO_2H: pleurotellinic acid.

Comparatively simple representatives of this type are the cyclopentanoid antitumor agents called pentenomycins and methylenomycins, e.g., sarkomycin, methylenomycin A, and xanthocidin[31] (Scheme 9).



Scheme 9. From left to right: sarkomycin, methylenomycin A, xanthocidin.

In view of the similarity of the ester group to the $P(O)(OR)_2$ group as π-acceptor (compare also the Horner-Wittig reaction), a corresponding modification of the lactone is of interest. As *Benezra* et al.[32] were able to demonstrate, the biological activity changes: cyclic phosphonates (Scheme 10) show no allergenic activity and only a very low cytotoxicity.



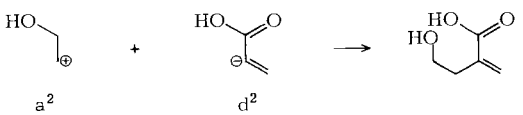
Scheme 10. 2-Methoxy-3-methylen-2-oxo-1,2λ⁵-oxaphospholane.

Because of their broad range of biological activities and their interesting structural features, α-methylene-γ-butyrolactones present a scientific challenge which is reflected in an increasing number of investigations and syntheses of these heterocycles.

4. Syntheses of α-Methylene-γ-butyrolactones

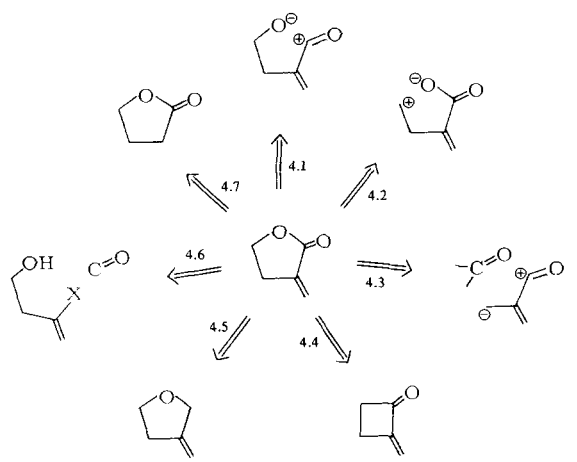
Two main problems dominate the synthesis of these lactones:

1. The construction of the unusual 1,4-functionality distance in the acrylic precursor of the heterocycle. This fundamental synthetic problem, which also appears in the synthesis of simpler five-membered heterocycles such as the furans, pyrroles, and thiophenes as well as their saturated derivatives, can be solved, among other methods, by "umpolung"[33], e.g., the combination a^2+d^2, where the d^2 component is frequently an enolate and the a^2 component an epoxide (umpolung). The combination a^1+d^3 is also feasible: in an efficient synthesis the d^3 building block (umpolung) is also an $a^1d^3d^{3'}$ component (cf. Section 4.3).



2. The construction of the nucleophile-sensitive α-acrylic ester moiety.

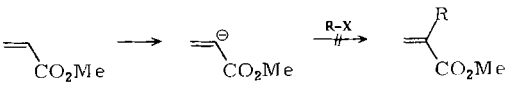
The presence of additional oxygen-containing functionality and the stereochemistry of the residual carbocyclic portion of the molecule increase the appeal of the naturally-occurring sesquiterpene lactones as a synthetic goal. However, the total syntheses of these complex compounds and the elegant work already carried out have recently been described comprehensively in a book by *Heathcock* et al.[34] and will remain largely neglected here. Instead, we will concentrate on the methods of synthesis of the simple, key five-membered-ring. Insofar as meaningful, we will use the retrosynthetic approach both for the classification and the mechanistic interpretation of the large number of synthetic methods. Thus, the organization of the article is predetermined (cf. Scheme 11).



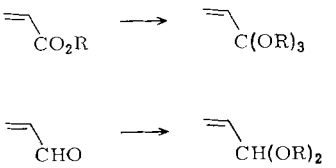
Scheme 11.

If the molecule is dissected as outlined in Sections 4.1—4.4, the educt can be regarded as a functionalized acrylic ester.

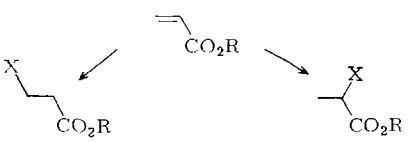
The direct α-functionalization of acrylic compounds via the α-anion is only of limited use due to the pronounced tendency of acrylic esters to polymerize under basic conditions[35]. For this reason, the detour via masked acrylic esters is often chosen, since these are generally easier to functionalize.



The problem of polymerization of α-acrylic esters can be circumvented in different ways. On the one hand, the reactivity of the carbonyl group can be masked by conversion of the ester group or the aldehyde group into an ortho ester or an acetal, respectively.



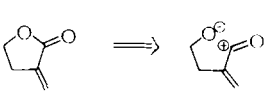
On the other hand, it is possible to mask the CC double bond, e.g., by adding groups in the α- and β-positions that are capable of undergoing elimination (Scheme 12). Masking is also possible by reversible cycloaddition (see Section 4.8).



Scheme 12. X = groups capable of elimination.

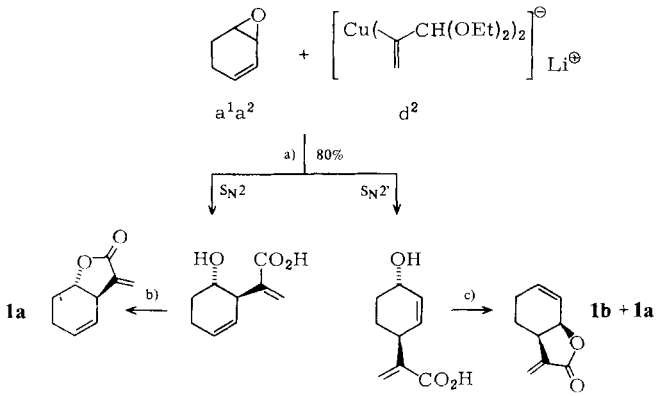
4.1. Cyclization of 4-Hydroxy-2-methylenebutanoic Acids

Dissection:



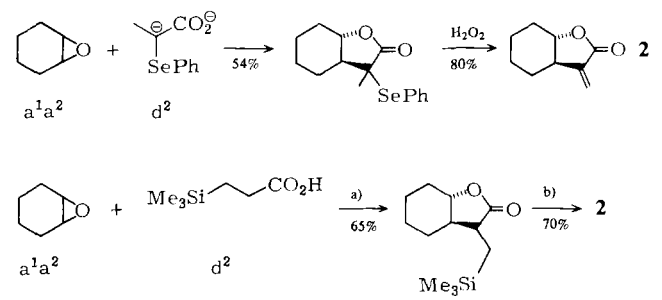
This dissection reduces the synthesis to the preparation of a homoallyl alcohol, the methylene group of which must also be part of an acrylic acid or a masked acrylic acid.

Marino et al.[36a,b] used the diethyl acetal of acrolein as acrylic acid equivalent and allowed it to react as the cuprate (d^2 building block) with epoxides (a^1a^2 building block) (Scheme 13). The two isomeric alcohols formed contain the desired 1,4-functionality distance or vinylogous 1,4-distance and can be cyclized to *trans*- and *cis*-fused α-methylene lactones **1a** and **1b**, respectively, following oxidation to their respective acids. As a d^2 component for the reaction with epoxides, dimethyl sodiomalonate has been used, also; subsequent decarboxylative methylenation (cf. Section 4.7) gives the α-methylene lactone[36c].



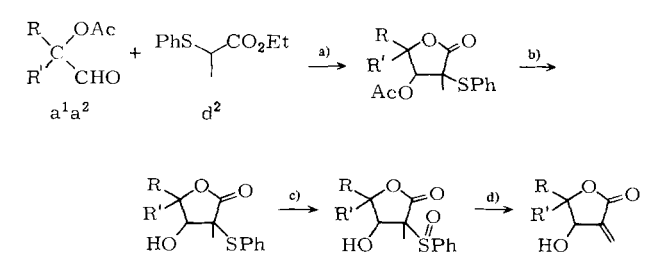
Scheme 13. (a) 1) Tetrahydrofuran (THF)/ −40 °C, 2) $Ag_2O/OH^{\ominus}$. (b) Dicyclohexylcarbodiimide (DCC), $CHCl_3$; 5-*exo-trig*. (c) TosOH (Tos = tosyl), C_6H_6; 5-*exo-trig*.

After masking of the double bond, acrylic compounds can also be functionalized. This can be accomplished by introducing a phenylseleno group via the dianion of 2-phenylselenopropionic acid according to *Petragnani* and *Ferraz*[37] or of a trimethylsilyl group according to *Fleming* et al.[38a] (Scheme 14). After cyclization, both groups can be eliminated with regeneration of the double bond. However, in the case of the silicon compound a bromination is necessary; the selenide, which only needs to be oxidized to the selenoxide, is especially useful, because intramolecular elimination is spontaneous. In both reactions the *trans*-lactone **2** is formed.



Scheme 14. (a) 1) 2 Lithium diisopropylamide (LDA), 0 °C, then reflux, 2) TosOH, toluene, reflux. (b) LDA, THF, −78 °C, 2) Br_2, CCl_4, −78 °C, 3) $(PhCH_2)Me_3N^{\oplus}F^{\ominus}$, THF.

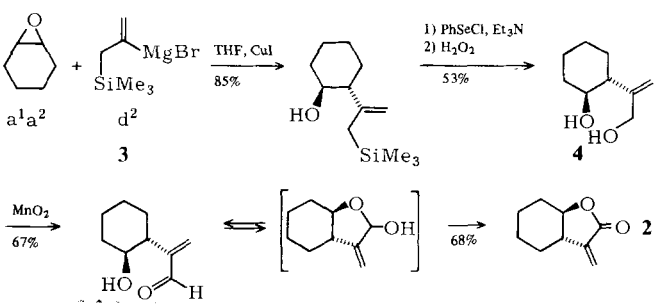
Benezra et al.[38a] used an α-phenylthiopropionic ester as a d^2 acrylic acid in the synthesis of β-hydroxy-α-methylenelactones (Scheme 15). Similarly to the selenide group, the sulfide group can be removed after oxidation to the sulfoxide. However, unlike the selenoxide, the sulfoxide requires heating for elimination to occur.



Scheme 15. (a) LDA, −78 °C (acyl-shift). (b) 1) $Ba(OH)_2$, 2) $H^{\oplus}$. (c) [O]. (d) Δ, toluene.

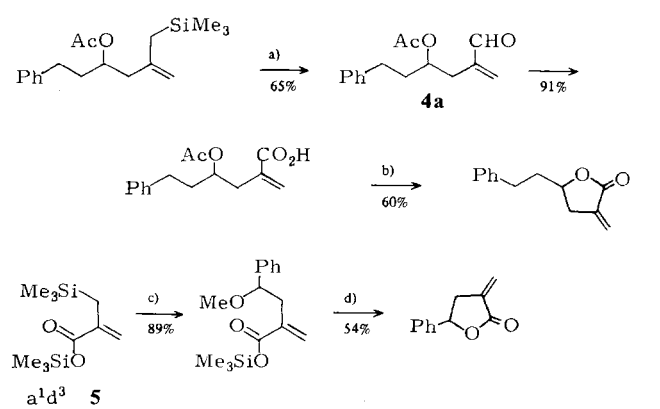
Homologues of α-phenylselenopropionic esters can generally be used in the synthesis of α-alkylidene-γ-butyrolactones also[39].

The allylsilane **3** was employed by *Itoh* et al.[40] as a masked d^2 acrylic acid and was allowed to react with an epoxide (a^2a^1) to give the functionalized homoallylic alcohol (Scheme 16). Reaction with PhSeCl and subsequently with H_2O_2 (desilylating oxidation via the allyl selenide and oxidative rearrangement) gave the allyl alcohol **4**, which was oxidized with MnO_2 to give selectively the α,β-unsaturated aldehyde. As also occurs in other examples (see below), the second hydroxyl function is not attacked by MnO_2; the aldehyde cyclizes to give the lactol, which is further oxidized in situ to the lactone. The starting material for the Grignard reagent **3** is 2-bromo-3-(trimethylsilyl)propene **21**, which was also used by *Trost* et al.[85], although in a different way, in the synthesis of α-methylene lactones (see Section 4.6).



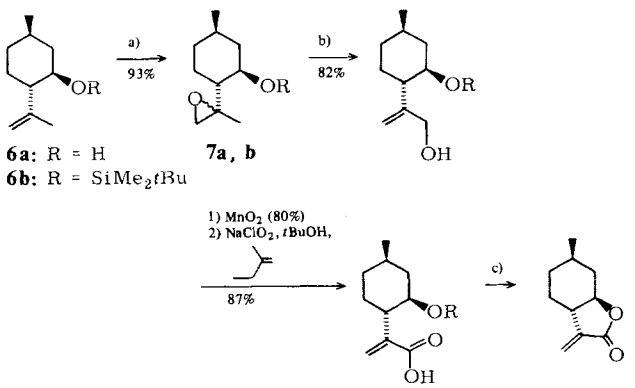
Scheme 16.

Functionalized allylsilanes appear as intermediates in the syntheses described by *Fujita* et al.[41] and *Sakurai* et al.[142a] also. The key step in *Fujita*'s (Scheme 17) work is a desilylating oxidation of an allylsilane to give an α,β-unsaturated aldehyde. This was achieved in a novel way, using iodosylbenzene, which was activated by coordination with a Lewis acid. In contrast to the oxidation of an allylsilane with *m*-chloroperbenzoic acid, which proceeds with allyl inversion (intermediate formation of the epoxide), the formation of **4** and **4a** proceeds with allyl retention. In the case of oxidation giving **4** and **4a**, an S_E2' attack on the electron-rich allylsilane is followed by an intramolecular 3,2-shift. *Sakurai* et al.[42a] allowed the trimethylsilyl ester **5** to react with an acetal and obtained by dealkylation the α-methylene-γ-butyrolactone (Scheme 17).



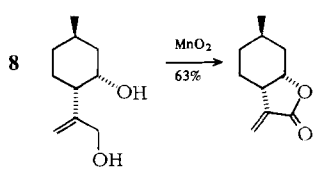
Scheme 17. (a) C_6H_5IO, $BF_3 \cdot Et_2O$. (b) DCC, pyridine. (c) $PhCH(OMe)_2$, $BF_3 \cdot Et_2O$. (d) 1) Me_3SiI, 2) MeOH.

The combined homoallylic alcohol-allylic alcohol such as **4**, formed in the reaction sequence of *Itoh*[40] (Scheme 16), is an intermediate in many other synthetic routes since the selective oxidation with MnO_2 yields a cyclizable compound and therefore offers convenient access to the desired lactones. Thus, in the work of *Pinnick* et al.[42b] (Scheme 18) the protected isopulegol **6b** is converted into the epoxide **7b**, which in the presence of the strong base $LiNEt_2$ undergoes a regioselective E2 reaction to give the allylic alcohol. The further oxidation of the α,β-unsaturated aldehyde, formed by reaction of the alcohol with MnO_2, to give the α,β-unsaturated carboxylic acid is not trivial, nor is the oxidation of other allylic alcohols to their carboxylic acids. Recently, inexpensive $NaClO_2$ has been recommended for this oxidation, also in the presence of sensitive functional groups.

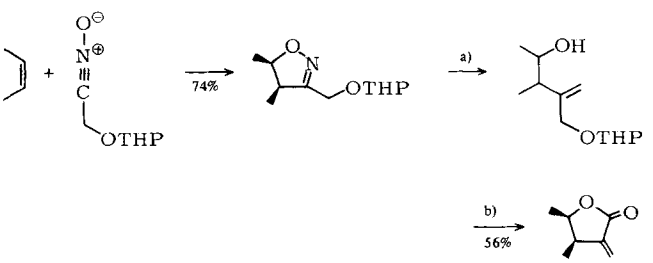


Scheme 18. (a) *m*-Chloroperoxybenzoic acid (CPBA). (b) $LiNEt_2$, −78°C→RT. (c) 1) Desilylation, 2) DCC, pyridine (77%); or 1) Me_3SiI, $CHCl_3$, Δ, 2) Distillation.

With MnO_2, the epimeric diol **8** is directly converted via the cyclic hemiacetal into *cis-p*-menthenolide[42b]. Thus, cyclization to the *cis*-fused lactone proceeds more easily than to the *trans*-fused isomer.

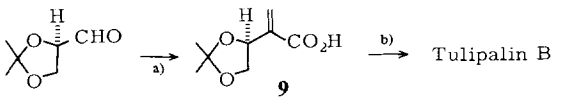


In the route described by *Kozikowski* et al.[43a] (Scheme 19) an isoxazoline, formed by cycloaddition, is reductively opened and the *exo*-methylene double bond is then formed by a Wittig reaction. Again, cleavage of the tetrahydropyranyl (THP) ether and oxidation with MnO_2 affords the α-methylene lactone.



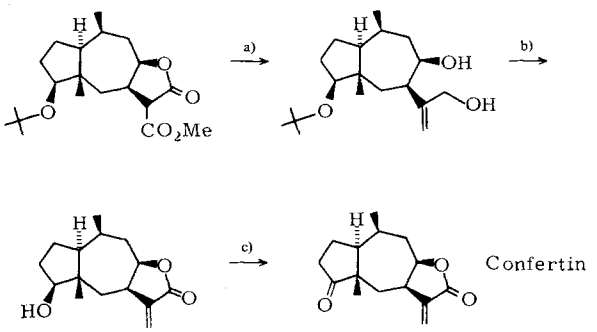
Scheme 19. (a) 1) H_2, Raney nickel, 2) $H_2C{=}PPh_3$. (b) 1) TosOH, MeOH (OTHP→OH), 2) MnO_2, CH_2Cl_2.

2,3-*O*-Isopropylideneglyceraldehyde—a chiral building block which has been used a great deal recently and has perhaps also become something like a vogue compound[43b]—was homologized in several steps to **9** and then cyclized to tulipalin B using acid catalysis[43c] (Scheme 20).



Scheme 20. (a) 5 steps. (b) 1 NHCl.

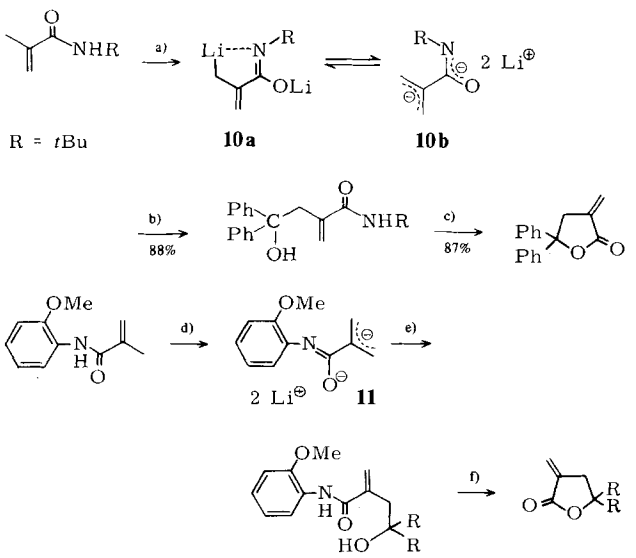
Another possibility for obtaining the desired "crossed" allylic-homoallylic alcohol was demonstrated by *Marshall* et al.[44] in the synthesis of confertin (Scheme 21). The enolate of a modified malonic ester, formed on using KH, is reduced by $LiAlH_4$ to the dialcohol stage. Oxidation with MnO_2 affords the α-methylene lactone, although in unreported yield. This method was already described in 1965 and is still used today[45,46].



Scheme 21. (a) 1) KH, 2) $LiAlH_4$. (b) 1) MnO_2, C_6H_6, 2) CF_3CO_2H, 3) *i*PrOH, NaOH. (c) CrO_3, pyridine, CH_2Cl_2 (Collins oxidation).

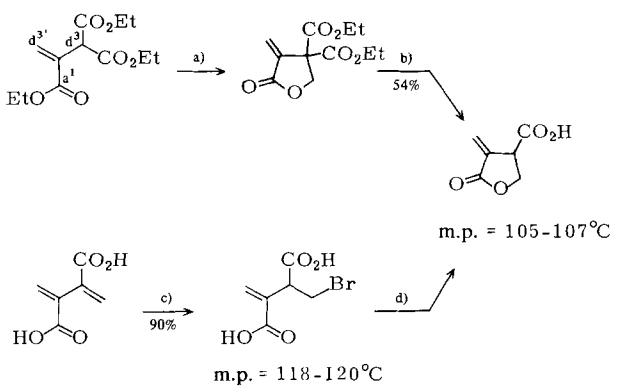
N-substituted methacrylamides can be used as synthetic equivalents of the hypothetical $a^1d^3d^{3'}$ methacrylic acid since they are more easily deprotonated and alkylated than acrylic esters. This method, developed in 1980, was used by three different research groups in the synthesis of α-substituted acrylamides[47] and of α-methylene lactones[48,49a] (Scheme 22). These syntheses proceed via the dianions **10b** and **11**, which polymerize less easily, probably because the amide nitrogen chelates a lithium ion and the reactivity of the carbonyl group is simultaneously reduced by electron delocalization. Trapping with ketones yields the cyclizable homoallylic alcohols (cf. also Section 4.3, i.e. the umpolung of (*Z*)-2-bromomethyl-2-alkenoic esters to give $a^1d^3d^{3'}$ components).

An interesting $a^1d^3d^{3'}$ building block is the readily accessible, doubly activated triethyl 2-propene-1,1,2-tricarboxylate, as shown recently by *Dowd* et al.[49b]. For this compound even catalytic amounts of potassium bicarbonate suffice for deprotonation and for bringing about the nucleophilic addition to formaldehyde. After decarboxylation of the crude lactone diester with hydrochloric acid, the crystalline β-carboxylic acid of α-methylene-γ-butyrolactone is obtained in 54% overall yield. Alternatively, butadiene-2,3-dicarboxylic acid has been converted smoothly into bromomethyl-itaconic acid, which in turn cyclizes



Scheme 22. (a) 2 BuLi/*N,N,N',N'*-tetramethylenediamine (TMEDA)/THF, −70→−20°C, 1 h. (b) Ph_2CO. (c) Xylene, reflux, 3 d. (d) KO*t*Bu/BuLi. (e) 1) R_2CO, 2) H_2O. (f) 10% HCl.

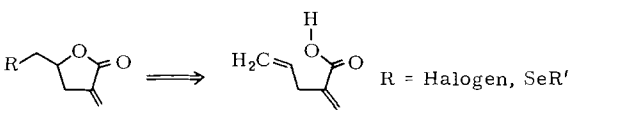
spontaneously to the same lactone in neutral or basic conditions[49b] (Scheme 23).



Scheme 23. a) 35% CH_2O, catalytic amounts $KHCO_3$, 65°C, 25 min. b) 20% HCl. c) HBr/AcOH (1 mol). d) neutral or basic solvent.

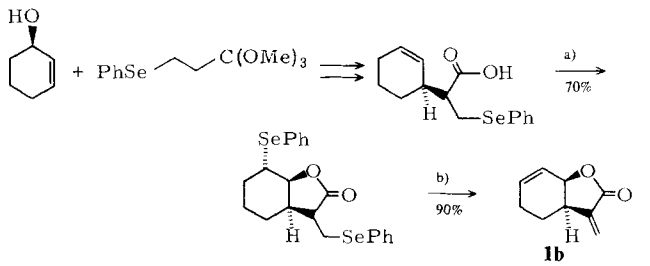
4.2. Cyclization of 2-Methylene-4-pentenoic Acids

Dissection:

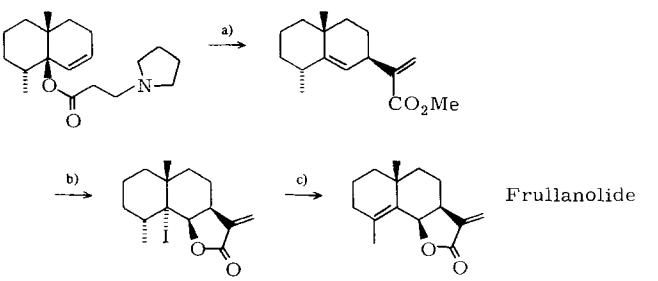


Raucher et al.[50] used the Claisen ortho ester rearrangement, which leads directly to the desired arrangement of carboxyl group and terminal CC double bond, i.e., to the γ,δ-unsaturated carboxylic acid or 4-pentenoic acid; cyclization was accomplished via seleno-lactonization. Oxidation of the selenium group and spontaneous elimination gave the α-methylene group and—thanks to the second phenylselenide group—another double bond (Scheme 24).

By analogy with the synthesis described by *Raucher* et al.[50], *Still* et al.[51] had previously started from an allylic alcohol and used a Claisen triethylsilylketene acetal rearrangement, i.e., the Ireland variant, for the synthesis of a functionalized acrylic ester, which was converted into the desired frullanolide in two steps in 30% total yield (Scheme 25).



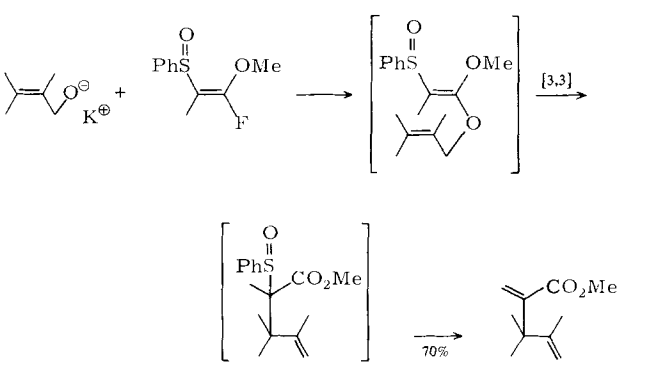
Scheme 24. (a) PhSeX. (b) 30% H_2O_2, THF. The two parallel arrows mean: 1) heating in mesitylene (160°C, 24 h) in the presence of trimethylacetic acid (0.1 equiv.); 2) demethylation with LiI in 2,6-dimethylpyridine, reflux, 2 h.



Scheme 25. (a) 1) LDA/THF, 2) Et_3SiCl, 3) Δ, 4) $(MeO)_2SO_2$, MeOH, K_2CO_3. (b) Iodolactonization; 5-*exo*-*trig*. (c) 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU).

Mechanistically related is the one-pot reaction recently described by *Vatele*[52] for the synthesis of α-methylene-γ,δ-unsaturated esters. An allylic alcohol is again used as starting material, which is transformed in three steps into a cyclizable 2-methylene-4-pentenoic acid (Scheme 26):

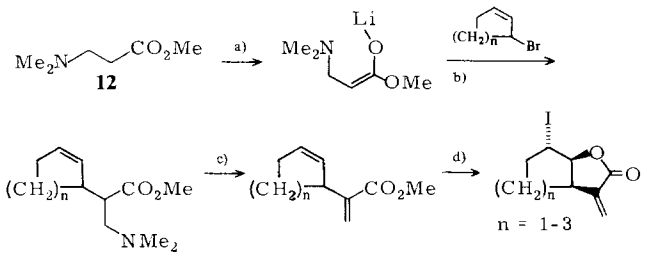
1. nucleophilic substitution at the activated vinylic carbon atom,
2. Claisen ester enolate rearrangement, and
3. sulfoxide elimination to introduce the double bond.



Scheme 26.

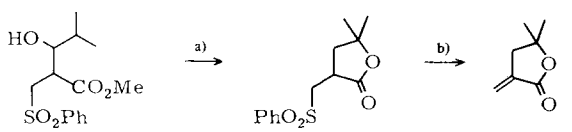
Helquist and *Yu*[53a] used methyl 3-(*N,N*-dimethylamino)propionate **12**, which is readily available via Michael addition of dimethylamine to acrylic ester, as d^2 acrylic building block. As in the case of the methacrylamides already described (Section 4.1), metalation of the ester is fa-

cilitated by complexation with nitrogen[53]. Reaction of the anion with allyl bromides gives the desired γ,δ-unsaturated ester, which, following elimination of the amino group, is subjected to iodolactonization.



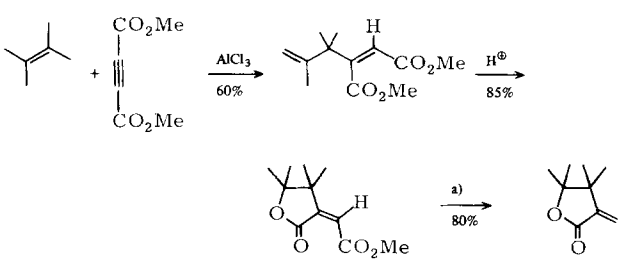
Scheme 27. (a) LDA, THF, −78°C. (b) THF, hexamethylphosphoric triamide (HMPT), −78°C→25°C. (c) 1) MeI, CH_3OH, 2) 1,5-Diazabicyclo[4.3.0]non-5-ene (DBN), C_6H_6. (d) 1) KOH, CH_3OH, H_2O, 2) HCl, H_2O, 3) KI, I_2, $NaHCO_3$.

The methods of *Shono* et al.[54] (Scheme 28) and *McCulloch* et al.[55] are mechanistically interesting but not generally applicable because of their drastic reaction conditions. *Shono* et al.[54] applied a method for lactone formation described by *Dobrev* and *Ivanov*[56] to the synthesis of α-methylene lactones.



Scheme 28. (a) Conc. H_2SO_4. (b) Na_2CO_3, dimethylformamide (DMF).

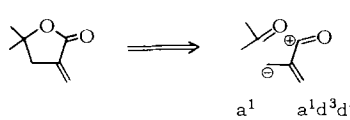
The synthesis of *McCulloch* et al.[55] (Scheme 29) begins with an $AlCl_3$-catalyzed ene reaction[57] of the strongly enophilic dimethyl acetylenedicarboxylate. After acid-catalyzed lactonization, the ester function is removed by reductive treatment with copper in quinoline. Since the reduction is only successful for highly substituted five-membered rings, the range of application of the reaction is limited.



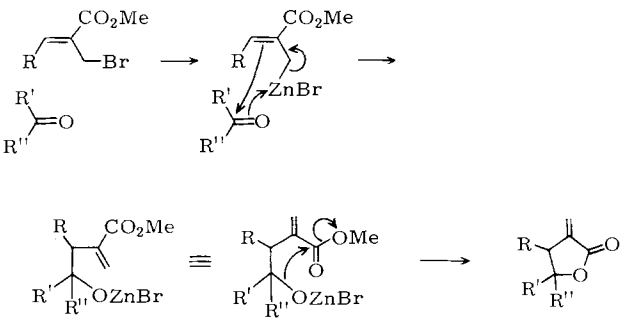
Scheme 29. (a) Cu, quinoline.

4.3. Metal-Promoted Reaction of Aldehydes and Ketones with $a^1a^3a^{3'}$ Components

Dissection:

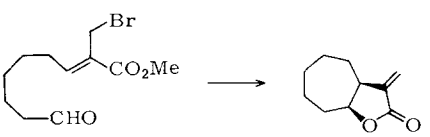


In this method (Scheme 30), developed by *Dreiding* et al.[58,59] and *U. Schmidt* et al.[60], a (*Z*)-2-bromomethyl-2-alkenoic ester ($a^1a^3a^{3'}$ building block) is treated with zinc to give an $a^1d^3d^{3'}$ intermediate with umpolung. The combination with the a^1 aldehyde takes place with allylic shift and yields an intermediate alkoxide, which cyclizes spontaneously to the α-methylene lactone. The Dreiding-Schmidt reaction, which is also incorrectly called a Reformatsky synthesis (in which d^2 enolate esters, but not d^3 components are used), has been very useful in the synthesis of monocyclic and spiro-α-methylenelactones[61].



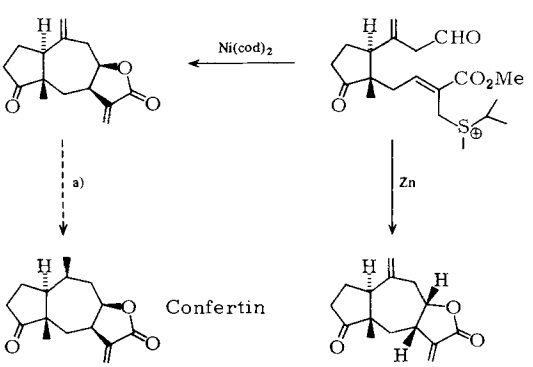
Scheme 30.

The intramolecularization of the reaction affords bicyclic α-methylenebutyrolactones from acyclic compounds in one pot[62] (Scheme 31).



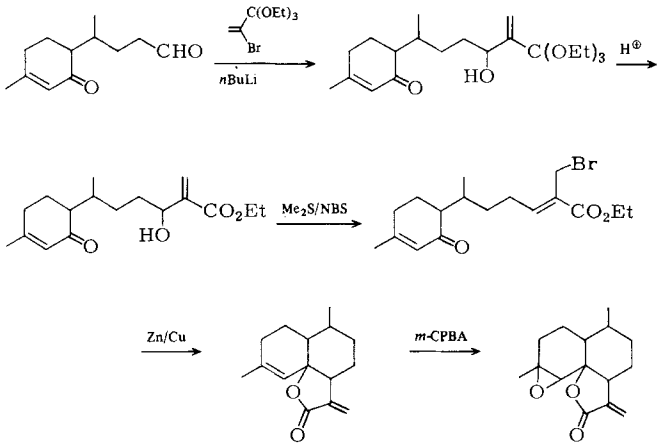
Scheme 31.

In this fashion, *Semmelhack* et al.[63] successfully synthesized (±)-confertin in 1978 (Scheme 32). They obtained the confertin isomer with the unnatural configuration by zinc-promoted cyclization, whereas nickel-promoted cyclization yielded the natural isomer. The selective hydrogenation of this precursor to confertin was unsuccessful; however, it was accomplished by a detour.



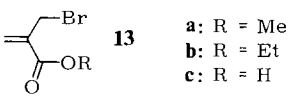
Scheme 32. (a) Low yield. cod = cyclooctadiene.

Dreiding et al.[64] synthesized compounds of the arteannuin type (Scheme 33).

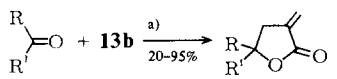


Scheme 33. NBS = *N*-bromosuccinimide.

Perhaps the most important building blocks in the synthesis of γ-monosubstituted and γ,γ-disubstituted α-methylene-γ-butyrolactones are the 2-(bromomethyl)acrylic ester **13a** and the ethyl ester **13b.**

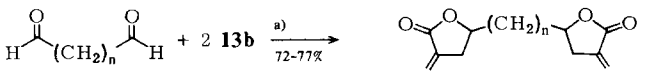


Recently, the synthesis of **13a** in three steps (50% yield) and that of **13b** in two steps (30% yield) have been described[65a]. 2-(Bromomethyl)acrylic acid **13c** is also available commercially[65b]. Starting from **13b**, *Benezra* et al.[10] reported the synthesis of more than thirty lactones, some of which are structurally quite complex (Scheme 34).



Scheme 34. (a) 1) Zn/THF, 2) dil. HCl.

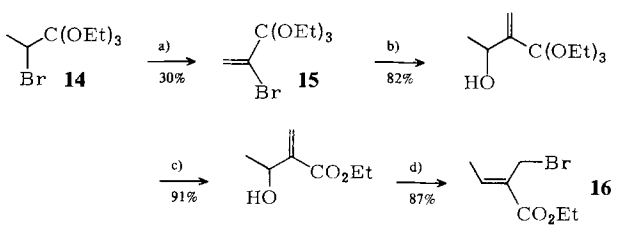
Heindel et al.[66a], *Lee* et al.[66b], and *Cassady* et al.[67a] (Scheme 35) proceeded similarly; *Cassady* et al. also obtained bislactones[67a], i.e., double haptens, from dialdehydes by using the corresponding one-pot reaction[67c].



Scheme 35. (a) 1) Zn/THF, 2) dil. H_2SO_4, 0°C.

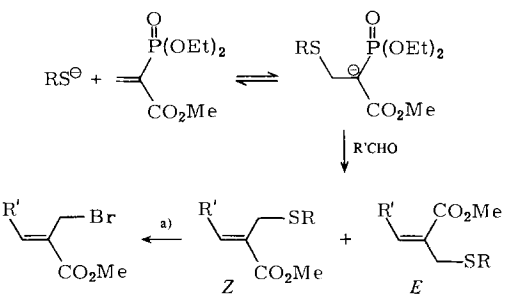
A synthetic difficulty in the metal-promoted cyclization to give bicyclic α-methylene lactones has been in the synthesis of the functionalized methacrylic acid as starting material.

Starting from the ortho ester **14**, *Dreiding* et al.[68a] synthesized the ortho ester **15** of 2-bromoacrylic acid in several steps. **15** was metalated with *n*-butyllithium to give the corresponding lithium compound, i.e., a d^2-acrylic ester. After trapping of the lithium compound with aldehydes, the hydroxy ester was rearranged to the substituted allyl bromides **16** (Scheme 36).



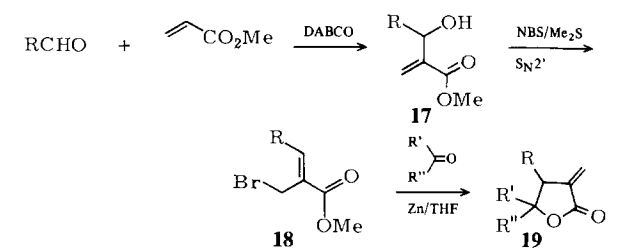
Scheme 36. (a) 1) KO*t*Bu, 2) Br_2, CuO, 3) KOH, EtOH. (b) 1) BuLi, 2) CH_3CHO. (c) H_2SO_4. (d) NBS/Me_2S.

The synthesis of the allylic sulfur compound used by *Semmelhack* et al.[68b] as $a^1a^3a^{3'}$ precursor, also requires several steps and is not (*Z*)-selective. The last step, the conversion of the allylic sulfide into the bromide, is not very simple either (Scheme 37).



Scheme 37. (a) 1) [O], 2) $(MeO)_3P$, 3) PBr_3 (overall yield 20—25%); or 1) $MeOSO_2F$, 2) LiBr (overall yield 93%).

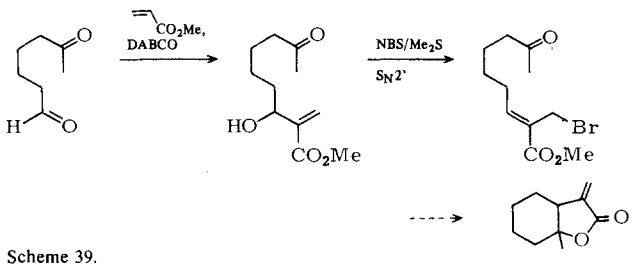
In connection with the synthesis of a wide range of allyl alcohols and their precursors, which are further functionalized on the central carbon atom[69], we have prepared the necessary $a^1a^3a^{3'}$ coupling reagents (the allylic bromides **18**) in excellent yields by DABCO (diazobicyclo[2.2.2]octane)-catalyzed coupling of acrylic esters and aldehydes to **17** and subsequent bromination accompanied by allylic rearrangement[70–72] (Scheme 38).



Scheme 38.

The reaction of 2-(hydroxyalkyl)acrylates **17** with *N*-bromosuccinimide/dimethyl sulfoxide yields regioselectively (S_N2' reaction) and stereoselectively (*Z*)-2-(bromomethyl)-2-alkenoic esters **18** irrespective of the group R[70–72]. Metal-induced coupling of **18** with carbonyl compounds allows ready access to β-substituted α-methylene lactones (compare **19**). Another advantage of this approach is that parent acrylic ester can be α-functionalized without loss of material, much additional functionality being tolerated. Esoteric acrylic acid building blocks and organometallic conditions are unnecessary. The selective coupling of a ketoaldehyde, e.g., 6-oxoheptanal, with an

acrylic ester in the presence of DABCO is also possible; the less reactive ketone group need not be masked, e.g. by ketalization. After bromination with NBS/Me_2S, which entails clean allylic rearrangement, a cyclizable molecule is obtained[73] (Scheme 39).

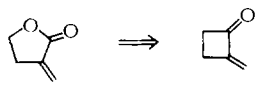


Scheme 39.

In addition to these compounds, other a^1d^3 components—as already described in Section 4.1—have been used in the cyclization: the allylsilane **5** and the dianions **10** and **11**. The allylic bromoester method offers the advantages of a simple synthesis, a high degree of convergence, mild reaction conditions, and compatibility with other functionality. At least for many of the structurally more simple α-methylene-γ-butyrolactones, this is the method of choice.

4.4. Insertion of the Oxygen via Baeyer-Villiger Oxidation of 2-Methylenecyclobutanones

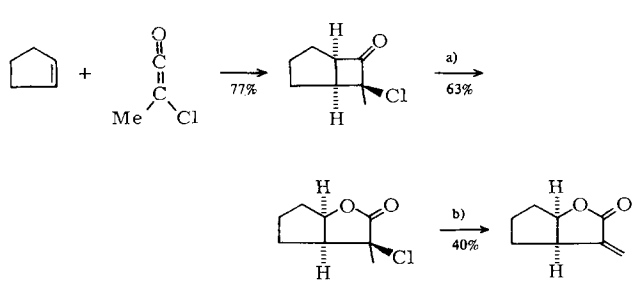
Dissection:



There are only a few examples of the synthesis of α-methylene lactones via the Baeyer-Villiger oxidation.

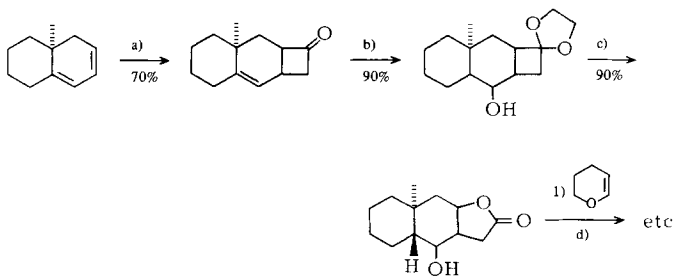
The syntheses of *Hassner* et al.[74] and *Roberts* et al.[75] will be presented here. As shown in Scheme 40, this approach begins with a [2+2]-cycloaddition of chloro- and bromoketenes to reactive double bonds to form a functionalized cyclobutanone. Baeyer-Villiger oxidation with exclusive migration of the bridgehead carbon atom and subsequent elimination of hydrogen halide yields the desired lactone.

In following the fate of the three carbon atoms of the chloroketene one may see that these are incorporated into the product as the desired acrylic moiety. In the example given here, the total yield of α-methylene lactone—starting from the haloketene precursor—is 20%. It remains to be seen whether this route can be developed preparatively. A limitation of the cycloaddition route is that only *cis*-fused lactones result (cf. also Section 4.8).



Scheme 40. (a) H_2O_2, CH_3CO_2H. (b) Diazabicyclo[2.2.2]octane (DABCO), NaI, dimethyl sulfoxide (DMSO).

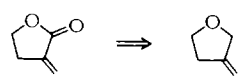
Grieco et al.[76] also used a Baeyer-Villiger oxidation to construct a γ-lactone and subsequently incorporated the α-methylene group by reaction of the enolate with formaldehyde (see Section 4.7) (Scheme 41).



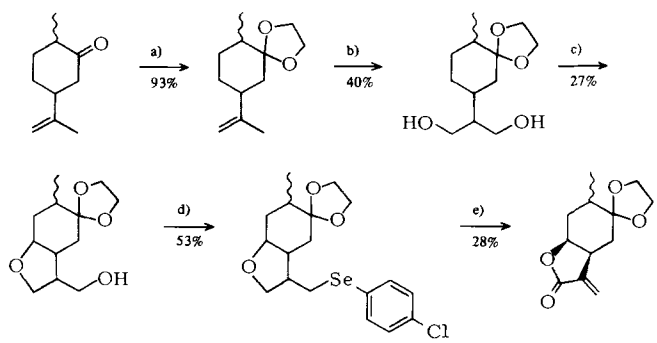
Scheme 41. (a) 1) $Cl_2CHCOCl$, 2) Zn/CH_3CO_2H. (b) 1) Ketal formation, 2) BH_3/THF, $NaOH/H_2O_2$. (c) 1) 10% HCl, 2) HOAc/30% H_2O_2. (d) α-Methylenation.

4.5. Introduction of the Carbonyl Oxygen by Oxidation of 3-Methylenetetrahydrofurans

Dissection:



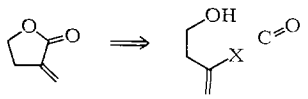
This very simple method, which could also be of biosynthetic interest, has only been described recently. Starting from dihydrocarvone, *Brocksom* and *Ferreira*[77] synthesized monoterpenoid α-methylene-γ-butyrolactones (Scheme 42). After an interesting oxidative cyclization using lead tetraacetate to give the furan derivative (compare also the Barton reaction), the *exo*-methylene group is formed by selenoxide elimination. Finally, the carbonyl oxygen is introduced, in analogy to the method of *Dauben* et al.[78], by Collins oxidation with $CrO_3 \cdot 2$ pyridine. It remains to be seen whether other oxidizing agents will bring about an improvement in yield.



Scheme 42. (a) TosOH, $HOCH_2CH_2OH$. (b) 1) *m*-CPBA, 2) LDA, 3) B_2H_6, H_2O_2, NaOH. (c) $Pb(OAc)_4$. (d) 1) TosCl, pyridine, 2) *p*-Cl–C_6H_4–$Se^{\ominus}$. (e) 1) H_2O_2, THF, 2) CrO_3, pyridine.

4.6. Insertion of a Carbonyl Group into Functionalized Homoallylic Alcohols

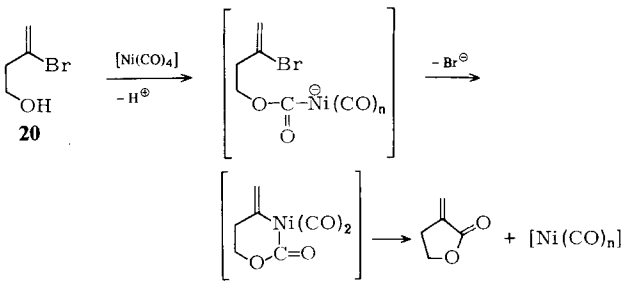
Dissection:



This synthesis can be realized using reactions taken from the organic chemist's "box of magic tricks", namely by

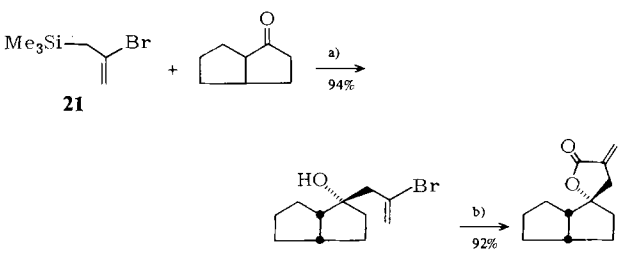
a) transition-metal-catalyzed carbonylation of a vinylically substituted homoallylic alcohol and
b) use of the Shapiro reaction.

a) In recent years the intramolecular version of the transition-metal-catalyzed carbonylation described by *Corey* and *Hegedus*[79] has been used increasingly for the synthesis of α-methylene lactones. Zero-valent transition metal compounds, usually of nickel or palladium, function as catalysts and reagents. Scheme 43 shows the proposed mechanism[80,81] of the nickel-induced reaction, in which 3-bromohomoallylic alcohols **20** have been employed as starting compounds. Recently, *Ban* et al. have also used the more reactive 3-iodohomoallylic alcohols[86b].



Scheme 43.

Representative of other syntheses[82–84] are those of *Trost* et al.[85] and *Stille* et al.[86], described here. *Trost* et al.[85] joined a functionalized allylsilane to a carbonyl compound to obtain the functionalized homoallylic alcohol which is necessary for the insertion of the carbonyl group. The tricyclic spiro-α-methylenelactone is formed stereoselectively and in high yield (Scheme 44).

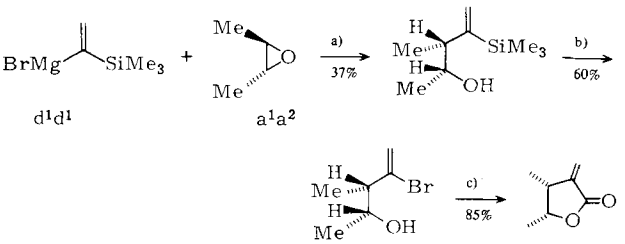


Scheme 44. (a) $TiCl_4$, CH_2Cl_2, −70→0°C. (b) 1.5 $[(Ph_3P)_2Ni(CO)_2]$, Et_3N, THF, reflux.

The Grignard reagent **3** prepared from 2-bromo-3-(trimethylsilyl)propene **21** can also be combined with epoxides to establish the desired 1,4-distance of functional groups[40] (cf. Section 4.1) and added to α,β-unsaturated enones in Michael fashion using CuI catalysis, cyclopentane precursors being formed[85]. The possibility of storing the carbanion reactivity of 2-bromo-3-(trimethylsilyl)propene while selectively activating the allylsilane (with $TiCl_4$), and subsequently metalating the bromide (with magnesium) makes **21** a valuable equivalent for the hypothetical dianion **22** (cf. also the conversion of **3** into **4**).

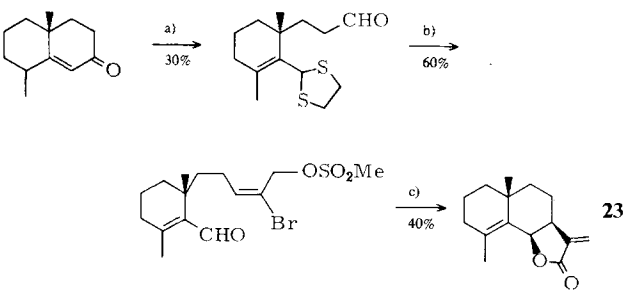


Stille et al.[86a] reacted a vinylic Grignard compound (a d^1d^1 ethylene building block) with epoxides (a^1a^2 components) and thus obtained the desired homoallylic alcohol. Electrophilic substitution of the trimethylsilyl group by bromine yielded the 3-bromohomoallyl alcohol required for the carbonylating cyclization[86a] (Scheme 45).



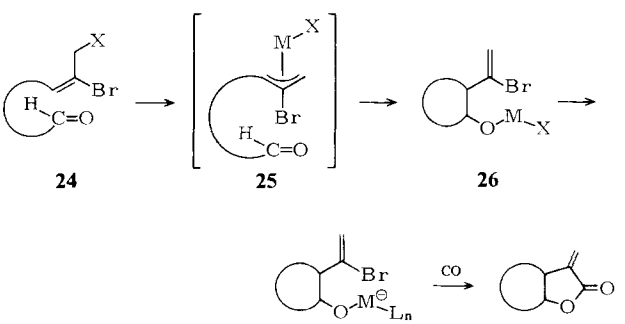
Scheme 45. (a) 1) CuI, THF, Et_2O, 2) $H^{\oplus}$. (b) 1) Br_2/CH_2Cl_2 −78°C, 2) NaOMe/MeOH. (c) 1) CO, $[Pd(PPh_3)_4]$, 2) CH_3CN, K_2CO_3.

Carbonylnickel plays an interesting double role in the synthesis of (±)-frullanolide (*Semmelhack* et al.[87], Scheme 46).



Scheme 46. (a) 4 steps. (b) 2 steps. (c) $[Ni(CO)_4]$, C_6H_6, 65°C.

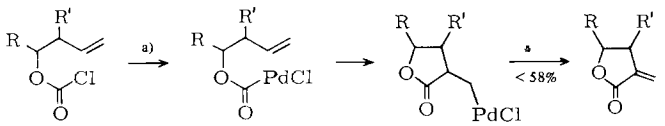
The allylic system in **24** can first be activated as π-allylnickel complex **25** (M = Ni)[88] and cyclized with the aldehyde function to give **26** (potentially a *cis/trans* mixture). In the next step, tetracarbonylnickel functions as carbonylating reagent to form the α-methylene lactone (Scheme 47).



Scheme 47.

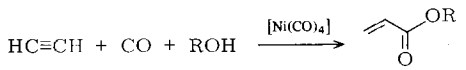
Experimentally, a very high selectivity is observed for the formation of a *cis*-fused lactone as well as for the *syn*-orientation of the lactone with respect to the angular methyl group (cf. **23**). The reason for these stereochemical results is not yet clear.

A variant of the transition-metal-catalyzed cyclization was recently presented by a French research group[92]. In this reaction, CO is not inserted and cyclized using Pd^0 catalysis. Instead, the homoallyl alcohol is esterified with phosgene as C_1 building block to give the chloroformate, which is then cyclized to give the α-methylene lactone (Scheme 48).



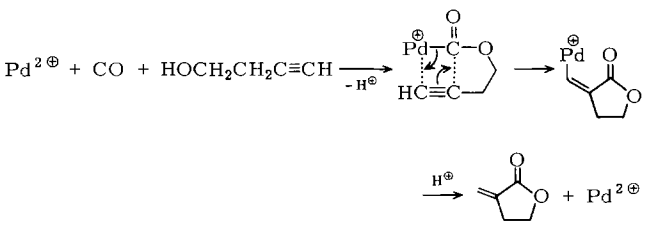
Scheme 48. (a) $[Pd(PPh_3)_4]$, Na_2CO_3.

A fundamental result of Reppe chemistry is the synthesis of acrylic esters by nickel-catalyzed carbonylation of acetylene[89] (Scheme 49).



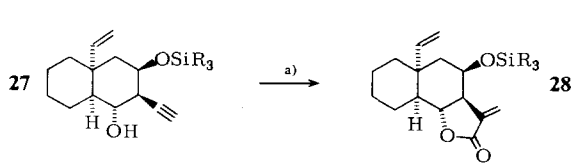
Scheme 49.

As *Norton* et al. were able to show, this reaction can also be intramolecularized by treating a homopropargyl alcohol with CO in the presence of catalytic $PdCl_2/SnCl_2$ and a tertiary phosphane[90] (Scheme 50).



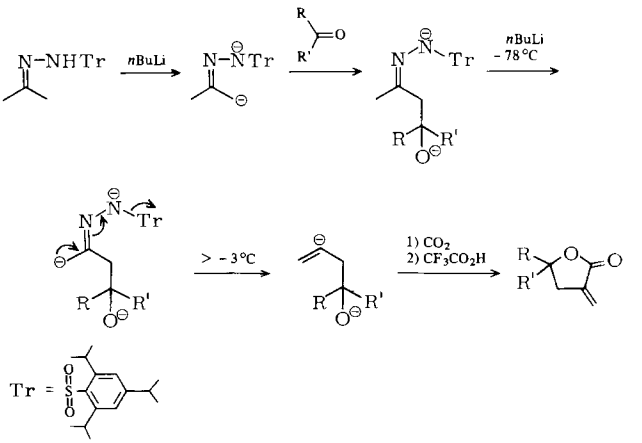
Scheme 50.

The reaction proceeds under comparatively mild conditions. In a model experiment for establishing the functionality in the BC ring, *Heathcock* et al.[91] converted the *trans*-homopropargyl alcohol **27** into the *trans*-fused lactone **28** (Scheme 51). Although the yield is low (21%), the α-methylene lactone is formed directly in this way, and the normally chosen α-methylenation of a γ-lactone precursor (cf. Section 4.7) is not necessary.



Scheme 51. (a) $PdCl_2$, CO, thiourea.

b) A further variant is the insertion of CO, according to *Barrett* et al., via the Shapiro reaction, in which CO_2 functions as CO building block[93] (Scheme 52).

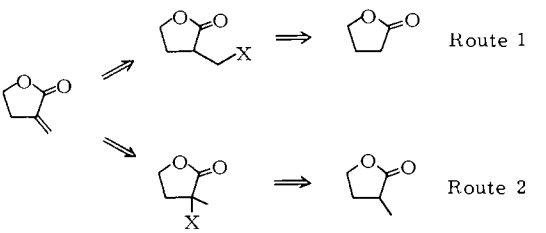


Scheme 52.

The dianion from the activated hydrazone of acetone is allowed to react with ketones. As usual, elimination of nitrogen yields a vinyl anion (cf. also **22**), which after trapping by carbon dioxide (carboxylation instead of carbonylation) is cyclized to the α-methylene lactone. This reaction sequence requires strongly basic conditions, which are not always tolerated by highly functionalized molecules.

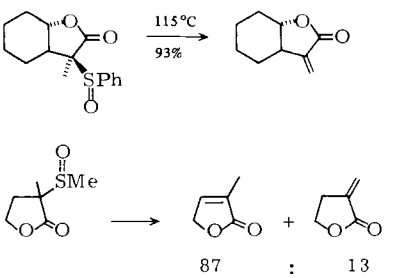
4.7. α-Methylenation of 2-Oxotetrahydrofurans

Dissection:



The later incorporation of the α-methylene group into a preformed lactone has been used for many years in the synthesis of α-methylene lactones. Since the various methods have also been reviewed, only variations and new methods will be mentioned here.

For the incorporation of the α-methylene moiety, a functionalized C_1 building block is usually introduced and the double bond is formed by subsequent elimination (Route 1). However, the introduction of a leaving group α to the carbonyl group, when the methyl group is already present, is also known (Route 2). In this case, elimination results in the exocyclic double bond, although the endocyclic double bond can also be formed[94–96] (Scheme 53).



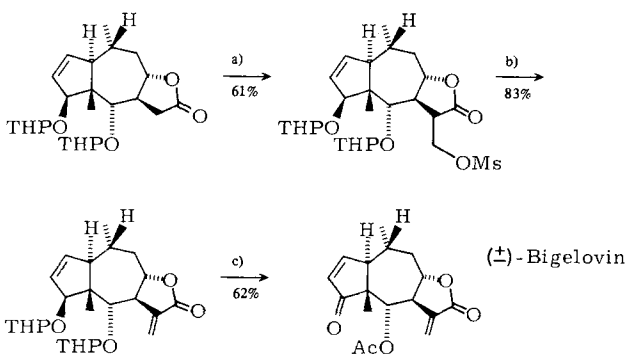
Scheme 53.

In order to avoid the formation of the endocyclic double bond, one introduces the leaving group advantageously β to the carbonyl group (Route 1).

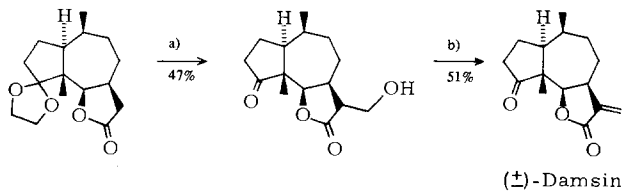
Two methods are used most frequently at present:

1. The lactone is converted into the enolate and subsequently trapped with formaldehyde to give the hydroxymethyl derivative. Alternatively, the anion is trapped with formic esters and reduced to give the hydroxymethyl derivative. After conversion of the hydroxy group into a tosylate or mesylate group, elimination is easily carried out with a base.

   As almost arbitrary examples the synthesis of (±)-bigelovin by *Grieco* et al.[97] (Scheme 54) and of (±)-damsin by *Vanderwalle* et al.[98] and *Kretchmer* et al.[99] (Scheme 55) are shown here.



Scheme 54. (a) 1) LDA, 2) CH_2O, 3) MsCl (Ms = methanesulfonyl), pyridine. (b) DBU. (c) 1) Hydrolysis, 2) MnO_2, 3) Ac_2O, dimethylaminopyridine (DMAP).

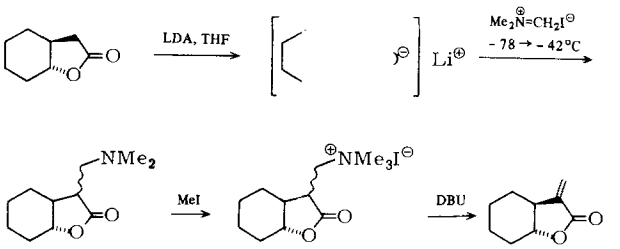


Scheme 55. (a) 1) NaH, HCO_2Et, 2) $NaBH_4$, MeOH, 3) HCl, MeOH. (b) 1) TosCl, 2) Δ, pyridine.

Other sesquiterpene lactones which have been obtained via α-methylenation are, e.g., (±)-ambrosin, (±)-psilostachyin C[100a], as well as (±)-eriolanin and (±)-eriolangin[100b]. This methodology, which was developed by *Grieco* et al.[101c], has also been applied to other representatives of the guaianolides (which have been investigated much less than the pseudoguaianolides), including, inter alia, (±)-compressanolide and (±)-estafiatin (*Vanderwalle* et al.[101a,b]).

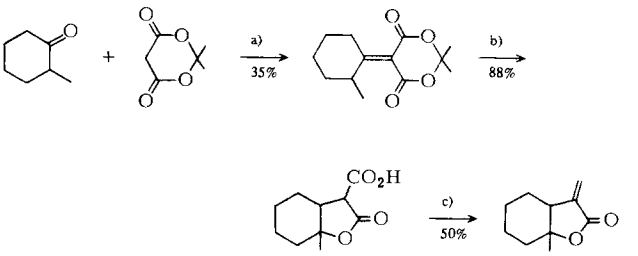
2. Another valuable method for introducing the α-methylene group uses the $-\overset{\oplus}{N}R_3$ group as leaving group. This can be introduced by trapping of the enolate of the lactone with dimethyl(methylene)ammonium salts. After quaternization of the nitrogen, elimination affords the double bond[102-105] (Scheme 56).

The synthesis of (±)-eriolanin by *Schlessinger* et al.[106a] and that of vernolepin by *Isobe* et al.[106b] were carried out similarly. The incorporation of the α-methylene group by reductive amination of an α-carboxy lactone with CH_2O/



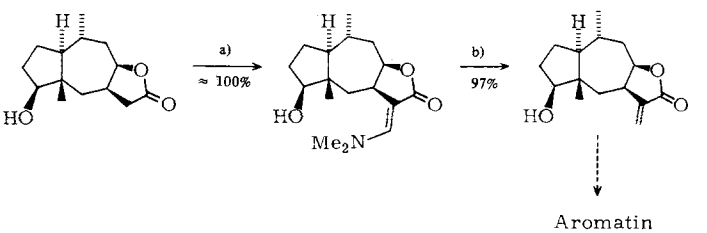
Scheme 56.

$HNEt_2$ has been known for ten years[107a] and was used again recently in the synthesis of bicyclic α-methylene lactones via Meldrum's acid[107b] (Scheme 57).



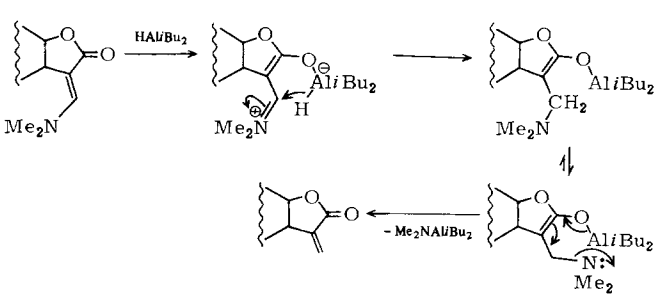
Scheme 57. (a) $TiCl_4$, THF, pyridine. (b) H_2SO_4. (c) 1) $H_2CO/HNEt_2$, 2) NaOAc/HOAc.

A disadvantage of many of the methods described until now is the use of strong bases for generating the lactone enolate. In this respect the introduction of the Bredereck reagent[108] by *Ziegler* et al.[109] has brought about an improvement (Scheme 58).



Scheme 58. (a) $(Me_2N)_2CHOMe$, Δ. (b) 1) $HAliBu_2$, THF, hexane, −78→25°C, 2) aq. NH_4Cl.

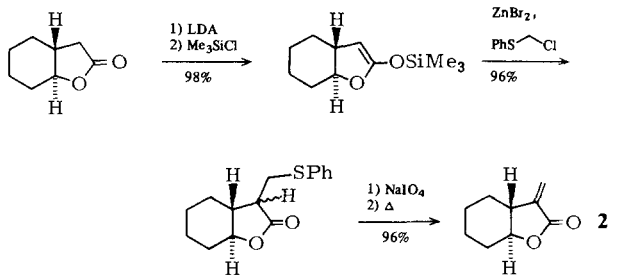
Using this reagent, one prepares the vinylogous carbamate in the first step. This is reduced to the α-methylene lactone selectively and in remarkably high yield with $HAli\text{-}Bu_2$ (Scheme 58). The use of strong bases, which are otherwise necessary for generating the lactone enolate, is thus avoided. The reaction mechanism formulated by us



Scheme 59.

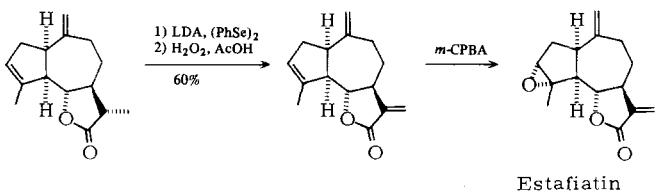
(Scheme 59) suggests that the specific deuteration of the methylene position[109a] should be feasible by reduction of the vinylogous carbamate with diisobutylaluminum deuteride ($DAliBu_2$).

Sulfur and especially selenium may also serve as leaving groups. The following synthesis, in which sulfur is incorporated exocyclically in the β-position (Route 1) was described by *Paterson* and *Fleming*[110a]. The sulfur, following its oxidation to the sulfoxide, is removed as usual in a pericyclic reaction by heating (Scheme 60).



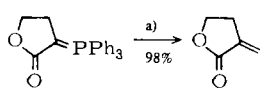
Scheme 60.

The incorporation of the phenylseleno group via electrophilic diphenyl diselenide and its elimination to give the double bond were steps in the synthesis of estafiatin[110b,c] (Scheme 61).



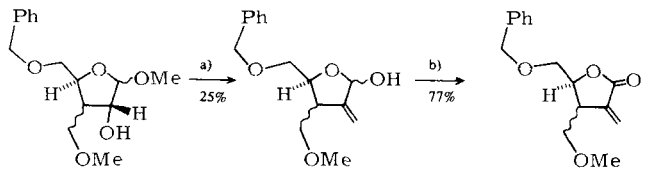
Scheme 61.

It has been known for several years that α-methylene lactones can be synthesized via a Wittig reaction[111,112], but this reaction has only been employed in specific cases (Scheme 62).



Scheme 62. a) Paraformaldehyde.

Fraser-Reid et al.[113] and *Nair* et al.[114a] have shown that chiral α-methylene lactones can be obtained from the chiral pool using a Wittig reaction (Scheme 63).

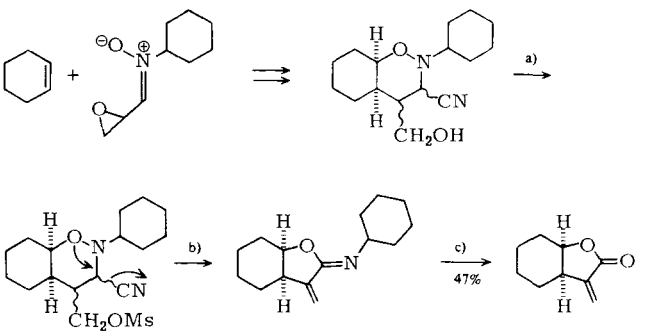


Scheme 63. a) 1) Pyridiniumchlorochromate (PCC), CH_2Cl_2, 2) $Ph_3P{=}CH_2$, 3) 1,2-Dimethoxyethane (DME)/H_2O. b) Ag_2CO_3-celite.

4.8. Other Methods

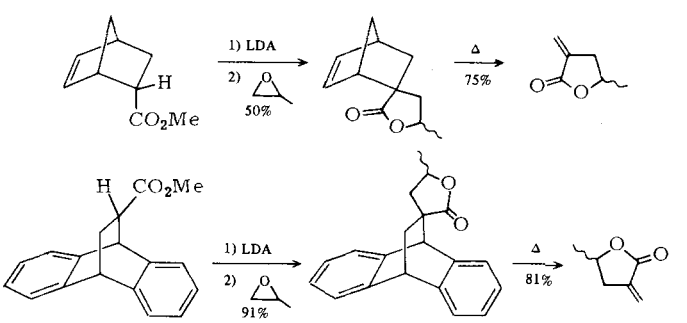
Synthetic methods which have not been considered in Scheme 2 will be dealt with in this section. These involve pericyclic reactions and rearrangements:

a) The cycloaddition of nitrones to olefins (Diels-Alder reaction with inverse electron demand) described by *Eschenmoser* et al.[115] was further studied by *Riediker* and *Graf*[116]. As already mentioned (see Section 4.4), the cycloaddition route is limited in its applicability insofar as only *cis*-fused lactone rings can be prepared (Scheme 64).



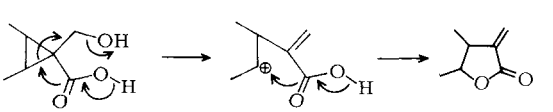
Scheme 64. a) MsCl/pyridine. b) KO*t*Bu/*t*BuOH. c) 0.25 N H_2SO_4, CCl_4.

b) The Diels-Alder reaction can be used for the protection of the CC double bond of acrylic ester as cycloadduct. After the deprotonation with lithium diisopropylamide (LDA), the S_N2 reaction with propylene oxide gives the desired 1,4-functionality distance and then the spirolactone is formed. In the final step, the protecting group is cleaved off by cycloreversion[117,118] (Scheme 65).



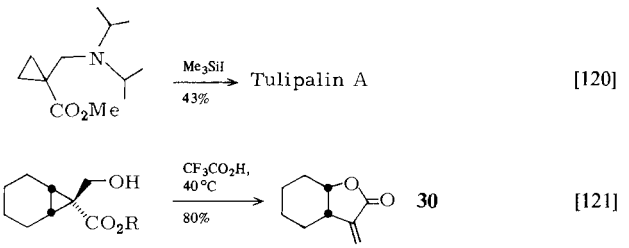
Scheme 65.

c) A third route to synthesize α-methylene lactones is the cyclopropane rearrangement developed by *Hudrlik* et al.[119]. All the atoms of the product are already present in the cyclopropane educt **29**. The cyclopropylmethyl-homoallyl rearrangement is facilitated by S_N1-like conditions (Scheme 66). In the case of the formation of the bicyclic lactone **30** the two rings are *cis*-fused (Scheme 67).



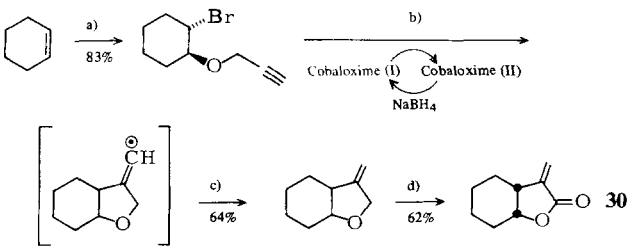
Scheme 66.

Recent examples have been described by *Hiyama* et al.[120] and *Hudrlik* et al.[121]. The remarkably sensitive tulipalin A is formed in 43% yield under almost neutral, anhydrous conditions[120].



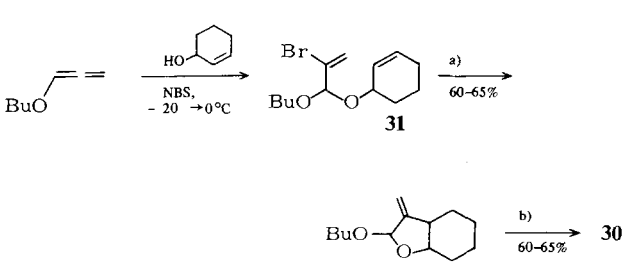
Scheme 67.

d) The formation of CC bonds can also be brought about by carbon radicals, and this approach has become a popular field of research in recent years. Carbon-centered radicals react with electron-rich and electron-deficient π-systems under neutral conditions. Thus, compounds with numerous further potential reaction centers are employable without the need for protecting groups. One example is the cyclization of a propargyl ether to a secondary carbon radical. This radical is formed by single electron transfer (SET) from catalytic amounts of cobaloxime(I), which is cyclically regenerated from cobaloxime(II)[123]. The last step, i.e. the oxidation of the 3-methylenetetrahydrofuran to the lactone, is still preparatively difficult (Scheme 68).



Scheme 68. (a) $HC{\equiv}C{-}CH_2OH$, NBS, $-30°C \rightarrow RT$. (b) $e^{\ominus}(-Br^{\ominus})$. (c) Solvent-H. (d) CrO_3, pyridine, CH_2Cl_2.

One other route starts from functionalized bisallyl ether **31**, which, once again, is prepared with NBS and an excess of allyl alcohol at low temperature, probably via an ionic intermediate. The generation of the vinyl radical from **31** takes place under normal conditions. Although **31** carries different types of labile hydrogen atoms (allylic and one acetal hydrogen), the cyclization proceeds in respectable yield (60—65%). Jones oxidation furnishes the desired lactone **30**[124] (Scheme 69).



Scheme 69. (a) Bu_3SnH, 2,2'-azobis(isobutyronitrile) (AIBN), C_6H_6. (b) Jones oxidation.

Besides 2-cyclohexenol, other allylic alcohols can be used for the reaction with the allenyl ether.

The various radical reactions illustrate that new synthetic methods must go through the trials of practical application and total synthesis. Conversely, it is clear that such an important class of heterocycles as the α-methylene-γ-butyrolactones mobilizes the whole arsenal of synthetic methods which are at our disposal.

5. Outlook

Kupchan's discovery in 1970 of the cytotoxic activity of the sesquiterpene lactones was the green light for a rapid development, which is continuing today and proceeding in various directions. The isolation and identification of many additional representatives, especially by *Bohlmann* et al.[125], the total syntheses, and the discovery of a broad spectrum of biological activities followed. At the same time the lactones functioned as a lead in the search for analogues and attention was focussed also on completely different constituents of the *Compositae*, as well as on their pharmaceutical and economic uses. Of the many new and ingenious methods that have been published on the preparation of the α-methylene-γ-butyrolactone moiety, a large number are of academic interest only. The most commonly used methods include:

1. oxidative cyclization of crossed allylic-homoallylic alcohols (Section 4.1),
2. halogeno-lactonization and seleno-lactonization of 2-methylene-4-pentenoic acids (Section 4.2),
3. metal-promoted cyclization of $a^1a^3a^{3'}$ components with carbonyl compounds (Section 4.3),
4. transition-metal-catalyzed carbonylation of 3-bromo- and 3-iodohomoallylic alcohols (Section 4.6);
5. α-methylenation of preformed γ-butyrolactones (Section 4.7).

The investigations carried out in this sector have enriched heterocyclic chemistry, terpene synthesis, and, at the same time, contributed to the development of new synthetic methods.

The future offers a wide choice for interdisciplinary efforts regarding the use of α-methylene-γ-butyrolactones in the fields of organic chemistry, biology, immunology, medicine, and pharmacology.

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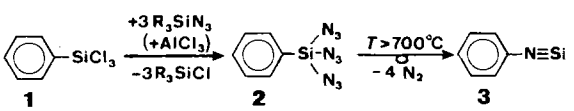
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Phenyl Silaisocyanide: The First Organosilicon Compound with a Formal Si≡N Triple Bond**

By *Hans Bock** and *Ralph Dammel*

Dedicated to Professor Gerhard Fritz on the occasion of his 65th birthday

The assumption that main-group elements of the higher (eight-membered) periods exhibit only limited ability to form $p_\pi p_\pi$-multiple bonds, the so-called "double bond rule", has been disproven more and more in the years since 1979 also for organosilicon compounds. It has been possible both to detect spectroscopically short-lived parent molecules such as silatoluene[1a], silabenzene[1b], or silaethene[1c] as well as to isolate derivatives with Si=C[1d] or Si=Si[1e] double bonds which are stabilized kinetically by bulky substituents. The matrix photolysis of azidosilane H_3SiN_3 to H–NSi had already been reported 20 years ago[2a], and, recently, calculations on the still unknown system RSi≡SiR↔R_2Si=Si have been published[3]. Here we present PE-spectroscopic evidence for phenyl silaisocyanide H_5C_6–N≡Si **3**, an organosilicon compound with a presumably linear[4] C–N≡Si group and terminal silicon of coordination number 1.



The starting material for the pyrolysis is triazido(phenyl)silane **2**, prepared from trichloro(phenyl)silane **1** by $AlCl_3$-catalyzed azide exchange with azidotrimethylsilane[5].

"Controlled explosion" of **2** in a flow system at low pressure requires temperatures in excess of 700 °C (!). As with other azides[6a–c] the pyrolysis can be carried out safely with small amounts of sample using PE-spectroscopic real-time gas analysis[6d, 7]. By inspection of the ionization patterns recorded as a function of temperature, the N_2 extrusion conditions can be optimized and—in the case of preponderantly homogeneous reaction channels—the resulting N_2 elimination products directly identified[6] (Fig. 1).

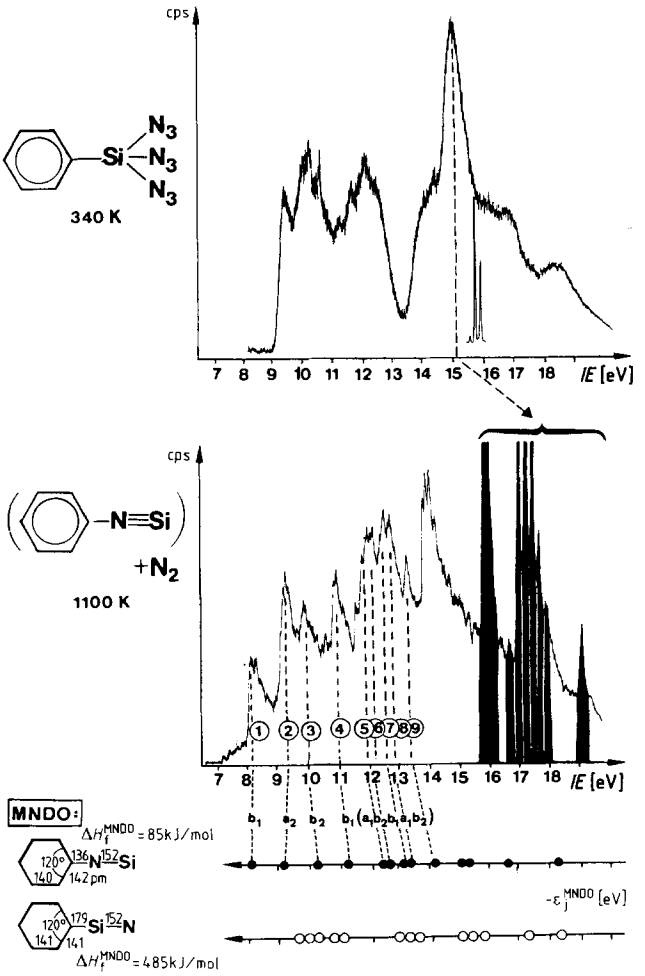


Fig. 1. He(I)-PE spectra of **2** at 340 K (top) and its pyrolysis product at 1100 K (middle) [7] (N_2 bands in black). The assignment of the 1100 K spectrum to one of the isomers H_5C_6–N≡Si **3** and H_5C_6–Si≡N via Koopmans correlation, $IE_n^v = -\varepsilon_j^{MNDO}$, is based on the eigenvalues obtained from geometry-optimized MNDO calculations (see text).

The PE spectra (Fig. 1) demonstrate that the triazidosilane **2** is completely decomposed[7] at 1100 K: its strong azide band between 15 eV and 16 eV has been replaced by intense N_2 bands (Fig. 1, black). In the low energy region between 8 eV and 14 eV the pyrolysis mixture exhibits an ionization pattern consisting of nine well-separated bands[7], assigned to phenylsilaisocyanide **3** with the following arguments:

- MNDO calculations with complete geometry optimization ($E_{total}^{MNDO} = -1140.13$ eV) reproduce the experimental ionization pattern (Fig. 1) via Koopmans theorem $IE_n^v = -\varepsilon_j^{MNDO}$.
- The assignment of the four lowest radical cation states of $H_5C_6NSi^{\odot\oplus}$ can be rationalized by means of MNDO orbital plots with a "molecules in molecule" (MIM) perturbation model (Fig. 2). Coupling of the subunits $H_5C_6(H)$ with $IE_{1,2}^v = 9.25$ eV and (H)NSi with $\varepsilon_1^{SCF} \approx 10.2$ eV[2b] to form H_5C_6–NSi leads to the π-interaction $\pi_s \pm \pi_{NSi}$ between the levels of equal (b_1) symmetry with comparable splittings $\Delta E \approx \pm 1$ eV (contri-

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[**] Gas-Phase Reactions, Part 48. Part of the Dissertation by *R. Dammel*. The results were presented at the VIIth Int. Symp. Organosilicon Chem. in Kyoto/Japan, September 1984. This work was supported by the Deutsche Forschungsgemeinschaft, the Land Hessen, and the Fonds der Chemischen Industrie.—Part 47: M. Binnewies, B. Solouki, H. Bock, R. Becherer, R. Ahlrichs, *Angew. Chem. 96* (1984) 704; *Angew. Chem. Int. Ed. Engl. 23* (1984) 731.

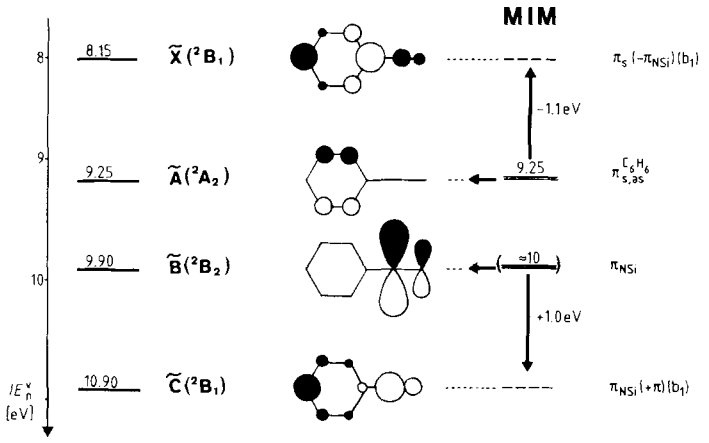


Fig. 2. MIM perturbation model for the first four radical cation states of phenyl silaisocyanide (cf. text).

butions $-\pi_{NSi}$ and $+\pi_s$ both ca. 20%). As expected, the second ionization energy of **3** is equal to the first ionization energy of benzene; the substituent $-N\equiv Si$ acts as a π-electron donor[8].

- The PE spectrum of the pyrolysis product of **2**, which is characteristic of a benzene derivative with an electron donor substituent, cannot be assigned to the isomeric silacyanide $H_5C_6-Si\equiv N$, for which an MNDO calculation of the same quality ($E^{MNDO}_{total} = -1135.98$ eV) predicts only two ionization humps of strongly overlapping bands between 9.5 and 11 eV and around 13 eV (Fig. 1, below).
- According to the MNDO heats of formation, $H_5C_6-Si\equiv N$ is predicted to be 400 kJ/mol less stable than $H_5C_6-N\equiv Si$ **3**. This is confirmed by highly correlated calculations on the parent molecules HNSi and HSiN[2b,c].
- Geometry-optimized MNDO calculations, the results of which are corroborated by Koopmans correlation and the perturbation model (Fig. 1, 2), yield other verifiable molecular parameters for the pyrolysis product $H_5C_6-N\equiv Si$ **3**: thus, the bond length d^{MNDO}_{N-Si} of ca. 152 pm is consistent with the HNSi bond distance $d_{N-Si} = 154$ pm determined spectroscopically[2a] or obtained from CI calculations[2b,c]. A comparison with known SiN single and triple bond lengths ($d_{Si-N} \sim 175$ pm, $d_{Si\equiv N} = 157$ pm[2c]) suggests triple bond contributions also for the $-N\equiv Si$ group in phenyl silaisocyanide which according to the calculations should be linear.

The pyrolysis of triazido(phenyl)silane **2**, which is driven by the energetically favorable extrusion of 4 N_2 molecules, according to the PE spectroscopic and quantum chemical arguments presented, enforces the formation of a polar $N\equiv Si$ triple bond. The optimum conditions determined here for the decomposition of **2** should facilitate corroboration of the interesting result by other physical measurements and by chemical trapping reactions[9].

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[7] The short path pyrolysis apparatus has been described in detail in *Chem. Ber. 115* (1982) 3747. The thermal decomposition of **3** 1100 K was carried out five times and yielded the following ionization regions for the respective bands: ① 8.14—8.19, ② 9.24—9.29, ③ 9.86—10.06, ④ 10.83—10.97, ⑤, ⑥ 11.76—12.0, ⑦, ⑧ 12.5—12.7, ⑨ 13.09—13.2 eV.

[8] The PE spectrum of pure phenyl isocyanide (V. Y. Young, K. L. Cheng, *J. Electron Spectr. Rel. Phen. 9* (1976) 317) was recorded again for purposes of comparison and was assigned by geometry-optimized MNDO-calculations in the region up to 13 eV as follows: 9.43 eV ($3b_1$), 10.01 eV ($1a_2$), 10.96 (sharp needle of high intensity: n_C, $13a_1$), 11.92 eV (b_2), 12.34 eV ($2b_1$). A perturbation treatment analogous to that shown in Figure 2 is not possible: since the effective nuclear charge at the nitrogen center is not compensated for by the isocyanide carbon atom, the $-N\equiv C$ group acts as a strong (−I)-substituent.

[9] Matrix isolation studies of the photolysis of $C_6H_5Si(N_3)_3$ **2** are currently being carried out by G. Gross, J. Michl, R. West (Salt Lake City, UT and Madison, WI, USA, resp.) (personal communication R. West); the pyrolysis products at the optimized temperature $T > 980$ K (Fig. 1) are being investigated by H. P. Reisenauer and G. Maier (Giessen).

Concerning the Mechanism of the Asymmetric Diels-Alder Reaction: First Crystal Structure Analysis of a Lewis Acid Complex of a Chiral Dienophile**

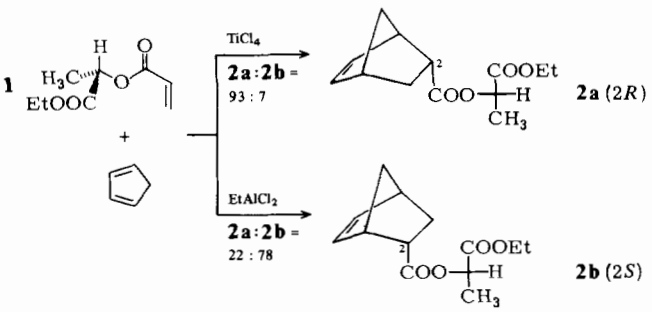
By *Thomas Poll, Joachim O. Metter,* and *Günter Helmchen**

The Lewis acid catalyzed addition of dienes to chiral acrylic acid esters is a promising method for the enantioselective preparation of numerous important building

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[**] This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie. The results were presented in a lecture at the 5th Int. Conf. Org. Synth. in Freiburg (*G. H.*) on August 28, 1984. We thank Dr. *E. Keller*, Freiburg, for supplying us with the program SCHAKAL.

blocks[1]. We recently found that very high levels of stereoselectivity can be achieved[3] even with extremely cheap acrylates of alkyl lactates such as **1**[2]. In contrast to other dienophiles, **1** reacts with cyclopentadiene[4] to give differently configurated adducts depending on the Lewis acid employed ("stereodichotomy"): with $TiCl_4$, formation of **2a** is favored; but with $EtAlCl_2$[5] formation of the diastereomer **2b** is preferred (Scheme 1)[6].



Scheme 1. Stereodichotomy in the Lewis acid-catalyzed Diels-Alder reaction (−63 °C; top arrow: 0.7 equiv. $TiCl_4$, CH_2Cl_2/*n*-hexane (1 : 1), bottom arrow: 2.5 equiv. $EtAlCl_2$, CH_2Cl_2).

The varying influence of the Lewis acids is also manifested in the dependence of diastereoselectivity (*ds*)[7] on the molar ratio Lewis acid : **1** (Fig. 1). With $TiCl_4$ an optimum is found at ca. 1 : 1, with $EtAlCl_2$ a continuous increase over the whole range of measurement. As has already been pointed out[3], these results suggest assumption of a **1**-$TiCl_4$ chelate complex as reacting species for the region of optimum selectivity of the $TiCl_4$-catalyzed reaction. However, on the basis of known model concepts on the asymmetric Diels-Alder reaction (modified Walborsky model[8]) no structure could be proposed which would explain the preference for adduct **2a**.

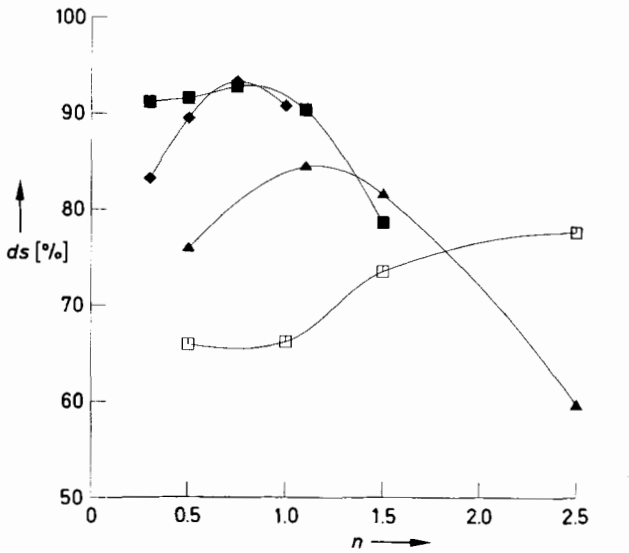


Fig. 1. Dependence of the diastereoselectivity *ds* [7] of the Lewis acid-catalyzed Diels-Alder reaction of **1** with cyclopentadiene (cf. Scheme 1) on the ratio *n*, Lewis acid: **1** (*T* = −63 °C). ■ $TiCl_4$, CH_2Cl_2; ◆ $TiCl_4$, CH_2Cl_2/*n*-hexane; ▲ $TiCl_4$, toluene; □ $EtAlCl_2$, CH_2Cl_2.

We have now been able to obtain crystals of a **1**-$TiCl_4$ complex and to determine its structure[9]. The complex **3** (Fig. 2, Scheme 2) shows several remarkable features. The enoate group[10] is not antiplanar, as had to be expected (vide infra), but synplanar. Furthermore, in the case of titanium compounds, a seven-membered ring chelate structure has, to our knowledge, not been reported hitherto. The geometry of the ring is such that the Ti atom lies far outside of the two planes delineated by the ester groups. Hence, these are partially π-coordinated.

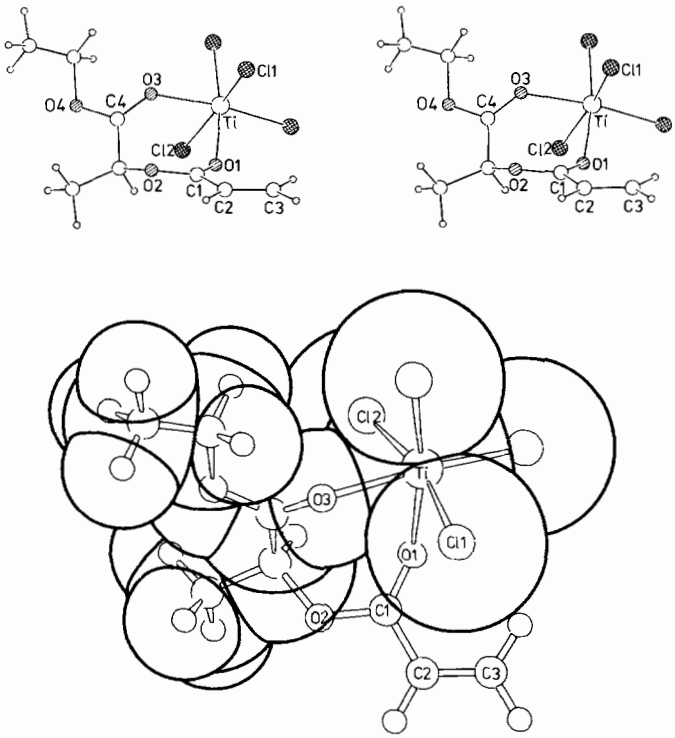
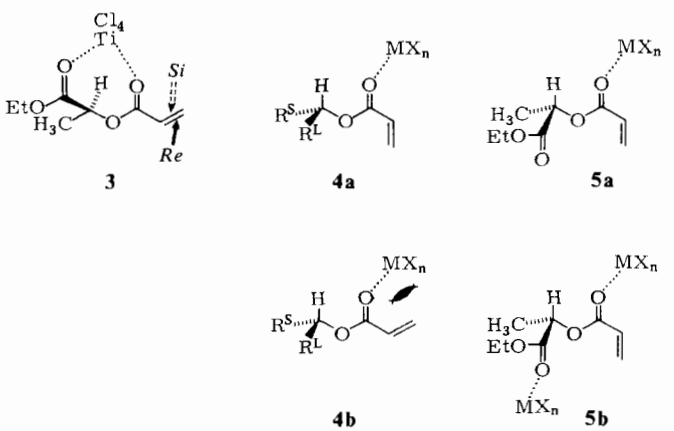


Fig. 2. Structure of **3** in the crystal [9]. Top: Stereograph. Selected bond lengths [Å], bond angles [°], and torsion angles [°]: C3–C2 1.311(7), C2–C1 1.456(7), C1–O2 1.316(5), C1–O1 1.243(5), O1–Ti 2.109(3), Ti–O3 2.136(3), Ti–Cl (averaged) 2.26, O3–C4 1.215(6), C4–O4 1.294(6), C3–C2–C1 120.55(45), C2–C1–O1 123.14(41), C2–C1–O2 114.18(39), C1–O1–Ti 134.14(30), O1–Ti–O3 81.36(12), Ti–O3–C4 132.00(32), C2–C2–C1–O1 8.9, O2–C1–O1–Ti 63.6, O4–C4–O3–Ti −132.2.—Bottom: Projection (SCHAKAL) onto the plane C1,C2,C3. The position of the hydrogen atoms was determined by force field calculations (MM2, N. L. Allinger, *J. Am. Chem. Soc. 99* (1977) 8127). Space filling model: Van-der-Waals radius according to L. Pauling, The Nature of the Chemical Bond, 3rd edit. Cornell University Press, Ithaca, 1960; small circles: 20% of the van-der-Waals radius.

If **3** is the species reacting in solution then the high diastereoselectivity of the upper reaction in Scheme 1 is explained by a shielding of the *Re* face of the ene part of the enoate group by one of the chlorine atoms (Fig. 2: Cl-1).



Scheme 2. Fundamental types of Lewis acid complexes of chiral acrylates. MX_n: Lewis acid; R^L, R^S: apolar groups of large (L) and small (S) steric bulk; for all cases the enoate group is considered to lie in the plane of the paper.

Remarkably, the enoate group lies in a concave[8] environment relative to the Lewis acid (Fig. 2); the substituents at the chirality center make *no* significant contribution to the diastereoface-differentiation.

How does this interpretation fit into the general picture? For complexes of "classical" chiral acrylates (prototype: menthyl acrylate) with only *one* center capable of coordination (carbonyl-O), reactive conformers **4a** with antiplanar enoate conformation are postulated on the basis of the configuration of their addition products[1,8]. Consistent with this postulation is the structure of a 2:1-methyl cinnamate-$SnCl_4$ complex in the crystal[11a]. This structure, as well as two additional structures of achiral ester complexes[11], further suggest that σ-coordination, with the position of the Lewis acid as given in **4**, is preferred for nonchelate complexes. The synplanar conformation of the enoate group in the complex **4b** could consequently be destabilized due to repulsive interactions[12]. Other than in the case of **3**, the σ-coordinated Lewis acid does not contribute to the diastereodifferentiation.

Complexes of the type **4** might also play a role for the reactions of the lactate **1**. We assume that **3** is in equilibrium with complexes **5** ($MX_n = TiCl_4$). For these, preferred *Re*-attack of the diene (to give **2b**) is to be expected. Since the formation of **5b** is favored by high concentration of $TiCl_4$, the stereoselectivity of the addition reaction is lowered if the ratio $TiCl_4$: **1** is > 1 (Fig. 1). Assumption of alternatives **3** and **5** also explains the stereodichotomic effect: with $TiCl_4$, predominantly the chelate complex **3** reacting to give **2a** is formed, whereas with tetracoordinating Lewis acids such as $EtAlCl_2$ or BF_3 the complexes **5** predominate, from which **2b** is then formed selectively.

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[2] The corresponding methyl, isopropyl, and isobutyl esters behave essentially like the ethyl ester **1**.

[3] T. Poll, G. Helmchen, B. Bauer, *Tetrahedron Lett. 25* (1984) 2191.

[4] The reaction with cyclopentadiene has been studied in great detail; but we found comparable results also with isoprene.

[5] $SnCl_4$ reacts similarly as $TiCl_4$; $AlCl_3$ and $BF_3 \cdot OEt_2$ react similarly as $EtAlCl_2$. High enantioselectivity with expectedly lower *endo-exo* selectivity was also found for the non-catalyzed reaction (preferred *endo*-adduct: **2b**).

[6] Because of the high *endo-exo* selectivity (> 30 : 1) of the Lewis acid-catalyzed reaction only the *endo*-adducts are considered here.

[7] Here, we define the *ds* value as the percent content of the predominating diastereomer in the mixture of the *endo* addition products **2a/2b**.

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[9] Crystal structure analysis of **3** (from CH_2Cl_2/*n*-hexane): $C_8H_{12}O_4TiCl_4$; orthorhombic, $P2_12_12_1$ (No. 19), $Z = 4$, $a = 8.743(2)$, $b = 9.532(2)$, $c = 17.373(4)$ Å, $\alpha = \beta = \gamma = 90(-)°$, $V = 1447.8$ Å^3; Syntex-P21 diffractometer, ca. −130°C, $Mo_{K\alpha 1}$, $5° < 2\vartheta < 48°$; 1317 reflections (1272 with $I > 1.96\sigma(I)$); direct methods (MULTAN 80, SHELX-2500), calculation of the positions of the H atoms with force field (MM2); $R_1 = 0.032$, $R_2 = 0.038$. Further details of the crystal structure investigation are available on request from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2 on quoting the depository number CSD 51 087, the names of the authors, and the journal citation.

[10] Enoate signifies an ester (*oate*) of an α,β-unsaturated (*ene*) carboxylic acid.

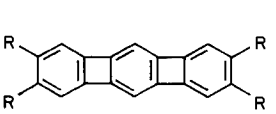
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[12] σ-Complexes of a fundamentally different type than those discussed here have been postulated for α-hydroxyenones: a) L. A. Reed, J. Davis, W. Choy, S. Masamune, *J. Org. Chem. 48* (1983) 4441; analogous compounds: b) W. Oppolzer, C. Chapuis, G. Bernardinelli, *Helv. Chim. Acta 67* (1984) 1397; c) D. A. Evans, K. T. Chapman, J. Bisaha, *J. Am. Chem. Soc. 106* (1984) 4261.

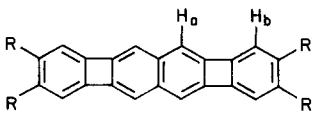
Synthesis of the First Linear (*o*-Phenyleno)naphthalenes; a New Class of Benzenoid Aromatics**

By *Harold E. Helson, K. Peter C. Vollhardt**, and *Zhen-Yu Yang*

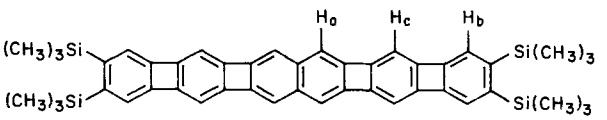
We have recently outlined a synthetic strategy which allows the iterative construction of the multiphenylene framework, an arrangement in which the aromatic benzene ring is juxtaposed to the cyclobutadiene moiety by alternating linear fusion[1]. This work led to the synthesis and investigation of the properties of the first members of the series, the terphenylenes **1** and **2**. Here we report the preparation of the (*o*-phenyleno)naphthalenes **3**, **4**, and **5**, of interest per se as novel benzenoid hydrocarbons, but also as key elements in our efforts to develop this methodology for the synthesis of potentially conducting organic materials[2]. While all systems contain a [4n+2] π-periphery, only **3** and **4** can avoid cyclobutadienoid[3] circuits[4], and might therefore show unusual naphthalene-type stability.



1, R = $Si(CH_3)_3$; **2**, R = H



3, R = $Si(CH_3)_3$; **4**, R = H



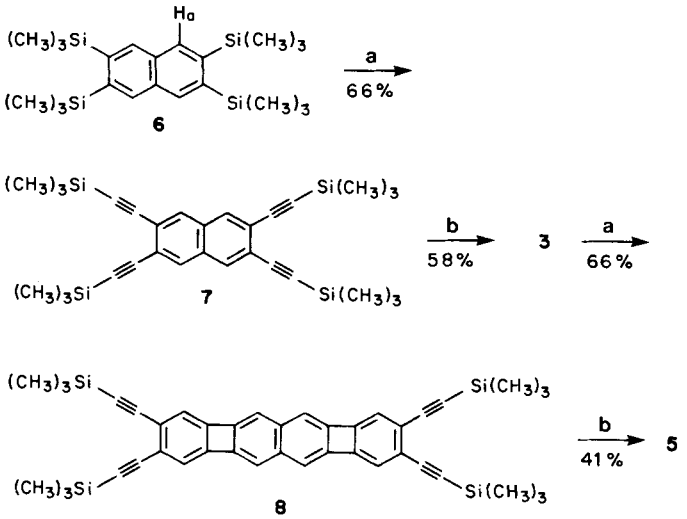
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Our synthetic approach is shown in Scheme 1 and begins with 2,3,6,7-tetrakis(trimethylsilyl)naphthalene **6**, prepared in one step from acyclic materials by cobalt catalysis[5]. Iodination, palladium-catalyzed ethynylation, desilylation, and cyclization with bis(trimethylsilyl)acetylene then proceed, as described previously[1a], to give **3**, and eventually **5**. Protodesilylation of **3** with trifluoroacetic acid afforded **4**[6], conditions under which **5** decomposed. The power of the methodology becomes apparent when one realizes that *all* of the component rings, involving eleven of the bonds in **3** and **4**, and seventeen (!) in **5**, are constructed by cobalt-catalyzed steps.

The physical properties of the key compounds are shown in Table 1. Even though **3** and **5** have an aromatic

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[**] This work was supported by the National Institutes of Health (CA 20713). *H. E. H.* was an undergraduate research participant (1982—1983) and *K. P. C. V.* a Camille and Henry Dreyfus Teacher-Scholar (1978—1983).



Scheme 1. **a**: 1) ICl, 2) trimethylsilylacetylene, $[PdCl_2(PPh_3)_2]$, CuI, Et_3N, piperidine; **b**: 1) CH_3OH, potassium hydroxide, 2) bis(trimethylsilylacetylene), $[(C_5H_5)Co(CO)_2]$.

π-electron count, the cumulative effect of the paratropism exerted by the increasing number of cyclobutadienoid rings along the series becomes apparent. The ^{1}H-NMR assignments, particularly of **5**, are tentative and based on analogies[1], the work of *Figeys* et al.[7], and knowledge of the deshielding effect of the trimethylsilyl group on *o*-hydrogen atoms[1,5]. Moreover, in **4**, where the assignments are unambiguous, the naphthalene absorption occurs at $\delta = 6.73$ (s), with the remaining signals occurring as an AA'BB' multiplet centered at 6.88 and 6.80. Thus, remarkably, the central naphthalene moiety experiences an extraordinary shielding, which must be due to not only the paratropic influence of the four-membered rings but also bond-fixation, and hence a reduced diamagnetic ring current in this portion of the molecule. In fact, the systems appear to prefer to behave as "phenylenophenylenes" rather than as "benzocyclobutanaphthalenes". For example, the key signals in the ^{13}C-NMR spectrum of **3** [$\delta(CDCl_3) = 149.4$, 149.1, 148.4, 136.3, 123.8, 117.3, 2.14] strongly resemble those of 2,3-bis(trimethylsilyl)biphenylene[1a] [$\delta(CDCl_3) = 152.5$, 150.5, 147.7, 128.1, 122.7, 117.6, 2.14]. The electronic spectra along the series exhibit a fairly constant bathochromic shift increment of 70 nm on cyclobutabenzoannelation, as seen earlier[1]. Interestingly, the UV spectrum of **3** is very similar to that of **1**. Finally, preliminary cyclic voltammetry data reveal that the phenylenes readily accept electrons. While the relatively stable **3** exhibits reversible one- and two-electron reduction waves, the heat-, air-, and acid- ($CDCl_3$, silica gel) sensitive **5** decomposes under these conditions. Nevertheless, the data suggest that the stoichiometric multiple redox chemistry of these systems should be interesting.

Table 1. Physical properties of **6**, **3**, and **5**.

	Appearance M.p. [°C]	^{1}H-NMR ($CDCl_3$), δ H_a	H_b	H_c	CH_3	UV (hexane) $\lambda_{max.}$ [nm], $\varepsilon \times 10^{-4}$	$E_{1/2}$ [V] [a]
6	colorless crystals, 288	8.06			0.44	244 (12.3)	−2.81
3	yellow crystals, 314 (dec.)	6.69	7.06		0.29	287 (3.0), 302 (6.9), 315 (13.6), 390 (0.65), 408 (1.6), 432 (2.6)	−2.23, −2.62
5	red powder, >360 (dec.)	6.42	6.77	6.32	0.30	321 sh, 331 (4.3), 360 (3.5), 472 (1.7), 490 sh, 504 (2.7)	(−1.41, −1.75, −1.98, −2.17)

[a] Pt electrode vs. $Ag/Ag^{\oplus}$, THF, 0.1 M $Bu_4N^{\oplus}PF_6^{\ominus}$.

In this vein, we have reduced **3** to its brown dianion by exposure to sodium in tetrahydrofuran (THF), the reaction proceeding via the green (presumed) radical anion intermediate. At −80 °C the ^{1}H-NMR spectrum reveals three singlets at $\delta = 6.70$, 6.37, and 0.17. Exposure of this sample to air led to re-formation of **3** [$\delta([D_8]THF) = 7.15$, 6.79, 0.36]. That the reduced species was indeed a di- and not a higher anion was shown by the ^{13}C-NMR spectrum [$\delta([D_8]THF) = 131.6$, 124.0, 123.7, 121.0, 114.0, 106.0, 3.5] in which the cumulative up-field shift was only compatible with a doubly negatively charged molecule. As observed in the reduction of **1**[1b], the strong shielding of the ^{1}H-NMR absorptions in $\mathbf{3}^{2\ominus}$, expected to occur since a $(4n+2)$ π- is converted into a $(4n)\pi$-system and a neutral compound into a dianion, does not materialize. Again, it is tempting to assume that the system has the capability of assuming an electronic structure which maximizes aromatic at the expense of antiaromatic ring currents[8]. This hypothesis might be testable in the reduction of **5**, which could furnish both the di- and the tetraanion.

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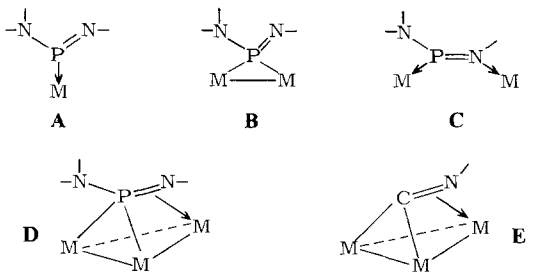
Amino(imino)phosphanes as Face-Bridging Complex Ligands

By *Otto J. Scherer**, *Richard Walter*, and *William S. Sheldrick*

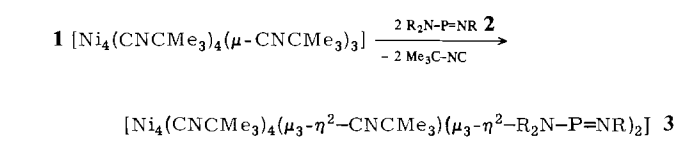
Amino(imino)phosphanes $>N-P=N-$ are versatile complex ligands[1]: Besides the preferred terminal *P*-coordination (**A**)[1], examples of μ-*P*- (**B**)[2a] and *N,P*-coordination (**C**) have also been described[2b].

We have now prepared the Ni_4-cluster **3**, in which three triangular faces are bridged by two μ_3-η^2-$R_2N-P=NR$ ligands and one μ_3-η^2-$C\equiv N-CMe_3$ ligand as in **D** and **E**, respectively, by reaction of the isocyanide cluster $[Ni_4(CNCMe_3)_7]$ **1**[3a] with $R_2N-P=NR$ **2**, $R = SiMe_3$ (Fig. 1).

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3 forms dark-red crystals[4] which are readily soluble in benzene, toluene, pentane, dichloromethane, and diethyl ether, but only sparingly soluble in acetonitrile. The ^{1}H-NMR spectrum[5] of the chiral Ni_4-cluster 3 shows five



Me_3C signals and four Me_3Si signals. Temperature-dependent measurements (−60 to +60 °C) show a change in the signal pattern only below 0 °C, since the rotation about the R_2N–P bonds is frozen-in. In the $^{31}P\{^1H\}$-NMR spectrum, an unusually large upfield shift is observed for the two doublets of the P atoms (different environment, Fig. 1).

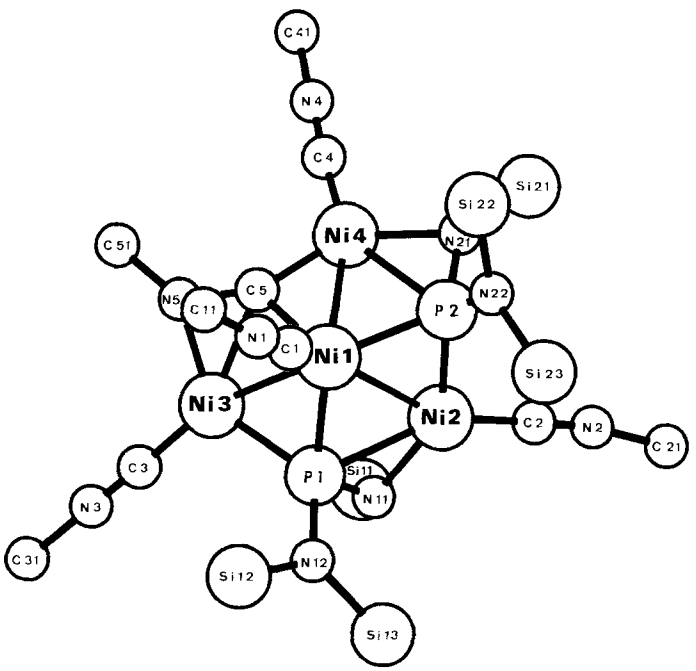


Fig. 1. Structure of 3 in the crystal (methyl groups have been omitted for the sake of clarity). Selected bond lengths [Å] and angles [°] (see also text): Ni1–Ni2 2.493(2), Ni1–Ni3 2.451(2), Ni1–Ni4 2.422(2), Ni2···Ni3 3.887(2), Ni2···Ni4 3.494(2), Ni3···Ni4 3.667(2), Ni1–C5 1.913(8), Ni4–C5 1.788(11), Ni3–C5 2.112(11), Ni3–N5 1.880(9), Ni1–P1 2.195(4), Ni3–P1 2.143(3), Ni2–P1 2.372(3), Ni2–N11 1.959(8), P1–N11 1.610(10), P1–N12 1.732(8), Ni1–P2 2.176(3), Ni2–P2 2.143(4), Ni4–P2 2.409(3), Ni4–N21 1.949(8), P2–N21 1.596(8), P2–N22 1.709(9), mean value of the terminal C≡N bonds 1.156, C5-plane Ni1,Ni3,Ni4 0.63, P1-plane Ni1,Ni2,Ni3 1.08, P2-plane Ni1,Ni2,Ni4 1.45; Ni3–C5–N5 61.4(6), Ni3–N5–C5 80.6(6), Ni2–P1–N11 55.0(3), Ni2–N11–P1 82.7(4), N11–P1–N12 104.3(4), Ni4–P2–N21 53.7(3), Ni4–N21–P2 85.0(4), N21–P2–N22 107.7(4); dihedral angle: N12–P1–N11–Si11 127.9, N22–P2–N21–Si21 77.7, Ni3–C5–N5–C51 154.2.

The crystal structure analysis[6] (Fig. 1) shows that 3, like the educt 1[3a], consists of a compressed trigonal pyramid (distance of Ni1 from the Ni2,Ni3,Ni4 plane = 1.22 Å), whose base (Ni2,Ni3,Ni4) exhibits marked differences in the Ni···Ni distances (3.494(2)—3.887(2) Å). The distances of the basal Ni atoms from the apical Ni1 atom, with a mean value of 2.455 Å are distinctly greater than those found in 1 (mean value 2.338 Å)[3a]. The difference between the distance Ni1–C1 (1.851(13) Å = longest bond) and the mean value (1.770 Å) of the Ni–C distances between the basal Ni atoms and their terminal Me_3C–NC ligands in 3 is, with a value of 0.081 Å, only slight; in 1, with a value of 0.34 Å, this is otherwise[3a]. The structurally most interesting aspect is the μ_3-η^2-coordination of the C≡N- and –P=N-ligand moieties (Fig. 1 and **D** and **E**). Me_3C–NC as four-electron donor (**E**) extends the recently found type of coordination in $[Fe_3(CO)_9(\mu_3\text{-}\eta^2\text{-}CNCMe_3)]$[7], in which Me_3C–NC functions as six-electron donor (2σ and 4π electrons), by a novel variant of face bridging. Characteristic of this type of structure are the C5–N5 distance (1.316(13) Å) and C5–N5–C51 angle (131.5(9)°) and the ν(CN) at 1595 (s) cm^{-1} (ν(CN) (pentane) of the terminal ligands = 2090 (s), 2060 (vs), 2015 (sh) cm^{-1}). Distinction between a face- or edge-bridging for the three bridging isocyanide ligands in 1 could not be made, because of disorder in the crystal[3a]; in later publications[3b,c], only the edge-bridging comes under discussion.

The coordination type **D** of a trivalent phosphazene found in 3 for the first time (cf. the recently verified μ_3-η^2-bridge of a phosphaalkene ligand generated on a Fe_3 cluster[8]), shows, in contrast to **B** and **C**, the following peculiarities: The P=N-bond is on average longer (1.603 Å) than in the educt 2 (1.545(2) Å)[9]. In the case of the coordination types **B** (Pt_3 cluster with two μ-R_2N–P=NR ligands and a μ-$CNCMe_3$ ligand)[2a] and **C** ($[Re_2(CO)_6(\mu\text{-}Br)_2(\mu\text{-}RR'N\text{–}P\text{=}NR')]$, R = $SiMe_3$, R′ = CMe_3)[2b] the P=N bond is, at a maximum, 0.02 Å longer. The $^{31}P\{^1H\}$-NMR signals[5] of 3 are shifted by ca. 155 ppm upfield compared to those of added 2 (δ = 327); in the case of coordination type **B**[2a] they are shifted only ca. 30—40 ppm, in **C**[2b] only ca. 24 ppm.

With the synthesis of 3[10], a further example has been found for the displacement of bridging isocyanide ligands by trivalent phosphazenes. It is clearly emerging that ligands of the type >N–P=N– exhibit a coordination behavior very similar to that of isocyanide ligands[11].

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[4] Procedure: 3: A solution of 2 (266 mg, 0.954 mmol) [12] in benzene (2 mL) was added dropwise within 5 min at room temperature to a solution of 1 [3b] (390 mg, 0.477 mmol) in benzene (6 mL) and the mixture stirred for a further 20 min. After removal of the benzene in vacuo, the stirred oily residue was treated with 5 mL acetonitrile, whereupon a red precipitate was formed. After pipetting off the solution, the precipitate was washed four times with 2 mL acetonitrile and dried in a vacuum. 3 was taken up in 2 mL toluene, treated with 3 mL acetonitrile and allowed to crystallize out within 1 d at −20 °C. The crystals were washed twice with 2 mL acetonitrile and dried for 2 h in a vacuum. Yield 203 mg (40%).

[5] ^{1}H-NMR (200 MHz, [D$_8$]toluene, 293 K, TMS int.): δ(Me$_3$C) = 1.71 (s, 9H), 1.36 (s, 9H), 1.32 (s, 9H), 1.19 (s, 9H), 1.08 (s, 9H); δ(Me$_3$Si) = 0.77 (s, 18H), 0.65 (s, 18H), 0.56 (s, 9H), 0.15 (s, 9H); ^{31}P{^{1}H}-NMR ([D$_8$]toluene, 293 K, H_3PO_4 ext.): δ = 170.6 (d), 173.8 (d), $^2J_{PP}$ = 40.6.

[6] Monoclinic, space group $P2_1/c$, a = 11.449(3), b = 48.931(8), c = 13.040(4) Å, β = 110.88(2)°, Z = 4, ρ_{calc} = 1.18 g·cm^{-3}. 8608 independent reflections (Mo$_{K\alpha}$, $F_0^2 \geq 3.0\sigma(F_0^2)$, $2\theta \leq 45°$); R = 0.071, R_w = 0.071. Further details of the crystal structure investigation are available on request from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2, on quoting the depository number CSD 51100, the names of the authors, and the full citation of the journal.

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[10] When **1** and **2** are allowed to react in the molar ratio 1 : 1 (analogously to the procedure for **3** [4]), red crystals of [Ni$_4$(CNCMe$_3$)$_4$(μ_3-η^2-CNCMe$_3$)$_2$(μ_3-η^2-R$_2$N–P=NR)] are formed in ca. 50% yield, R = SiMe$_3$. ^{1}H-NMR (cf. [5]): δ(Me$_3$C) = 1.77 (s, 9H), 1.65 (s, 9H), 1.32 (s, 9H), 1.24 (s, 9H), 1.23 (s, 9H), 0.81 (s, 9H); δ(Me$_3$Si) 0.73 (s, 18H), 0.39 (s, 9H); ^{31}P{^{1}H}-NMR (cf. [5]): δ = 178.0 (s). IR (pentane) ν(CN) = 2090 (s), 2055 (vs), 1600 (m) cm^{-1}.

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[Mn(S$_2$C$_6$H$_3$Me)$_2$]$^{n-}$: Mononuclear Manganese Complexes with Square-Planar (n = 1) and Distorted Tetrahedral (n = 2) Sulfur Coordination**

By *Gerald Henkel**, *Klaus Greiwe*, and *Bernt Krebs*

Transition metal ions are essential components of important enzymes, and, as such, participate in many biological processes. In addition to the widely disseminated elements iron, copper and molybdenum, even manganese centers have been observed in proteins, but in several cases the nature of such centers has not been completely clarified[1]. Because of the overall significance of metal centers in proteins containing sulfur atoms as coordination sites we have extended our investigations of sulfur-containing transition metal complexes to the elements of the manganese group.

We report here on the synthesis, properties, and structural principles of the mononuclear anions [Mn(tdt)$_2$]$^{2-}$ **1** and [Mn(tdt)$_2$]$^-$ **2** (tdt^{2-} = toluene-3,4-dithiolate), complex anions which can be isolated as the crystalline salts [Ph$_4$P]$_2$[Mn(tdt)$_2$]·2 MeOH **3** and [Ph$_4$P]$_2$[Mn(tdt)$_2$]-[Mn(tdt)$_2$MeOH]·3 MeOH **4**, respectively. According to the structure analysis the crystals of **4** contain not only anions **2** but also mononuclear [Mn(tdt)$_2$MeOH]$^-$ ions **5** with fivefold coordinated Mn[2].

Reaction of $MnCl_2 \cdot 4H_2O$ with Na_2tdt in MeOH in the molar ratio $\leq$ 1 : 2 leads in the absence of oxygen to the formation of a yellowish-brown solution, from which brown columnar-shaped crystals of **3** precipitate out on addition of Ph$_4$PBr. If the solution is brought into contact with atmospheric oxygen prior to the addition of the precipitating reagent, the color immediately turns dark brown. Black crystals of **4** can be precipitated from the oxidized reaction mixture with Ph$_4$PBr. The formation of a mononuclear tris-chelate complex [Mn(tdt)$_3$]$^{2-}$[3] was not observed.

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The effective magnetic moment determined for **4** is 5.2 μ_B per manganese at room temperature. While this value suggests the presence of trivalent metal centers in **2** and **5** with d^4 high-spin configuration, **3** shows the typical high-spin behavior for monomeric thiolate-substituted manganese complexes with tetrahedrally arranged sulfur atoms and d^5 configuration[4b,5]. In the UV spectrum of **4**[6] the band at 900 nm could be assigned to a d-d excitation characteristic for Mn^{III} complexes[7]. The transition Mn$^{III} \rightarrow$ Mn^{II} is observed in the cyclovoltammogram[8] of **4** at -1.09 V (dimethylformamide (DMF) solution) or at -0.82 V (CH_2Cl_2 solution). The potential difference between the oxidation peak and the reduction peak shows a distinct dependence on the solvent (0.610 V for DMF, 0.270 V for CH_2Cl_2). According to results of polarographic investigations a one-electron transfer probably takes place here. Further waves, in which corresponding oxidation and reduction currents are of about the same magnitude, do not occur. On the basis of magnetic and electrochemical investigations the assignment of discrete oxidation states for manganese in **1** (+2) as well as in **2** (+3) and in **5** (+3) would seem justified.

The ^{1}H-NMR spectrum of **4** shows signals shifted upfield (referred to TMS) for the aromatic protons. Thus, resonances are observed at δ = 4.6, 9.3 and 20.8 in [D$_6$]Me$_2$SO, while the signals of the methyl protons appear downfield at δ = -15.7. Further isotropically shifted signals were not observed, so that only solvated [Mn(tdt)$_2$]$^-$ ions should be present in solution.

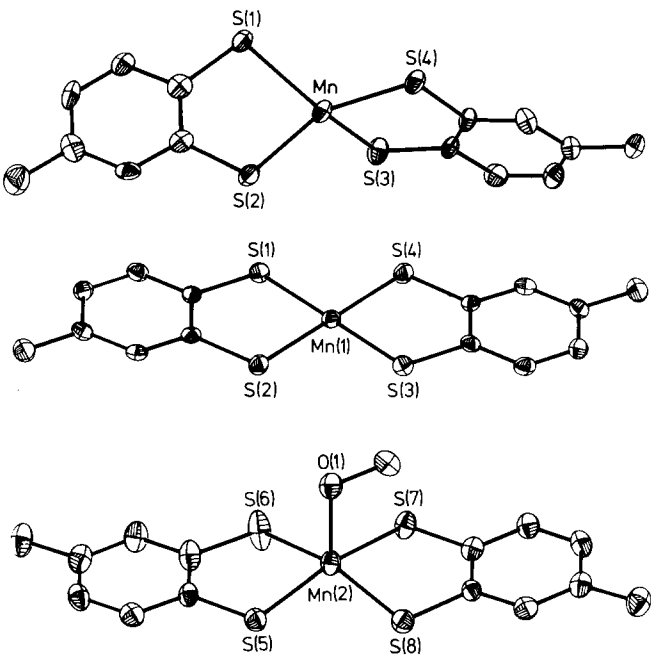


Fig. 1. Top: Structure of **1** in the crystal of **3**. Mn–S bond lengths (σ = 0.002 Å): 2.395, 2.414, 2.425, 2.434 Å; S–Mn–S valence angles (σ = 0.07°): 88.59, 89.15, 117.13, 117.41, 123.06, 124.59°. Center: Structure of **2** in the crystal of **4**. Mn–S bond lengths (σ = 0.001 Å): 2.280, 2.281, 2.282, 2.283 Å; S–Mn–S valence angles (σ = 0.04°): 89.77, 89.81, 90.18, 90.23, 179.86, 180.00°. Bottom: Structure of **5** in the crystal of **4**. Mn–S bond lengths (σ = 0.001 Å): 2.306 (2×), 2.312, 2.314; Mn–O 2.224(2) Å; S–Mn–S valence angles (σ = 0.04°): 88.16, 88.76, 88.99, 89.45, 161.17, 165.78°; S–Mn–O valence angles (σ = 0.06°): 95.48, 98.17, 98.74, 100.65°. All structures with vibration ellipsoids (50% probability, without H-atoms, -130°C). Further details of the crystal structure investigations are available on request from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2, on quoting the depository number CSD 51174, the names of the authors, and the journal citation.

The structures of **1** and **2** are shown in Figure 1 (top and center, respectively). Since the planes of the tdt^{2-} ligands in **1** are oriented almost perpendicular to each other (89.0°) a strongly distorted tetrahedral sulfur coordination is present. The short S···S distances within the bidentate chelate ligands (mean value 3.384 Å) lead to two very small (mean value 88.87°) and four larger S–Mn–S valence angles which are much wider than the ideal tetrahedral angle and which can join together as two pairs of 117.27 and 123.83° (mean values). The Mn–S distances in **1** vary between 2.395(2) (Mn–S(3)) and 2.434(2) Å (Mn–S(1)). In comparison to the likewise tetrahedral mononuclear thiolate complexes $[Mn(SPh)_4]^{2-}$[4] and $[Mn(SCH_2CH_2S)_2]^{2-}$[5], a shortening of the mean Mn–S distance by about 0.025 and 0.015 Å, respectively, is observed.

The oxidation of the dianion **1** to the monoanion **2** forces the transition from the distorted tetrahedral to the square-planar sulfur coordination. In contrast to the identically composed Fe^{III} complex[9] and to the analogous Mn^{III} complex with ethanethiolate (edt^{2-}) ligands[5, 10] in which monomeric $[Fe(tdt)_2]^-$ and $[Mn(edt)_2]^-$ moieties are associated pairwise via metal-sulfur bridges, the shortest metal-metal distances in **4** are greater than 9.7 Å and thus even indirect interactions between the metal centers can be excluded.

The Mn–S bonds in **2** ranging from 2.280(1) (Mn(1)–S(1)) to 2.283(1) Å (Mn(1)–S(2)) are of almost exactly the same length and, because of the higher oxidation state of manganese are on average 0.14 Å shorter than the corresponding bonds in **1**. The additional coordination of a neutral methanol molecule extends the ligand sphere of manganese and leads to the formation of anions **5**, which occur along with **2** in crystals of **4**. Figure 1 (bottom) shows a projection of **5** in crystals of **4**. The resulting coordination polyhedron in **5** is a square pyramid whose apex is occupied by the O-atom of the MeOH molecule (Mn–O: 2.224(2) Å), while the S-atoms define the basal plane. The extended coordination in **5** leads, in comparison to the case of **2**, with square-planar metal environment, to somewhat longer Mn–S distances (mean value: 2.310 Å).

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Ag_2O_3, a Novel Binary Silver Oxide**

By *Burkhard Standke* and *Martin Jansen**

In the group of coinage metals copper, silver, gold there are many instances where the homology principle is not satisfied. Thus, in aqueous solution the species Cu^{2+}, Ag^+ and Au^{3+} dominate, without, for example, the oxidation state +2 being realized in the case of silver and gold in this medium. In principle, according to the present state of our knowledge the circumstances are similar in the solid-state chemistry of these elements. Here there are inexplicable discrepancies, even when only one element is considered: a whole series of well-defined *ternary* fluorides, such as $CaAgF_4$ or $KAgF_4$, of bi- and trivalent silver are well-known[1], but still no corresponding oxides[2]. It is surprising, therefore, that there is more than ample evidence for the existence of *binary* oxides or peroxides with silver in a higher valency state[3] which, without exception, call for a final confirmation. During attempts to characterize these phases in more detail, which, as constituents of the anodes in zinc/silver oxide primary cells, are also of practical importance, we have been able to isolate well-defined single crystals of Ag_2O_3 for the first time by anodic oxidation in aqueous solution.

The electrolysis was carried out at 0°C in a platinum dish (as cathode) with an approximately 12 cm-long spirally wound 0.3 mm-diameter platinum wire anode. To avoid short-circuiting between the silver depositing on the cathode and the oxide forming on the anode a watch glass was placed under the anode so as to collect the precipitating product and, at the same time, protect it against reduction at the cathode. The nature of the oxidation product depends strongly on the anion of the silver salt employed: for example, $Ag_7O_8NO_3$ is formed from $AgNO_3$ solutions, whereas in the case of anions such as PF_6^-, which apparently can no longer be accomodated in the $Ag_7O_8^+$ framework, the novel compound Ag_2O_3 is formed. Suitable electrolytes are neutral, 0.1 N aqueous solutions of $AgClO_4$, $AgBF_4$ or $AgPF_6$. The anodic current density should be ca. 8 mA/cm^2. Since the pH is not regulated, the electrolysis must be terminated after 2 h; otherwise dissolution of the product takes place.

The black, shiny metallic Ag_2O_3 crystals (maximum dimensions $0.4 \times 0.6 \times 1.0$ mm^3) thus obtained, mostly consist of intergrown single crystals and slowly lose oxygen at room temperature and atmospheric pressure, but can be stored for some time at −20°C. Ag_2O_3 is rapidly decomposed by strong acids. According to the X-ray structure analysis[5], silver is coordinated by an almost square-planar array of oxygen atoms (Fig. 1), with the Ag projecting

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about 9 pm from the best plane defined by them. The AgO_4 groups are linked via common O-atoms to give a three-dimensional network structure. From the empirical formula it essentially follows that O1 and O2 thus perform different topological functions: O1 with the coordination number (C.N.) 3 and O2 with C.N. 2 referred to silver. The slight deviations of the AgO_4 polyhedron (cf. Fig. 1) from the ideal D_{4h} point symmetry are chiefly due to the different coordinative demands on the oxygen atoms. Consistent with this, the Ag–O2 distance is the shortest, with a value of 197.6 pm. The average Ag–O distance of 202 pm is conspicuously close to the corresponding value in the isotypic Au_2O_3 (201 pm)[6]. The differences in the bond lengths within the AgO_4 group are qualitatively in agreement with those in Au_2O_3. However, the *trans*-effect discussed in the case of Au_2O_3 is not noticeable in Ag_2O_3.

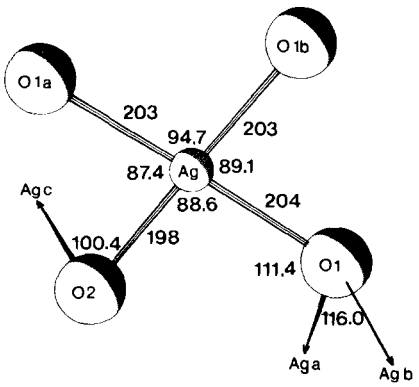


Fig. 1. Projection of the AgO_4 moiety on the best plane defined by oxygen with bond lengths [pm] and angles [°]. Symmetry-equivalent atoms are indicated in small Roman letters. The Ag–O1–Agb angle is 108.7°. The shortest Ag–Ag distance is 304 pm. Maximum standard deviations: 3 pm (bond lengths) and 0.8° (bond angles).

The existence of Ag_2O_3 strikingly contrasts with the previously mentioned lack of ternary oxides containing higher valency silver and emphatically underscores our opinion that in principle no obstacles, for instance in the chemical nature of silver, stand in the way of formation of such oxides.

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CAS Registry number:
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Nonacarbonylbis(μ_3-fluoromethylidyne)triiron: Formation of a Biscarbyne Cluster from Carbonyliron and Tribromofluoromethane

By *Dieter Lentz**, *Irene Brüdgam*, and *Hans Hartl*

Bismethylidyne complexes, in particular those of cobalt and of rhodium, have been the subject of intensive investigations in recent years[1], not least because of their importance in acetylene cleavage, acetylene metathesis, and the Fischer-Tropsch process. $[(\mu_3\text{-CF})\{Co(CO)_3\}_3]$, its derivatives[2], and the hetero-clusters obtainable therefrom by metal exchange[3], were hitherto the only fluoromethylidyne complexes known. According to the 18-electron rule or the Wade rules[4] a further CF ligand can be incorporated in the analogous Fe-cluster, which should lead to a trigonal-bipyramidal iron-carbon cluster. In contrast to numerous compounds containing the $Co_3(CR)_2$ system $[Fe_3(CO)_9(\mu_3\text{-}CCH_3)(\mu_3\text{-}COCH_3)]$ was the only known compound containing an $Fe_3(CR)_2$ moiety[5].

Reaction of $Fe(CO)_5$ or $Fe_2(CO)_9$ with $CFBr_3$ leads to formation of **1** (yield 2–3%) as the major component of the reaction products that are soluble in hexane.

$$Fe_2(CO)_9 \text{ or } Fe(CO)_5 \xrightarrow[60-80\,^\circ C]{CFBr_3/n\text{-heptane}} [Fe_3(CO)_9(\mu_3\text{-}CF)_2]\ \mathbf{1}$$

The trace amounts of byproducts soluble in hexane can be readily separated by preparative thin-layer chromatography (silica gel, Merck 0.5 mm, hexane). According to its spectroscopic data[6] **1** is a bis(fluoromethylidyne) complex. The presence of the isomeric difluoroacetylene complex could be ruled out, in particular by the extreme downfield shift of the ^{13}C-NMR resonance of the carbyne carbon atom ($\delta = 365.8$, $^1J_{CF} = 452$ Hz). The very large ^{19}F-^{13}C coupling constant is indicative of a strong s-part in the CF bond. The resonance of the CF-group lies at $\delta = 69.5$ in a region unusual for CF-compounds and clearly demonstrates the influence of the metal array on the CF-bond.

According to the X-ray structure analysis[7] the two CF-ligands and the three iron atoms form a trigonal bipyramid with the CF-ligands in the axial positions (Fig. 1). Three of the carbonyl ligands are in the Fe_3-plane. The remaining

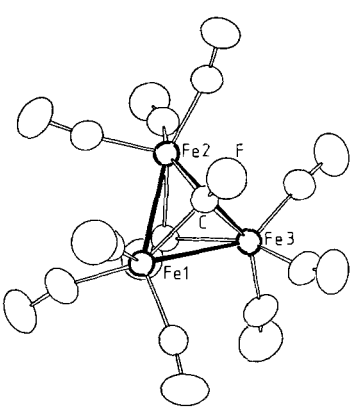


Fig. 1. Molecular structure of **1**. Important bond lengths [pm] and angles [°]: Fe–Fe 253.6–254.4(2). Fe–CF 189.4–194.9(4), C–F 135.4(4), Fe–C (in the Fe_3 plane) 178–179(2), Fe–C (above and below the Fe_3 plane) 182.5–187.9(4), Fe···C 295–301(2), C–O 104–116(2); Fe–CF–Fe 82.6–84.0(2), C–Fe–C 93.0–99.7(3), Fe–C–O 165.0–174.0(10).

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CO-ligands are located in pairs above and below the Fe_3-plane, which forms a mirror plane of the molecule. The symmetry of the molecule is approximately 3/m (C_{3h}). The nine CO-ligands are terminal; carbonyl bridges do not occur. Each iron atom is coordinated by a distorted square-pyramidal array of three CO- and two CF-ligands. Further CO-ligands, which, because of their large Fe···C distances can no longer be regarded as bound, extend these arrays to distorted octahedra (Fig. 1). The three $Fe(CO)_4(CF)_2$ octahedra are coupled via common faces (inverse $Cs_{11}O_3$-structure[8]) to give the trinuclear cluster **1** with a common CF–CF edge.

The Fe-cluster occupies two different point positions, each of population parameter 1/2 and linked via a mirror plane (Fig. 2). The CO/CF molecular framework in both arrangements is almost identical; only the positions of the three carbonyl C-atoms in the Fe_3-plane are so different (distance between C-atom pairs: 52–64(2) pm) that they can be refined as split atom sites. The two arrangements are interconvertable by a slight cooperative shift of the Fe atoms within the octahedron. A disorder of the Fe-triangle by rotation, as was predicted for $Fe_3(CO)_{12}$ on the basis of solid-state ^{13}C-NMR spectra[9] would also appear possible in this case. However, the small anisotropy of the temperature factors of the Fe atoms and the Mössbauer spectrum[10] make a dynamic disorder below 300 K improbable in this case. Whether the observed disorder is a random disorder or concerns domain twins is still unclear. $[Fe_3(CO)_9As_2]$[11] and $[Fe_3(CO)_{12}]$[12] have analogous structural features in the solid state: the Fe_3-triangles are arranged statistically in two different positions without changing the ligand sphere.

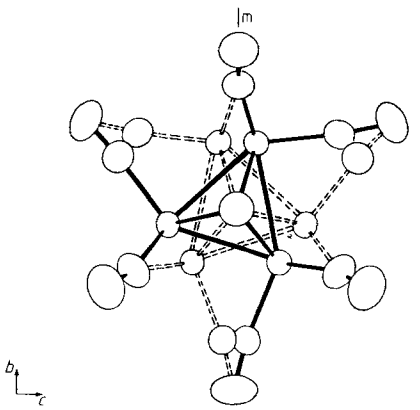


Fig. 2. Disordered structure of **1**; projection on plane bc. The two partial structures (dashed and full lines) are interconvertible through the mirror plane in $z = 1/4$.

In the ^{13}C-NMR spectrum[6], the carbonyl carbon atoms give rise to only one triplet, thus indicating that they are equivalent on the NMR time scale. This is consistent with a non-rigid structure in solution. Also according to IR data[6] there are no carbonyl bridges present in solution. Because of the sparing solubility of the compound it was impossible to carry out low-temperature ^{13}C-NMR measurements for the elucidation of the exchange process.

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[6] **1**: Orange crystals, m.p. 143–144°C, soluble in organic solvents, sublimes at 60°C/10^{-2} mbar: MS (mass numbers referred to ^{56}Fe): *m/z* 482 ($M^{\oplus}$), 454 ($M^{\oplus}-CO$), 426 ($M^{\oplus}-2CO$), 398 ($M^{\oplus}-3CO$), 370 ($M^{\oplus}-4CO$), 342 ($M^{\oplus}-5CO$), 314 ($M^{\oplus}-6CO$), 286 ($M^{\oplus}-7CO$), 258 ($M^{\oplus}-8CO$), 230 ($M^{\oplus}-9CO$) and further smaller fragments; IR (KBr): 2057 (vs), 2009 (vs), 1989 (vs) (CO), 1166 (m), 1125 (m), 713 (s), 596 (m), 554 (s), 507 (w), 451 (w), 428 (w), 404 (w), 383 (vw) cm^{-1}; IR (*n*-hexane): 2061 (vs), 2041 (vs), 2004 (s) (CO) cm^{-1}; Raman (solid): 98 (vs), 115 (vs), 192 (w), 242 (s), 252 (vs), 419 (s), 427 (m), 507 (w), 1975 (w), 1988 (m), 2029 (s), 2038 (s), 2048 (w), 2102 (s) cm^{-1}; ^{19}F-NMR (CH_2Cl_2, $CFCl_3$ ext.): $\delta = 69.5$; ^{13}C-NMR ($CDCl_3$, TMS ext.): $\delta = 206.3$ (CO, $^3J(CF) = 5$ Hz), 365.8 (CF, $^1J(CF) = 452$ Hz).
[7] **1**: Cmcm, $a = 1101.7(3)$, $b = 1313.2(4)$, $c = 1068.1(4)$ pm, $Z = 4$; $\rho_{calc} = 2.07$ g cm^{-3}; $R = 0.031$ ($Mo_{K\alpha} = 71.06$ pm, 945 reflections, 798 with $I > 2\sigma(I)$, absorption correction ($\mu = 29.0$ cm^{-1}), anisotropic temperature factors, 171 refined parameters). Further details of the crystal structure investigation are available on request from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2, on quoting the depository number CSD 51169, the names of the authors, and full citation of the journal.
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Synthesis and structure of $[Pt_2(\mu\text{-}H)(\mu\text{-}CHCH_2Ph)(diphos)_2][BF_4]$**

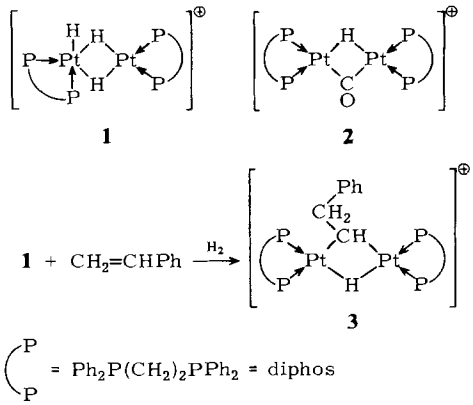
By *Giovanni Minghetti**, *Alberto Albinati*, *Anna Laura Bandini*, and *Guido Banditelli*

Several binuclear platinum hydrides $[Pt_2H_3(L{-}L)_2]$, where L–L is a chelating bisphosphane, have previously been described[1]. Complex **1** was shown by X-ray analysis to contain one terminal and two bridging hydride ligands: the $Pt(\mu\text{-}H)_2Pt$ fragment was found by neutron diffraction to be markedly unsymmetrical[2]. The hydrides $[Pt_2H_3(L{-}L)_2]^{\oplus}$ react with two-electron ligands such as CO or CNR to give diplatinum(I) derivatives: in **2**, both the hydrogen atom and the carbonyl group are in bridging positions[3].

Here we report the reaction of complex **1** with styrene in the presence of hydrogen to give the binuclear species **3**, which, to our knowledge[4], is the first compound containing one hydride and one alkylidene ligand bridging two platinum atoms:

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1 **2**

3

P = $Ph_2P(CH_2)_2PPh_2$ = diphos

Complex **3** (pale yellow crystals) is stable in the solid state and in $CHCl_3$ solution. **3** has been characterized by NMR spectroscopy (^1H, ^{13}C, ^{31}P, ^{195}Pt)[5] and X-ray structure determination.

The chemical shift of the bridging C atom is in the range expected for a μ-alkylidene (or μ-carbene) group[6]: the C atom of bridging alkylidyne (or μ-carbyne) groups is reported to absorb at much lower field[4, 7]. The NMR spectra are in agreement with the existence of a binuclear species where each bisphosphane ligand (diphos) is chelated to a Pt atom and the two (diphos)Pt fragments are linked by a hydride and an alkylidene group.

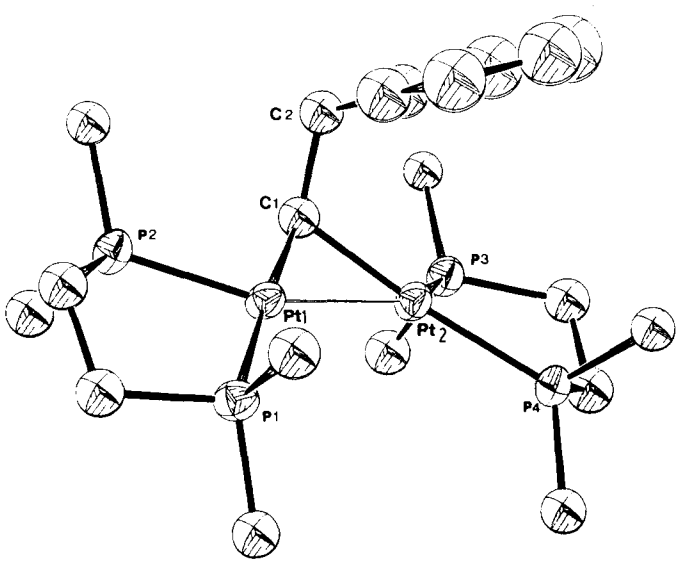


Fig. 1. ORTEP view of the structure of cation **3** in the crystal of $\{Pt_2(\mu\text{-}H)(\mu\text{-}CHCH_2Ph)(diphos)_2\}[BF_4]$. Bridging hydride not located; only one C atom of each *P*-phenyl group is shown. Selected bond lengths [Å] and angles [°]: Pt1–Pt2 2.735(1), Pt1–C1 2.02(2), Pt2–C1 2.07(2), Pt1–P1 2.316(4), Pt1–P2 2.277(4), Pt2–P3 2.217(4), Pt2–P4 2.286(4), C1–C2 1.52(2); Pt1–C1–Pt2 84.1(6), P1–Pt1–C1 172.8(2), P4–Pt2–C1 176.5(2), P1–Pt1–P2 84.5(1), P3–Pt2–P4 87.2(1).

Figure 1 shows the structure of **3** in the crystal[8]. The coordination of each platinum atom can be described as distorted square-planar, with the two coordination planes defined by Pt and P atoms making an angle of 23.9°. The Pt1–Pt2 distance (2.735(1) Å) is comparable with that found in other binuclear complexes having two bridging groups[9] (e.g. complex **1**: 2.728(1)[1]; complex **2**: 2.716(1) Å[3]) and is consistent with a bonding metal-metal interaction.

The μ-alkylidene ligand is symmetrically bonded to the two metal centers (average Pt–C 2.04(3) Å); the angle Pt1–C1–Pt2 (84.1(6)°) is almost equal to that found in complex **2** (84.6(2)°[3]). The bridging hydride ligand could not be located with certainty; however, its presence was inferred from the ^1H-NMR spectrum. It is noteworthy that the Pt–P distances *trans* to the hydride bridge (2.277(4) and 2.217(6) Å for Pt1–P2 and Pt2–P3, respectively) are significantly different. Thus, it is likely that the position of the H atom is unsymmetrical even in this case.

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[5] a) Experimental: A solution of **1** (600 mg, 0.47 mmol) in CH_2Cl_2 (25 mL) was allowed to react with styrene (3 mL) at room temperature under H_2 (1 atm) for two days. Addition of diethyl ether gave the crude product; recrystallization from CH_2Cl_2/Et_2O gave 510 mg **3** (yield 78%), dec. > 195 °C. Correct elemental analysis (C, H, F, Pt). Crystals suitable for X-ray diffraction were obtained by slow evaporation from CH_2Cl_2/Et_2O. **3** can also be obtained under nitrogen. — b) NMR data: ^1H: hydride region: $\delta = -0.35$, triplets ($^2J(Pt_{trans}\text{-}H) = 76$ Hz) of triplets ($^2J(P_{cis}\text{-}H) = 7.8$ Hz) with two sets of satellites (ca. 1 : 8 : 18 : 8 : 1), ($^1J(Pt\text{–}H) = 578$ Hz). $^{31}P\{^1H\}$: two sets of resonances at $\delta = 48.2$ ($^1J(Pt\text{–}P) = 4350$ Hz; $^3J(Pt\text{–}P) = 173$ Hz) and 39.8 ($^1J(Pt\text{–}P) = 2082$ Hz) (standard: ext. H_3PO_4). $^{13}C\{^1H\}$: μ-CH resonance at $\delta = 124.5$ ($^1J(Pt\text{–}C) = 518$; $^2J(P\text{–}C) = 133$ Hz). $^{195}Pt\{^1H\}$: $\delta = -5580$ ppm (standard: ext. Na_2PtCl_6).

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[8] **3**, space group C_c, $Z = 4$; $a = 13.960(1)$, $b = 22.010(2)$, $c = 17.870(3)$ Å; $\beta = 85.19(1)°$, $V = 5471.4$ Å^3. Data collected at room temperature, automated CAD4 diffractometer, $Mo_{K\alpha}$ radiation ($2\vartheta \leq 50.0°$). 3100 independent absorption corrected reflections ($F_0 \geq 3\sigma(F_0)$). Atomic positions obtained by Patterson and Fourier methods, refined by block diagonal least squares (anisotropic temperature factors for Pt, P, B; isotropic for the other atoms) to $R = 0.041$.

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Cationic 2-Azaallenylidene Complexes, Novel Compounds with Unusual Photochemical Properties**

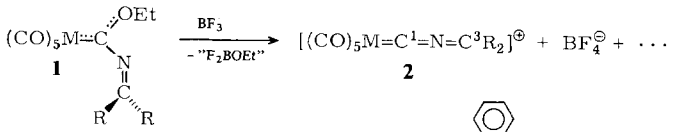
By *Helmut Fischer**, *Friedrich Seitz*, *Jürgen Riede*, and *Jürgen Vogel*

Complexes in which the ligand-metal fragment is a component of a cumulated π-electron system have recently attracted increasing interest[1], since the properties of metal-carbon double bonds change considerably on incorporation in a cumulated multiple-bond system. This is readily

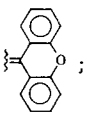
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demonstrated by comparing carbene complexes[2] with vinylidene and allenylidene complexes[1]. We report here on novel complexes which formally derive from allenylidene complexes by replacement of the central C-atom by $N^{\oplus}$.



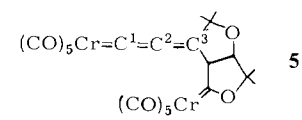
1 → $\xrightarrow[-\text{"}F_2BOEt\text{"}]{BF_3}$ $[(CO)_5M{=}C^1{=}N{=}C^3R_2]^{\oplus}$ + $BF_4^{\ominus}$ + ... **2**

a, M = Cr, CR_2 = CPh_2; **b**, M = Cr, CR_2 =  ; **c**, M = W, CR_2 = CPh_2

The pentacarbonyl[diorganomethyleneamino(ethoxy)-carbene] complexes **1a**—**1c**[3,4] already react with BF_3 in dichloromethane/pentane between −100 and −60 °C with cleavage of the ethoxy group[5] to give deep-blue diamagnetic cations **2a**—**c** which can be isolated as $BF_4^{\ominus}$ salts ([**2a**—**2c**]BF_4); these salts are insoluble in pentane but readily soluble in CH_2Cl_2. The IR spectra of the cations **2a**—**2c** each show—in addition to the three bands expected to appear in the ν(CO)-region for pentacarbonylmetal fragments—an absorption (between 1880 and 1926 cm^{-1}) which can be assigned to the asymmetric stretching vibration of the 2-azaallenylidene ligand[6]. The ^{13}C-NMR spectrum[6] of **2a** shows a signal at $\delta = 200.4$ for the metal-bonded C-atom and a signal at $\delta = 166.5$ for the other cumulene C-atom. These values are comparable with those of the corresponding signals in the allenylidene complex **3** [$\delta(C^1) = 226.6$, $\delta(C^3) = 155.6$, [D$_8$]tetrahydrofuran (THF)][7] and in the isocyanide complex **4** [$\delta(C^1) = 200.0$, [D$_8$]THF][8]. In complete contrast, the signal of the carbyne carbon atom of the cationic complex $[(CO)_5Cr{\equiv}C{-}NPh_2]SbCl_6$ appears at $\delta = 273.7$[9]. The change in the central metal atom on going from **2a** to **2c** leads to a diamagnetic shift of the signal for the metal-bound C-atom (**2c**: $\delta(C^1) = 182.3$), while the resonance of the terminal cumulene C-atom remains virtually unchanged ($\delta(C^3) = 166.1$).

$[(CO)_5Cr{=}C^1{=}C^2{=}C^3(Ph)NMe_2]$ **3** $[(CO)_5Cr{=}C^1{=}N{-}C^3{\equiv}N]$ **4**

An X-ray structure analysis was carried out on **2b** (Fig. 1)[10]. The Cr—C^6 distance (189.9(6) pm) is almost the same as that found in the corresponding allenylidene complex **5** (191.3(7) pm)[11] and in the isocyanide complex **4** (Cr—C^1 188.3(3) pm)[8]. The Cr—C (carbyne) bond in $[(CO)_5Cr{\equiv}C{-}NEt_2]BF_4$, on the other hand is considerably shorter (179.7(9) pm)[12]. The two NC distances in **2b** (C6—N 118.2(8) and N—C61 134.5(8) pm) show a large deviation in length (C^1—N in **4**: 116.7(5) pm). Different bond lengths in the cumulene ligand are, however, also a structural feature of allenylidene complexes (e.g. in **5**: C^1—C^2 126(1), C^2—C^3 135.9(9) pm). The same holds for the small but significant deviation of the cumulene system from a linear arrangement (**2a**: C6—N—C61 170.9(6); **5**: C^1—C^2—C^3 174.3(7)°). The formation of two orthogonal π-systems is only slightly affected by the observed puckering. **2a**—**2c** are therefore best described in terms of the resonance structure **A** with participation of structure **B** (isocyanide complex with a carbenium center in the α-position to the isocyanide group). For resonance structure **C** a reversed sequence of the C—N distances would be expected.



5

$[(CO)_5M{=}C{=}\overset{\oplus}{N}{=}CR_2]$ ⟷ $[(CO)_5\overset{\ominus}{M}{-}C{\equiv}\overset{\oplus}{N}{-}\overset{\oplus}{C}R_2]$ ⟷ $[(CO)_5\overset{\oplus}{M}{\equiv}C{-}\ddot{N}{=}CR_2$

A **B** **C**

In their UV/VIS spectra **2a**—**2c** each show four absorption bands, two of which, respectively, strongly overlap. The two lower energy bands ($S_1 \leftarrow S_0$, $S_2 \leftarrow S_0$) can, according to an HMO calculation carried out on **2b**, be assigned to CT-transitions from metal d-orbitals into the LUMO of the complex mainly localized in the ligand. In the case of the higher energy transitions ($S_3 \leftarrow S_0$...) there are more possibilities to be taken into consideration (M→π^*(CO)-, intraligand-, d-d-transitions).

The photochemical behavior of **2a** and **2b** is unusual. On irradiation in the long-wavelength group of bands[13] the ligands fragment with cleavage of CR_2; the dimer $R_2C{=}CR_2$ can be isolated in ca. 30% yield. The second fragmentation product $[(CO)_5M{-}CN]^{\oplus}$ is unstable under the reaction conditions and reacts to give compounds which no longer absorb in the ν(CO)-region. No indications of a rupture of the M—C^1 bond could be found. On the other hand, if irradiation is carried out only with light of wavelength 300 nm $< \lambda <$ 500 nm (region of the two short-wave absorptions) no photoreaction can be observed under otherwise the same conditions, even on prolonged irradiation. Surprisingly, no relaxation from the higher excited states to the first excited state takes place. On irradiation in the short-wavelength group of bands, however, fluorescence occurs (maximum emission: **2a**: $\lambda = 480$ nm, **2b**: 425 nm, **2c**: 460 nm). The singlet character of the excited states follows from the high extinction coefficients in the absorption spectrum, which do not get smaller on going from the tungsten to the chromium complex (**2c**→**2a**: decreasing spin-orbit coupling), and from the short fluorescence lifetime of **2b** (11 ns). However, because of the low fluorescence quantum yields ($< 10^{-3}$) it can be assumed that triplet states participate in the relaxation of the

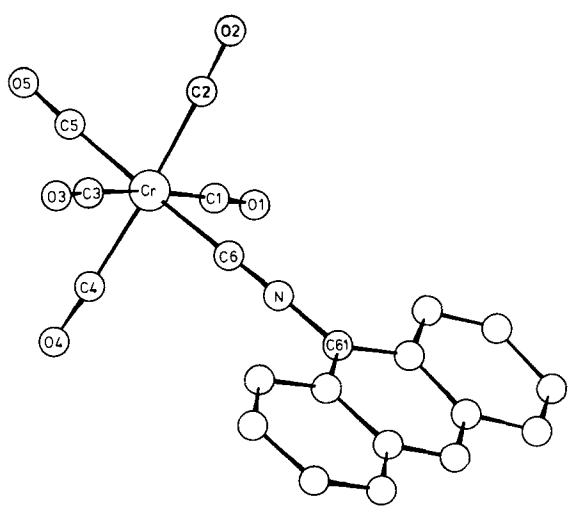


Fig. 1. Structure of the cation **2b** in the crystal. Important bond lengths [pm] and angles [°]: Cr—C6 189.9(6), C6—N 118.2(8), N—C61 134.5(8), Cr—CO(*cis*) 191.2 (mean), Cr—CO(*trans*) 191.8(7); Cr—C6—N 179.0(6), C6—N—C61 170.9(6).

higher excited states. The complexes **2a**—**2c** thus belong to the few compounds in which fluorescence from higher excited states is observed[14].

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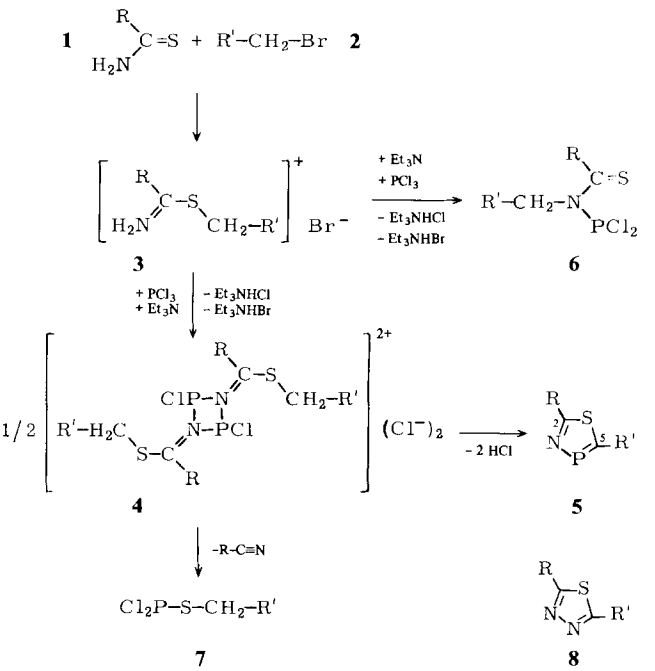
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[6] IR (CH_2Cl_2, −10°C, [cm^{-1}]): **2a**: ν(CO) = 2103 (s), 2031 (s), 2008 (s), ν(C=N=C) = 1888 (m); **2b**: ν(CO) = 2107 (m), 2005 (sh), 1994 (s), ν(C=N=C) = 1926 (vs); **2c**: ν(CO) = 2117 (s), 2024 (s), 1999 (s), ν(C=N=C) = 1880 (m). - ^{13}C-NMR (CD_2Cl_2 (solvent and standard), −30°C): **2a**: δ = 211.8 (*trans*-CO), 209.5 (*cis*-CO), 200.4 (C^1), 166.5 (C^3); **2c**: δ = 191.7 (*trans*-CO), 189.1 (*cis*-CO), 182.3 (C^1), 166.1 (C^3).—UV/VIS (CH_2Cl_2, −30°C [nm], lgε each ca. 3.9): **2a**: λ = 695, 630, 418, 395; **2b**: λ = 676, 605, 377, 355; **2c**: λ = 625, 580, 418, 395.
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[10] [**2b**]BF_4: monoclinic, space group $P2_1/c$, a = 15.811(4), b = 12.657(4), c = 12.966(3) Å, β = 111.98(2)°, V = 2406 Å^3, ρ_{calc} = 1.57 g cm^{-3}, 2364 reflections, R_w = 0.048 (measurement at −50°C, Syntex $P2_1$, $Mo_{K\alpha}$). Further details of the crystal structure investigation are available on request from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2, on quoting the depository number CSD 51135, the names of the authors, and the full citation of the journal.
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1,3,4-Thiazaphospholes**

By *Alfred Schmidpeter**, *Konstantin Karaghiosoff*, *Cornelia Cleve*, and *Dietmar Schomburg*

During the past 15 years a series of heterophospholes have been synthesized which substantiate that twofold coordinated phosphorus(III) can form a five-membered ring arene equally as well as the classical heterocyclic members nitrogen and sulfur. However, only in exceptional cases can the synthesis of the phospha systems follow the routes leading to analogous aza systems. Thus, the customary synthetic route to 1,3,4-thiadiazoles such as **8a**[1] cannot be extended to that of 1,3,4-thiazaphospholes **5**, if only because of the lack of precursors. Their synthesis can, however, be accomplished by incorporating phosphorus as last member into the ring by condensation. Compounds **5** represent the first examples of a system containing S, N, and P as members of one and the same ring (all in twofold coordination), thus enabling an intramolecular comparison.

The synthesis of the 1,3,4-thiazaphospholes starts from thiocarboxamides or *N,N*-disubstituted thioureas (examples investigated: **1**, R = Ph, NMe_2), whose NCS chain is extended in the first step at the sulfur by alkylation with a benzyl bromide or ethyl bromoacetate **2**. Condensation of the resulting salt **3** with PCl_3 then closes the chain to give the ring **5**.



Scheme 1. **5a**—**f** and **8a**: R, R′, yield [%]: **a**: Ph, Ph, 20; **b**: Ph, C_6H_4Me-4, 55; **c**: Ph, $C_6H_4NO_2$-4, 65; **d**: Ph, CO_2Et, 98; **e**: NMe_2, Ph, 62; **f**: NMe_2, C_6H_4CN-4, 71.

The triethylamine used in the condensation reaction should not be added prematurely. Otherwise, migration of the alkyl moiety from S to N takes place, leading to formation of the *N*-(dichlorophosphino)thioamides **6**. If, on the other hand, it is added in the presence of PCl_3 the thiazaphospholes **5** are formed (in various yields) (Table 1)[2]. In those cases where the yields are low it is found that the alkylthio-chlorophosphanes $PCl_{3-n}(S-CH_2-R')_n$, n = 1 (**7**), 2, 3, are formed as products of a secondary reaction. To explain their formation, we assume that the condensation starts at the amide group, initially leading to the (here not detectable) 1,3,2,4-diazadiphosphetidines **4**[3]. If there is sufficient CH_2-activation (R′ = CO_2Et) this intermediate reacts exclusively in a second condensation step with formation of **5**. Failing this, the 1,3-shift of the alkylthio group from carbon to phosphorus competes, resulting in elimination of nitrile. If R′ = H, only this reaction is ob-

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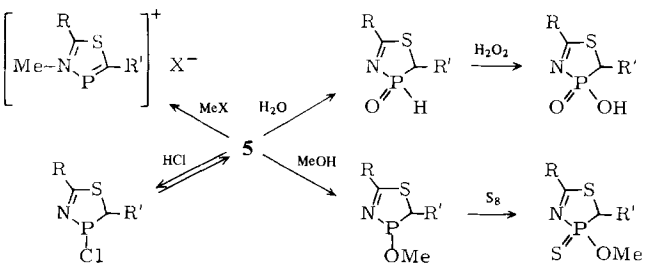
[**] Four- and Five-Membered Phosphorus Heterocycles, Part 65. Presented in part at the International Conference on Phosphorus Chemistry, September 1983, Nice; cf. *Phosphorus Sulfur 18* (1983) 456. This work was supported by the Fonds der Chemischen Industrie.—Part 64: A. Schmidpeter, A. Willhalm, *Angew. Chem. 96* (1984) 901; *Angew. Chem. Int. Ed. Engl. 23* (1984) 903.

served; that is, heterocycles **5** with R′ = H are not accessible in this way.

Table 1. Data of the 1,3,4-thiazaphospholes **5**.

	Color	M.p. [°C]	δ^{31}P	δ^{13}C($^{1,2}J$(PC) [Hz]) C-2	C-5
5a	colorless	85–87	250.0	176.6 (19.6)	182.1 (74.0)
5b	yellow	75–76	256.9	176.5 (19.4)	182.7 (74.0)
5c	red	210–212	270.0		
5d	pale yellow	43–45	300.0	181.6 (21.2)	167.7 (75.8)
5e	yellow	54–56	248.7	175.0 (18.8)	170.2 (64.1)
5f	yellow	103–104	262.2	176.2 (19.1)	167.1 (65.2)

Thiazaphospholes **5**, like other azaphospholes, are stable towards oxidation, but sensitive to hydrolysis. They absorb at longer wavelengths than the correspondingly substituted thiadiazoles **8**[4] do. Since synthetic routes to non-aromatic P^{III}- and P^{V}-compounds containing a 1,3,4-thiazaphosphole skeleton are also still missing, reactions which enable conversion of **5** into such compounds are of preparative importance.



With reference to the introductory remark, the question arises as to what kind of structural changes accompany the homologous replacement of N by P in a five-membered arene. Compounds **5a** and **8a**, whose structure has already been determined by X-ray crystallography[5], offered themselves for comparison.

The X-ray structure analysis of **5a**[6] shows that it crystallizes isomorphically with **8a**, thus indicating very similar molecular structures (Fig. 1). In **8a** the molecular axis through the S atom is coincident with a crystallographic C_2 axis. Despite its lack of symmetry, the thiazaphosphole molecule **5a** also lies along this axis. The crystallographic symmetry arises through a statistical disorder, in the sense of a rotation of the molecule about this axis, i.e. an interchange of P and N. By cautious refinement it is possible to separate the two disordered atoms P and N (distance 38.5 pm), but their bonding parameters are subjected to large standard deviations (Fig. 1). Nevertheless, it becomes evident that all bonds of the planar (maximal deviation from the plane 3 pm) five-membered ring have an increased bond order. Since the NC bond is longer and the CS bond shorter than in **8a** (Fig. 1), resonance seems to equalize bonds in the thiazaphospholes **5** even better so than in the thiadiazole **8**. However, the poor quality of the comparison material makes a check on a further pair of examples necessary.

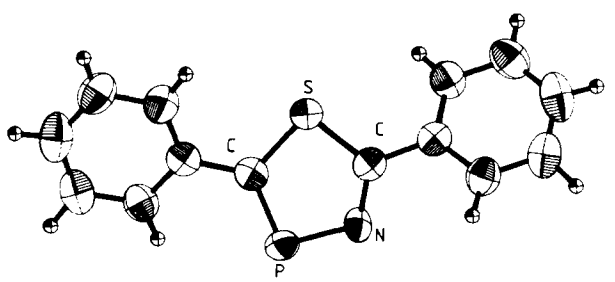


Fig. 1. Structure of **5a** in the crystal. Comparison with **8a** [4] (bond lengths [pm] and angles [°]):

Lattice parameters	**5a**	**8a**	Bond lengths	**5a**	**8a**	Bond angles	**5a**	**8a**
	C2/c	C2/c	PC	166.9(10)		CPN	98.0(14)	
a	2773.9(3)	2784	PN/NN	168.4(15)	119.0	PNC/NNC	115.7(18)	110.5
b	622.5(1)	577	NC	132.4(25)	126.1	PCS	114.3(5)	
c	732.1(1)	737	$\overline{CS}$	172.8(6)	176.9	NCS	117.4(12)	112.8
β	104.8(1)	107.1	$\overline{CC}$(Ph)	147.9(7)	151.3	CSC	94.3(4)	89.8
Z	4	4						

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revised: November 14, 1984 [Z 993 IE]
German version: *Angew. Chem.* 97 (1985) 125

[1] L. L. Bambas in A. Weissberger: *The Chemistry of Heterocyclic Compounds, Vol. 4*, Interscience, New York 1952, p. 88.

[2] A solution of **3** (5 g) and an equimolar amount of PCl_3 in acetonitrile (100 mL) was stirred vigorously at 0°C. To it was added dropwise a fourfold molar amount of triethylamine within 0.5 h. During addition of the last quarter of the triethylamine the solution turned yellow to orange-yellow. The triethylammonium halide precipitate was filtered off, washed with a little acetonitrile, and the filtrate evaporated to dryness. The residue was digested with 100 mL ether and the etheral solution filtered. After removal of the ether there remained analytically pure **5**. **5c** was insoluble in acetonitrile; it was separated together with the triethylammonium halides, from which it was extracted with a large volume of benzene.

[3] O. J. Scherer, *Nachr. Chem. Tech. Lab. 28* (1980) 392.

[4] For example, 2-dimethylamino-5-phenyl-1,3,4-thiadiazole is colorless: E. Hoggarth, *J. Chem. Soc. 1949*, 1163.

[5] Z. V. Zvonkova, A. V. Khvatkina, *Kristallografija (Moscow) 10* (1965) 734, no standard deviations given.

[6] $\rho_{calc} = 1.387$ g cm^{-3}, 1074 independent reflections, 869 observed ($I \geq 2.0\sigma(I)$), $R = 0.063$. Syntex $P2_1$ four-circle diffractometer, $\lambda = 154.178$ pm ($Cu_{K\alpha}$), $2\theta_{max} = 135°$. Empirical absorption corrections, refinement of the H-atoms: isotropic, free. Further details of the crystal structure investigation are available on request from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2, on quoting the depository number CSD 51 138, the names of the authors, and the full citation of the journal.

1,2,3,5-Diazadiphospholes — The First 1,3-Diphospha-1,3-diene System**

By *Alfred Schmidpeter**, *Christian Leyh*, and *Konstantin Karaghiosoff*

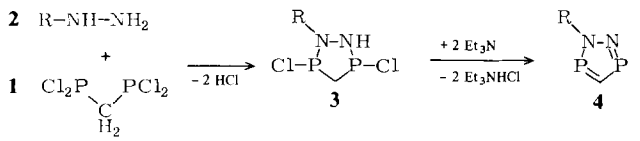
The incorporation of phosphorus(III) in a 6π system favors the twofold rather than threefold coordination of phosphorus and enables the preparation of stable cyclic phosphaalkenes −P=CH− and iminophosphanes −P=N−[1], whereas comparably substituted acyclic compounds are unstable. Is this stabilization also adequate

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[**] Four and Five-Membered Phosphorus Heterocycles, Part 66. This work was supported by the Fonds der Chemischen Industrie.—Part 65: A. Schmidpeter, K. Karaghiosoff, C. Cleve, D. Schomburg, *Angew. Chem. 97* (1985) 125; *Angew. Chem. Int. Ed. Engl. 24* (1985) 123.

enough to hold two phosphorus atoms in one ring with twofold coordination and thus, in particular, to permit the isolation of a cyclic 1,3-diphospha-1,3-diene system? Attempts to synthesize an acyclic 1,3-diphospha-1,3-diene have so far failed[3,4].

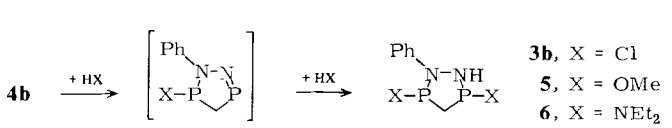
The condensation of bis(dichlorophosphino)methane **1**[5] with primary hydrazines **2** seemed a simple and direct route to a five-membered ring with conjugated phosphaethene and iminophosphane unit $-P{=}CH-P{=}N-$. Indeed, **1** reacts with phenylhydrazine (in excess or with pyridine as auxiliary base) to give the isolable but unstable 1,2,3,5-diazaphospholane **3b**. With triethylamine as auxiliary base, the reaction proceeds further with loss of more HCl to give the desired 1-phenyl-1,2,3,5-diazadiphosphole **4b**[6], which can be purified by distillation. However, due to the formation of insoluble byproducts, its yield is low[7].



a, R = Me; **b**, R = Ph

4b is a colorless liquid. On heating, it remains unchanged up to 80 °C, and then solidifies within a few seconds; correspondingly, an insoluble and unmeltable precipitate separates at 80 °C from a solution of **4b** in toluene. While azaphospholes typically are insensitive towards oxidation[8], **4b** is extraordinarily sensitive towards O_2: when oxygen is admitted, **4b** gets warm, becomes orange-colored and turns within 2 h into a viscous, then gelatinous, and finally hard brown insoluble mass, which does not melt up to 300 °C. According to a chemical analysis the product is formed by the take-up of two (or three) atoms of oxygen per molecule of **4b**. α-Diones such as diacetyl or 1,2-naphthoquinone do not react with **4b** even at 50 °C. **4b** cannot be methylated with MeI or with $[Me_3O]BF_4$.

The conjugative stabilization of the twofold coordination of the two phosphorus atoms in **4b** is apparent in that additions always take place at both double bonds, i.e. that the adduct of the first step no longer stabilized by resonance adds more readily than the starting compound. Thus, **4b** takes up HCl in the molar ratio 1 : 2 with reformation of **3b**; if less HCl is offered, a part of **4b** remains unchanged. In the same way, with methanol and diethylamine the diazaphospholanes **5** and **6**, respectively, are formed (Table 1). In each case only one (on the basis of the ^{1}H-NMR (CH_2)-splitting pattern most likely the *trans*) isomer is observed.



Corresponding to the preparation of **4b**, reaction of **1** with methylhydrazine afforded (via **3a**) the 1-methyl-1,2,3,5-diazadiphosphole **4a**, but it could not be purified by distillation. The reactions of **1** with **2**, R = 4-$NO_2C_6H_4$ or Ph_2PO, remained unsuccessful. Noteworthy in the NMR spectra of **4** (Table 1) are the downfield shifts of the phosphorus resonance, characteristic for 1,2-azaphospholes, and the unusual downfield position of the 4-H signal.

Table 1. NMR data of **4**, **3**, **5**, and **6**; if not otherwise stated, in $CDCl_3$ (J [Hz]).

		4a	4b	3a	3b	5	6
δ^{31}P	P-3	265.1[a,b]	265.8[a,b]	103.3[d]	108.9[e]	118.1	72.0
	P-5	279.5[a,c]	274.6[a,c]	111.4[d]	113.6[e]	124.8	78.9
J(PCP)		22.7	24.7	38.3	25.5	10.6	12.0
δ^{13}C	C-4	162.2	162.2	55.3	55.9	45.0	35.0
J((P-3)C)		77.7[b]	78.3[b]	43.3	43.6	28.6	18.6
J((P-5)C)		52.7[c]	53.2[c]	39.7	40.1	23.9	15.4
δ^{13}C	CH_3	29.6		38.2			54.2, 54.3
J(PN,OC)				16.5			11.7, 15.1
δ^1H	4-H	9.10	9.23		2.89, 3.75	[f]	2.08, 2.41
J((P-3)CH)		30.1[b]	29.3[b]				
J((P-5)CH)		43.6[c]	45.1[c]				
δ^1H	2-H				5.74	4.76	4.19
J(PNH)					47.5	39.4	38.2
δ^1H	CH_3	4.3					3.26, 3.29
J(PN,OCH)		8.4					12.9, 13.5

[a] Broad. [b, c] Assignment on the basis of the corresponding and equally scaled J(PCH) values in 1*H*- and 2*H*-1,2,3-diazaphospholes [8]; the remaining assignments are not confirmed. [d] In benzene. [e] In acetonitrile. [f] Superposed.

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CAS Registry numbers:
1, 28240-68-8; **2a**, 60-34-4; **2b**, 100-63-0; **3a**, 94570-36-2; **3b**, 94570-37-3; **4a**, 94570-38-4; **4b**, 94570-39-5; **5**, 94570-40-8; **6**, 94570-41-9; HCl, 7647-01-0; Et_3N, 121-44-8; MeOH, 67-56-1; Et_2NH, 109-89-7.

[1] Cf. J. H. Weinmaier, J. Luber, A. Schmidpeter, S. Pohl, *Angew. Chem. 91* (1979) 442; *Angew. Chem. Int. Ed. Engl. 18* (1979) 412.

[2] With the CF_3-persubstituted 1,4-diphosphinine and 1,2,5-thiadiphosphole, two special examples have already been described: Y. Kobayashi, S. Fujino, I. Kumadaki, *J. Am. Chem. Soc. 103* (1981) 2465.

[3] R. Appel, V. Barth, F. Knoch, *Chem. Ber. 116* (1983) 938.

[4] In contrast to the conjugated 1,3-diphospha-1,3-diene, a cumulated 1,3-phosphoalkene has recently been described: M. Yoshifuji, K. Toyota, N. Inamoto, *J. Chem. Soc. Chem. Commun. 1984*, 689; H. H. Karsch, H.-U. Reisacher, G. Müller, *Angew. Chem. 96* (1984) 619; *Angew. Chem. Int. Ed. Engl. 23* (1984) 618; H. H. Karsch, F. H. Köhler, H.-U. Reisacher, *Tetrahedron Lett. 25* (1984) 3687; R. Appel, P. Fölling, B. Josten, M. Siray, V. Winkhaus, F. Knoch, *Angew. Chem. 96* (1984) 620; *Angew. Chem. Int. Ed. Engl. 23* (1984) 619.

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[6] In comparison, the reaction of **1** with $NaN(SiMe_3)_2$(A. A. Prishchenko, A. A. Borisenko, N. E. Nifantev, Z. S. Novikova, I. F. Lutsenko, *Zh. Obshch. Khim. 51* (1981) 482) does not lead to formation of a corresponding acyclic diphosphadiene $(Me_3Si)_2N-P{=}CH-P{=}NSiMe_3$, even though it would, as a phosphavinylogue of $(Me_3Si)_2N-P{=}NSiMe_3$ (E. Niecke, O. J. Scherer, *Nachr. Chem. Tech. 23* (1975) 395) appear especially favorable.

[7] A solution of PhN_2H_3 (3.09 mL, 31.4 mmol) and Et_3N (17.5 mL, 125.5 mmol) in ether (30 mL) was added dropwise at 0 °C to a stirred solution of $CH_2(PCl_2)_2$ [5] (5.00 mL, 31.4 mmol) in anhydrous ether (120 mL). After 20 min at room temperature the colorless precipitate was separated and washed with ether. The residue left after evaporating the filtrate distilled at 50–60 °C (bath temperature)/10^{-4} torr and yielded 732 mg **4b** (13%).

[8] J. H. Weinmaier, G. Brunnhuber, A. Schmidpeter, *Chem. Ber. 113* (1980) 2278.

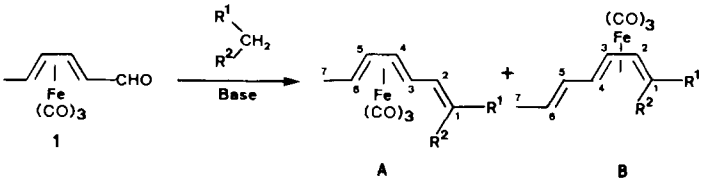
Reactions of Tricarbonyl(sorbaldehyde)iron with Carbanions: A Repeatable Organometallic Reaction with $Fe(CO)_3$-Migration**

By *Andreas Hafner, Wolfgang von Philipsborn,* and *Albrecht Salzer**

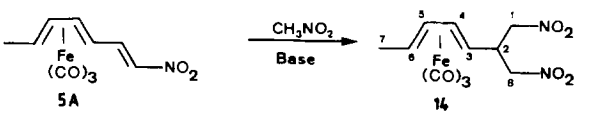
Dedicated to Professor Karl Schlögl on the occasion of his 60th birthday

Unsaturated aldehydes of the crotonaldehyde or sorbaldehyde type are only of limited suitability for the synthesis of linear polyenes by aldol condensation[1]. Since the terminal methyl group exhibits the same reactivity as the α-methylene group of unsaturated aldehydes, self-condensation to give polymeric products always occurs as main reaction. Moreover, some C–H acidic methylene groups undergo extensive Michael addition at the double bonds without any noticeable Knoevenagel condensation taking place[2]. We have now found that in the case of sorbaldehyde these side reactions can be completely suppressed by coordination to an $Fe(CO)_3$ group and that a large number of functionalized polyolefins are accessible in good yields as $Fe(CO)_3$-complexes. The complexation of the olefinic π-system and its extremely weaker conjugation with the reactive functional group can be recognized, inter alia, by way of the $^{13}C,^{13}C$-coupling constants. [Sorbaldehyde-$Fe(CO)_3$] **1** and [1,3-pentadiene-$Fe(CO)_3$] exhibit very similar sets of $^1J_{CC}$ values that are typical for compensated bond orders in an η^4-1,3-diene system ($J_{CC}=44.5+1.5$ Hz)[4]. The same holds for the complexed ketones and esters[5].

Some reactions of the 1,3-diene complex **1** with C–H acidic compounds require only catalytic amounts of base[6a] and afford the corresponding triolefin complexes **2A**–**7A** (Table 1) in yields of between 75 and 95% with complete diastereoselectivity regarding the newly formed double bond. The importance of compounds of the type **4A** in enantioselective syntheses has already been pointed out by *Monpert* et al.[7] and *Franck-Neumann* et al.[8].



Only the reaction of **1** with acetaldehyde proceeds primarily with self-condensation of the aliphatic aldehyde and with little formation of **8**, an indication that the reactivity of the aldehyde carbon in **1** is reduced by the diene-$Fe(CO)_3$ unit. A double addition was observed on carrying out the reaction in pure nitromethane, with the Michael addition of the second nucleophile taking place exclusively at the unprotected double bond of **5A**[9a].



Surprisingly, the reaction with strongly basic nucleophiles follows a somewhat different course. The reaction of **1** with acetone in $KOH/CH_3OH/H_2O$ yields only the expected product **9A**. On using KOH/CH_3OH, only the isomeric **9B** can be isolated[6a]. Also the reactions of $LiCH_2CN$ and $LiCH_2CO_2C_2H_5$ with **1** at −78°C lead, on breaking off the reaction after 15 min, initially to condensation products of the type **A** (as *cis/trans* mixture) together with unreacted **1**. On prolonged reaction, however,

Table 1. ^{13}C-NMR chemical shifts of tricarbonyl(triene)iron complexes of the types **A** and **B** [a] [13].

		C-1	C-2	C-3	C-4	C-5	C-6	C-7	R^1	R^2
2A	$R^1=R^2=CO_2CH_2CH_3$	122.4	151.4	52.2	84.3	88.0	59.2	19.2	14.2*	14.1*
									61.0*	60.9*
									165.1*	164.3*
3A	$R^1=R^2=CN$	79.4	167.7	51.3	82.6	89.8	61.5	18.9	113.4	111.6
4A	$R^1=CO_2CH_2CH_3$, $R^2=CN$	102.8	163.9	53.5	85.5	90.9	62.4	19.6	14.7	115.2 [b]
									62.7	
									162.7 [b]	
5A	$R^1=NO_2$, $R^2=H$	135.1	144.3	49.2	82.7	88.0	59.4	18.6	—	—
6A	$R^1=R^2=COOH$	114.5	163.1	54.5	87.2	90.4	61.5	19.3	170.0*	166.6*
7A	$R^1=R^2=COCH_3$	138.3	149.8	52.3	84.3	88.3	59.9	19.0	31.3*	26.0*
									201.9*	196.2*
8A	$R^1=CHO$, $R^2=H$	129.2	157.8	54.9	82.7	87.7	59.3	19.1	192.8	—
8B	$R^1=CHO$, $R^2=H$	54.2	80.8	85.3	65.9	131.0*	129.9*	18.3	195.7	—
9A	$R^1=COCH_3$, $R^2=H$	127.6	148.0	55.9	82.8	87.2	58.7	19.0	26.8	
									197.1	
9B	$R^1=COCH_3$, $R^2=H$	53.6	80.8	84.5	64.8	129.2	131.6	18.2	29.4	—
									202.6	
10B	$R^1=CN$, $R^2=H$	23.3	80.4	85.3	65.5	130.5*	130.4*	18.3	121.4	—
11B	$R^1=CO_2CH_2CH_3$, $R^2=H$	44.5	81.2	82.8	63.3	130.3*	127.7*	17.1	12.9	—
									59.0	
									170.6	
12A	$R^1=CO_2CH_2CH_3$, $R^2=CH_3$	125.8	142.3	54.4	83.1	86.9	58.0	19.1	12.6	14.3
									60.4	
									167.6	

[a] $\delta(^{13}C)$, from ^1H-decoupled spectra, in $CDCl_3$, **4a** and **6a** in [D_6]acetone. Numbers marked with an asterisk in a particular column can be interchanged. [b] The position of R^1 and R^2 follows from the coupling of the carbonyl and nitrile C-atoms, respectively, with H–C-2. $^3J(CH)=5.5$ and 12.5 Hz, respectively.

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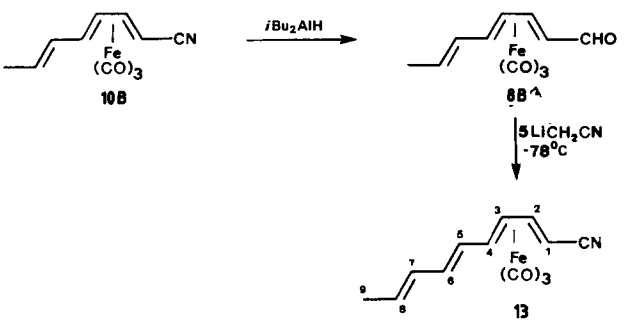
[**] Reactions of Metal-Coordinated Olefins, Part 3.—Part 2: [3].

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no product **A** is isolated, but **10B** and **11B** in 80—90% yield. At least two molar equivalents of nucleophile are required for this reaction[6b]. The formation of **9B** — **11B** with migration of the $Fe(CO)_3$ group at low temperatures (according to quenching experiments partially at −78 °C, completely at room temperature) is apparently base-catalyzed and essentially kinetically controlled. **9A** — **11A** cannot be rearranged to the isomeric complexes in the same base system, so that the migration must take place via an intermediate formed in the reaction. The migration does not take place, however, if the carbanion carries a further substituent R^2. Thus, the reaction of **1** with ethyl propionate leads to **12A** (85%).

Metal shifts of this type were, to our knowledge, previously without example. Thermal 1,3-migrations of an $Fe(CO)_3$ group in acyclic triolefin complexes normally require activation energies of >130 KJ/mol[10]. We found that on prolonged heating of **11B** in boiling toluene, **11A** is partly formed as a *cis/trans* mixture. According to investigations by *Goldsmith* et al.[11], the composition of this product mixture probably corresponds to that of the isomers at thermodynamic equilibrium. Complexes of type **B** are more stable when R^1 is an electron-attracting moiety[10].

Compounds of type **B** can be employed for an unusual repeatable reaction: Thus, **10B** can, after reduction to the aldehyde **8B** (90%)[6a], be subjected to a further condensation/migration sequence leading to the nitrile **13** in 85% yield. The $Fe(CO)_3$ group, which once again experiences a 1,3-shift, here also effects a uniform reaction course.



The free polyolefins are obtainable in approximately 90—95% yield by oxidative decomplexation (1.5 equivalents $Ce(NH_4)_2(NO_3)_6$, acetonitrile, 0 °C, reaction time <1 h). If $FeCl_3$ is used instead of $Ce(NH_4)_2(NO_3)_6$ under the same reaction conditions the yields are 85%[12].

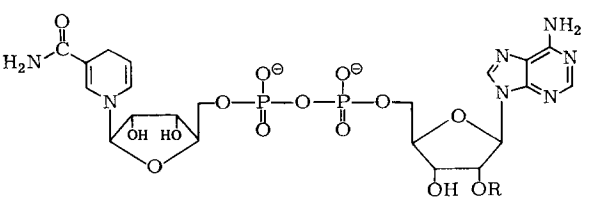
Received: October 2, 1984;
supplemented: November 16, 1984 [Z 1022 IE]
German version: *Angew. Chem. 97* (1985) 136

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[6] a) **2A** — **7A**: 4.5 mmol **1**, 4.9 mmol $CH_2R^1R^2$, catalytic amounts piperidine, room temperature, 35 mL benzene; **8A**: 4.5 mmol **1**, 20 mL CH_3OH, 0.02 g KOH, 20 mmol CH_3CHO; **8B**: 4.0 mmol **10B**, 8.0 mmol iBu_2AlH, $T = -78$ °C, $t = 5$ h; **9A**: 4.5 mmol **1**, 9.5 mmol acetone, 0.02 g KOH in 0.1 mL H_2O; **9B**: 4.5 mmol **1**, 9.5 mmol acetone, 0.02 g KOH in 0.1 mL CH_3OH; **10B**, **11B**, **12A**: 4.5 mmol **1**, 9.0 mmol $LiCHR^1R^2$, $T = -78$ °C, $t = 12$ h, 30 mL tetrahydrofuran (THF); b) Experimental: **10B**: A solution of CH_3CN (10 mmol, 0.95 mL) in absolute THF (20 mL) was cooled to −78 °C, treated with a solution of *n*BuLi in hexane, and the mixture kept at this temperature for 2 h. After slow dropwise addition of a solution of **1** (9 mmol, 2.0 g) in absolute THF (10 mL), the mixture was stirred at −78 °C for a further 5 h and then warmed to room temperature within 7 h. After neutralization with 10% HCl the THF was removed and the residue extracted with $CHCl_3$. After filtration on Alox 90 (Activity III) the product could be recrystallized from hexane/ether or be purified by chromatography (Li-Chroprep-Si 60, 15—25 nm) with CH_2Cl_2. Yield: 2.1 g **10B** (90%). For the preparation of **13** from **8B**, 5 equivalents of $LiCH_2CN$ are necessary. After warming, the solution must be kept at room temperature for 60 h.
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[9] a) **14**: ^{13}C-NMR (25.2 MHz, $CDCl_3$, TMS): $\delta = 18.9$ (C-7), 40.7 (C-2), 54.0 (C-3), 60.2 (C-6), 77.5, 78.0 (C-1,8), 82.0 (C-4), 86.9 (C-5), 210.7 (CO). b) **13**: ^{13}C-NMR (50.4 MHz, $CDCl_3$, TMS): $\delta = 18.3$ (C-9), 23.4 (C-1), 66.0 (C-4), 80.6 (C-2), 85.5 (C-3), 121.4 (CN), 129.5, 131.0, 131.9, 133.9 (C-5,6,7,8), 208.0 (CO).
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[13] The structures of all the products have been confirmed by ^{1}H-NMR and ^{13}C-NMR spectra and by MS and CH-analyses.

Synthesis of 1,4-Dihydropyridine Nucleosides by Photochemical Cycloaddition**

By *Lutz F. Tietze** and *Andreas Bergmann*

1,4-Dihydropyridine nucleotide coenzymes such as NADH **1a** and NADPH **1b** count among some of the biologically most important compounds[1]. Consequently numerous NADH and NADPH analogues have been prepared and examined regarding their physiological and chemical activities. However, the synthetic methods available hitherto are far from being satisfactory in that they are generally unselective, permit only slight variation of the substituents, and the yields are, at best, only moderate[2].



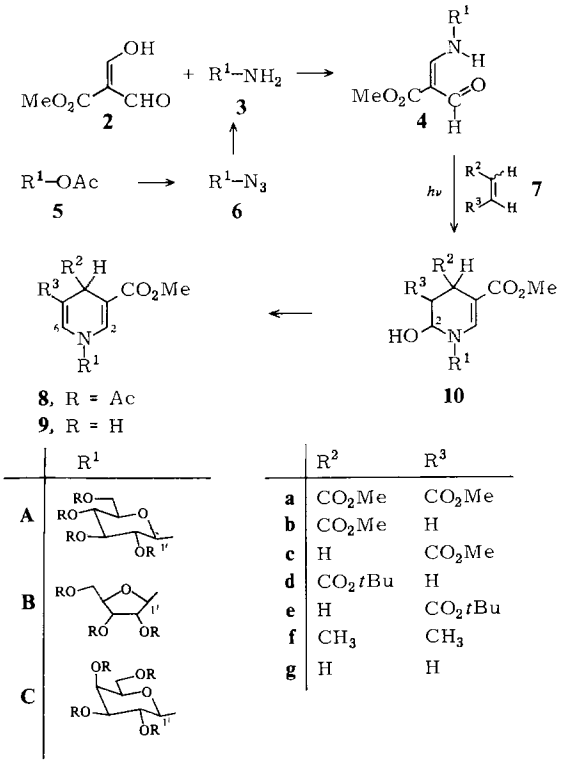
1a, R = H
1b, R = $HPO_3^{\ominus}$

Herein we describe a novel method which leads directly and in almost quantitative yields to 1,4-dihydropyridine nucleosides **8**. The particular advantage of this new method lies in the possibility of widely varying the substituents on the dihydropyridine nucleus and in the simple introduction of labeling at the ring[3]. A mixture of an *N*-glycosyl enaminecarbaldehyde **4** and an alkene **7** (ratio 1 : 100) in dichloromethane or acetonitrile is irradiated at −20 to −40 °C in a ring reactor (Duran) with a 500 W mercury high-pressure lamp[4]. After 1—5 h the 2-hydroxytetrahydropyridines **10** are obtained in almost quantitative

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[**] Dihydropyridines, Part 4. This work was supported by the State Niedersachsen and the Fonds der Chemischen Industrie.—Part 3: [4].

yield and, without isolation, are converted by heating in toluene (1—3 h, 110°C) in the presence of molecular sieves (4 Å) into the 1,4-dihydropyridine nucleosides **8**, also in almost quantitative yield (Table 1). A chromatographic purification of the products, in which decomposition can occur due to the high reactivity of 1,4-dihydropyridines, is seldom necessary. When the prochiral alkenes **7b**—**7f** are employed, diastereomeric mixtures of **8** are obtained (Table 1). On using the unsymmetric alkenes **7b** and **7d**, small amounts of the regioisomeric cycloadducts **8Ac** (7%) and **8Ae** (8%) are isolated in addition to the 1,4-dihydropyridines **8Ab** and **8Ad**.



	R^1
A	
B	
C	

	R^2	R^3
a	CO_2Me	CO_2Me
b	CO_2Me	H
c	H	CO_2Me
d	CO_2tBu	H
e	H	CO_2tBu
f	CH_3	CH_3
g	H	H

Table 1. Photoaddition of enaminecarbaldehydes **4** and alkenes **7**.

Reactants	Products	Yield [%] [a]	Ratio of the diastereomers	^{1}H-NMR (200 MHz, $CDCl_3$, δ-values) 1′-H	6-H
4A + **7a**	**8Aa**	≥95 (79)	—	4.63	7.37 and 7.40 [b]
4A + **7b**	**8Ab**	≥90 (85)	44 : 56	4.51	6.15/6.13
4A + **7d**	**8Ad**	≥90 (81)	38 : 62	4.47/4.46	6.08/6.14
4A + **7f**	**8Af**	≥95 (50)	46 : 54	4.43/4.45	5.75/5.86
4B + **7g**	**8Bg**	≥95 (70)	91 : 9 (β : α)	4.97/5.20	5.93/5.87
4C + **7g**	**8Cg**	≥95 (95)	—	4.33	5.97

[a] Yields determined by NMR and UV spectroscopy; in brackets, yields after chromatography on silica gel (ethyl acetate/petroleum ether = 1 : 2). [b] 2-H and 6-H are diastereotopic.

Cleavage of the acetate protecting groups in **8** under standard conditions according to the method of *Zemplèn*[5] affords the water-soluble 1,4-dihydropyridine nucleosides **9** in good yields[6] (**9Aa**: 87%, ^{1}H-NMR (200 MHz, CD_3OD): δ(1′-H) = 4.57; **9Ab**: 79%, δ = 4.37 and 4.35; **9Cg**: 62%, δ = 4.16).

For the synthesis of the *N*-glycosyl enaminecarbaldehydes **4**, methyl diformylacetate **2**[7] is condensed with the anomeric glycosylamines **3** in ethyl acetate in the presence of sodium sulfate (20°C, 20 h, 90% yield). The anomeric compounds **4** are stable and can be separated by chromatography on silica gel (ethyl acetate/petroleum ether = 1 : 2). The glycosylamines **3** are prepared by reduction of the azides **6**, which are readily accessible from the peracetylated sugars **5** (PtO_2, −5°C, 3 bar H_2, 90% yield)[8].

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Preparation of an *N*-Acetylneuraminic Acid-Containing Trisaccharide and Its Use in Oligosaccharide Syntheses**

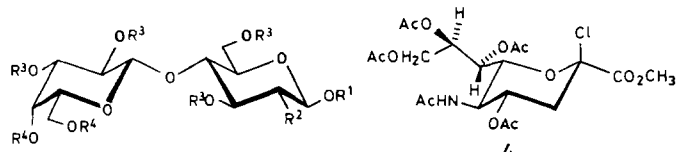
By *Hans Paulsen** and *Holger Tietz*

N-Acetylneuraminic acid is terminally bound to many glycoproteins and glycolipids[2]. The coupling of *N*-acetylneuraminic acid to larger oligosaccharides, however, is difficult. It was therefore of interest to search for an oligosaccharide building block already containing *N*-acetylneuraminic acid and capable of coupling. We have now been able to prepare a trisaccharide building block capable of coupling from *N*-acetylneuraminic acid and lactosamine.

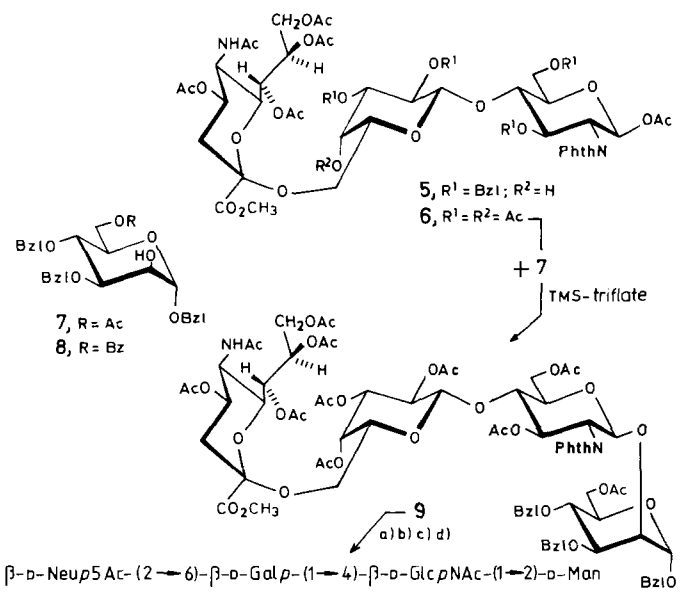
The allylglycoside **1** (Scheme 1), which is capable of functionalization on C-1 and which can be prepared by reaction of the corresponding *O*-acetylated α-1-nitrate[3,4] with sodium allylate[5], was chosen as starting material for the reaction. Benzylidenation and subsequent benzylation of **1** (standard methods) afforded **2** (73%). After reduction of the azido group with H_2S and conversion of the resulting amino group into a phthalimido group[6], the allyl group is removed with $PdCl_2$ and replaced by an acetyl residue (61%). Selective deblocking (80% AcOH, 1 h, 80°C) of the benzylidene group gives the desired glycosyl acceptor **3** (67%), which, under the conditions tested by us, reacts with the chloride of the *N*-acetylneuraminic acid **4**. In the presence of $Hg(CN)_2/HgBr_2$ (CH_2Cl_2), **3** reacts with **4** to give the anomeric mixture of the trisaccharides **5** and

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[**] Oligosaccharide Building Blocks, Part 62.—Part 61: [1].

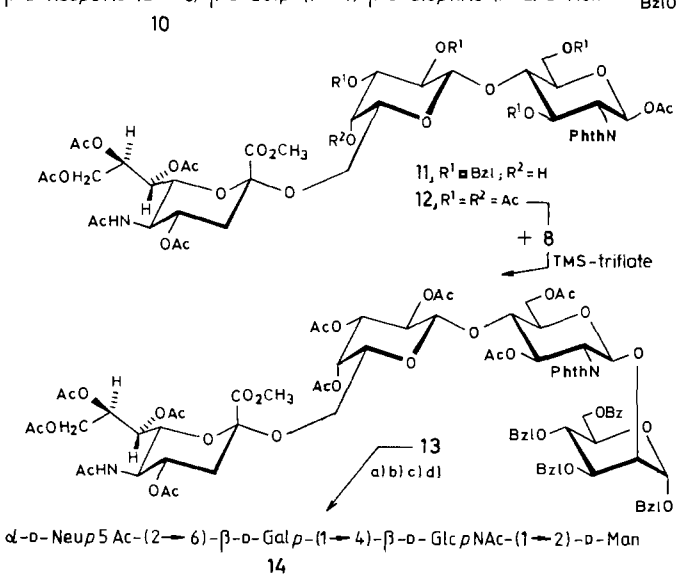
11 in yields of over 60%. Subsequent chromatographic separation furnishes **5** in 37% yield and **11** in 25% yield (assignment by ^{1}H-NMR spectroscopy[6]). Both compounds are capable of coupling and are suitable for a glycoside synthesis.



1, $R^1 = CH_2-CH=CH_2$; $R^2 = N_3$; $R^3 = R^4 = H$
2, $R^1 = CH_2-CH=CH_2$; $R^2 = N_3$; $R^3 = Bzl$; $R^4 = \geq CHPh$
3, $R^1 = Ac$; $R^2 = NPhth$; $R^3 = Bzl$; $R^4 = H$



5, $R^1 = Bzl$; $R^2 = H$
6, $R^1 = R^2 = Ac$
7, R = Ac
8, R = Bz
9
10: β-D-Neu*p*5Ac-(2→6)-β-D-Gal*p*-(1→4)-β-D-Glc*p*NAc-(1→2)-D-Man



11, $R^1 = Bzl$; $R^2 = H$
12, $R^1 = R^2 = Ac$
13
14: α-D-Neu*p*5Ac-(2→6)-β-D-Gal*p*-(1→4)-β-D-Glc*p*NAc-(1→2)-D-Man

Scheme 1. a) CH_3OH, 1N NaOH (50:6, v/v), 3 h, 20°C. b) C_2H_5OH, $NH_2-NH_2 \cdot H_2O$ (15:1), 3.5 h, 80°C. c) CH_3OH, Ac_2O (10:3), 20 h, 20°C. d) CH_3OH, H_2O (1:3), Pd–C, 6 h, 30 bar.—Bzl = benzyl, Phth = phthaloyl, Ac = acetyl, Bz = benzoyl, TMS-triflate = trimethylsilyl trifluoromethanesulfonate.

For stabilization of **5** the benzyl groups are replaced by acetyl groups by hydrogenolysis and acetylation (**5**→**6**, 88%). Despite the complexity of the molecule in the case of **6**, a glycosidation by the trimethylsilyl trifluoromethanesulfonate (triflate) method[5] was possible, with the β-*O*-acetyl group on C-1 functioning as leaving group (neighboring group participation). A prerequisite for this reaction is that the glycosyl donor and glycosyl acceptor do not contain any acid-labile groups. Consequently, the 6-*O*-acetate of mannose **7** is resorted to as glycosyl acceptor since 6-*O*-benzyl derivatives are sensitive towards acids. The tetrasaccharide **9** [$[\alpha]_D^{20} = -18.3$ ($c = 3.6$, $CHCl_3$); 400-MHz ^{1}H-NMR (C_6D_6, TMS): $\delta = 5.46$ (1′-H), 4.91 (1-H), 4.43 (1″-H), 2.58 (3‴-H_e), 1.74 (3‴-H_a)] is obtained in 76% yield on reaction of **6** with **7** in the presence of trimethylsilyl triflate and 4 Å molecular sieve (CH_2Cl_2).

For the deblocking of **9**, the *O*-acetyl groups are cleaved and the methyl ester is hydrolyzed in one step with aqueous 1N NaOH; this leads to partial opening of the phthalimido group. On subsequent treatment with hydrazine the phthalimido group is completely removed; the product is purified on Sephadex LH-20 and *N*-acetylated with acetic anhydride in methanol. Finally, the benzyl groups are cleaved hydrogenolytically in methanol. The overall yield of this four-step conversion from **9** to the deblocked tetrasaccharide **10** is 48% [$[\alpha]_D^{20} = -25.2$ ($c = 0.8$, H_2O); 400-MHz ^{1}H-NMR (D_2O, referred to HDO, $\delta = 4.75$): $\delta = 5.20$ (1-H), 4.61 (1′-H), 4.47 (1″-H), 2.40 (3‴-H_e), 2.06 (2 NAc), 1.65 (3‴-H_a)].

The α-product **11** is likewise converted into the acetate **12** and used as a glycosyl donor under similar conditions. The benzoate **8** is used as glycosyl acceptor since the product then obtained is better to purify. Surprisingly, the acetate **12** is less reactive than **6**; consequently, more trimethylsilyl triflate and longer reaction times are required. The tetrasaccharide **13** is formed in 47% yield [$[\alpha]_D^{20} = -16.3$ ($c = 1.6$, $CHCl_3$); 400-MHz ^{1}H-NMR (C_6D_6, TMS): $\delta = 5.56$ (1′-H), 5.05 (1-H), 4.66 (1″-H), 2.64 (3‴-H_e), 2.00 (3‴-H_a)].

13 can be deblocked in the same was as **9**. The α-glycosidically coupled tetrasaccharide **14** is obtained in 48% yield [$[\alpha]_D^{20} = -21.0$ ($c = 1.0$, H_2O); 400-MHz ^{1}H-NMR (D_2O, HDO): $\delta = 5.20$ (1-H), 4.62 (1′-H), 4.44 (1″-H), 2.67 (3‴-H_e), 2.05, 2.02 (2 NAc), 1.72 (3‴-H_a)]. These values agree with the data of the oligosaccharide obtained via another route[7] and with those of the natural products which contain this sequence[8].

Both examples demonstrate that glycoside coupling with the trisaccharides **6** and **12** is possible and that the trimethylsilyl triflate method can also be used even with this complex molecule. The method has the advantage that the *N*-acetylneuraminic acid-containing building block can be coupled to any saccharide.

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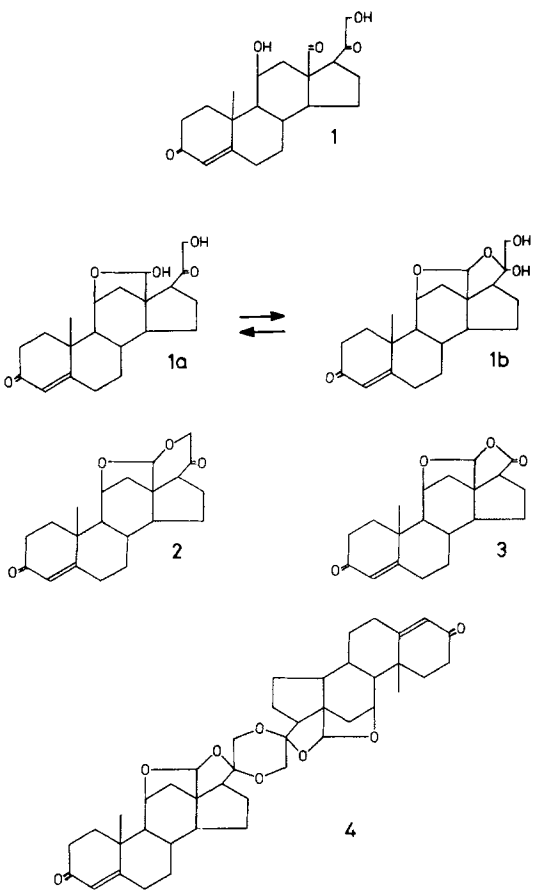
CAS Registry numbers:
1, 94537-63-0; **2**, 94570-56-6; **3**, 94537-64-1; **4**, 67670-69-3; **5**, 94537-65-2; **6**, 94537-66-3; **7**, 94537-67-4; **8**, 94537-68-5; **9**, 94537-69-6; **10**, 94537-70-9; **11**, 94537-71-0; **12**, 94537-72-1; **13**, 94537-73-2; **14**, 94537-74-3.

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"Dimers" of Aldosterone**

By *Klaus Lichtwald** and *Michael Przybylski*

The aldehyde function in position 18 was the determining factor in changing the name electrocrotin to aldosterone **1**[1]. As an adrenocortical steroid, **1** exerts a regulatory influence on the metabolism of electrolytes and water (electrolyte balance). Although a general mechanism has indeed been formulated for steroid activity at the cellular level[2], much further effort is required for the resolution of events at the molecular level. Structural investigations have shown that the pattern of substitution in rings C and D of the steroids is of great importance for the mineralocorticoid activity[3].



Depending on its molecular environment, **1** exists as an isomeric mixture or as a pure tautomer[4]; thus, according to *Kirk* et al., mainly the tautomers analogous to **1a** and **1b** are present in the case of 3α,5β-tetrahydroaldosterone in chloroform[5]. The ^{13}C-NMR spectrum of aldosterone in chloroform shows a signal distribution that is not compatible with formula **1**. Consistent with this finding, a thin-layer chromatographic analysis revealed the presence of a mixture of at least six substances. The R_f values indicated that the starting material **1**, aldosterone acetal **2**, and aldosterone-γ-lactone **3**[6,7] were components of the mixture. Their separation by HPLC and their retention times lent further support to this finding. The eluate of the most intense spot (UV) in the thin-layer chromatogram yielded two components **4a** and **4b** on HPLC separation.

The chromatographic behavior of the substances on silica gel [R_f(**1**) < R_f(**4a,b**) < R_f(**2**)] was exactly the converse of that observed on reversed phase (C-18) HPLC separation [R_t(**1**) < R_t(**2**) < R_t(**4a**) < R_t(**4b**)]. This finding suggested an increase in molecular weight with higher lipophilicity of **4a**, **b** compared to **2**. Consistent with this inference, mass spectroscopic investigations (Fast Atom Bombardment (FAB) and Field Desorption (FD)) revealed protonated molecular ions ($MH^{\oplus}$; *m/z* 685) of high intensity in the case of **4a** (Fig. 1). The molecular weight (MW) of 684 corresponds to an aldosterone dimer minus two molecules of water. This was further supported by the observation that FAB mass spectra were obtained with high sensitivity in a solvent/tetraethylene glycol (TEG) matrix, but not in the highly polar matrix glycerine[8]. The FAB mass spectra of **4b** likewise gave a MW of 684, indicative of an isomer which showed similar fragmentation pattern. The proposed structure of **4** is based on the assumption of an oxygen-bridging of C-20 with C-21. Besides the conceivable coupling of both C-20 positions with each other and both C-21 positions with each other, in each case via an oxygen atom, possible variations at the four chiral centers have also not been taken into consideration. An X-ray structure analysis should provide more information in this respect.

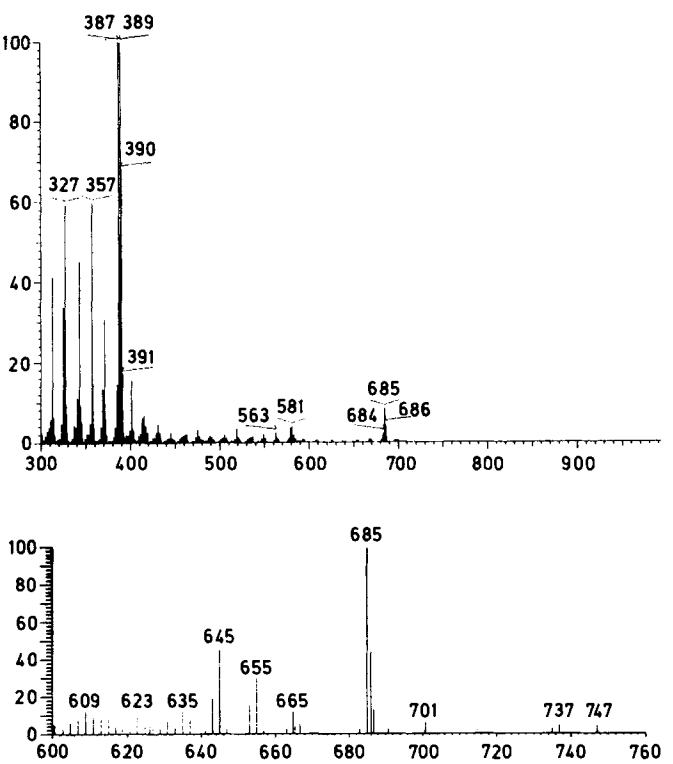


Fig. 1. Mass spectra of the aldosterone derivative **4a** obtained by a) FAB-MS (CH_2Cl_2/TEG matrix) and b) FD-MS (CH_2Cl_2 solution).

It may be assumed that the formation of the "dimers" **4a**, **b** is proton-catalyzed; support for this hypothesis is provided by the additional formation of the substances **2** and **3** which have been reported to be formed under acidic conditions[9]. The existence of such aldosterone derivatives

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might be taken into account on considering molecular events during the reaction of aldosterone—assuming their formation is also possible under physiological conditions. In this respect, the finding that the physiological site of aldosterone action in the kidney is close by the site of proton release could be of importance.

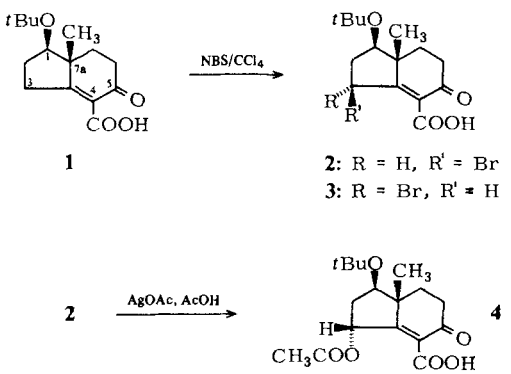
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Stereospecific Synthesis of 3-Substituted Hexahydroindane Derivatives

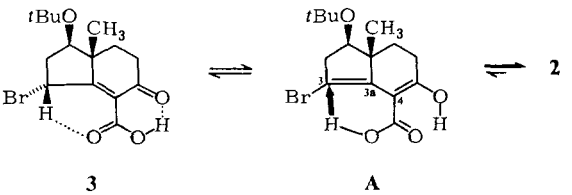
By *Hans-Eckart Radunz** and *Günter Schneider*

The aim of our investigations was to insert an oxygen function stereospecifically into the 3-position of the readily accessible carboxylic acid **1**[1]. Compounds of this type are suitable synthons for rigidified postaglandin analogues. Halogenation of **1** with *N*-bromosuccinimide (NBS) affords the readily crystallizable bromide **2** in 68% yield.



The isomeric bromide **3** can be isolated in amounts less than 10% by rapid chromatography of the mother liquor on silica gel (A60, E. Merck). The relative stereochemistry of the two allyl bromides could be elucidated by ^{1}H-NMR spectroscopy[2]. The observed product pattern was surprising in view of the fact that a high stereoselectivity could not be expected in the NBS bromination, which proceeds via a radical mechanism[3]. In the absence of a radical initiator (e.g. benzoyl peroxide or UV light), no bromination takes place.

It was assumed that **3** is transformed into the bromide **2** via the dienol A (Scheme 1). This assumption is supported by the following findings: (a) in methanol, **3** is slowly transformed into **2**, and (b) an epimeric transformation is not observed with the methyl ester of **3**[4].

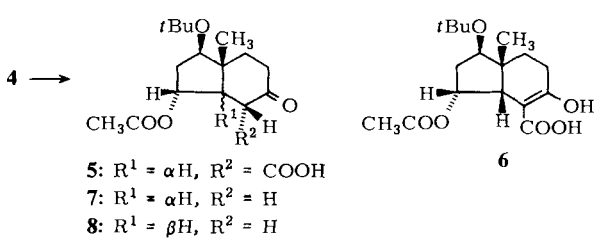


Scheme 1.

The signal of the 7αβ-methyl group of the allyl bromide **2** appears at unusually low field ($\delta = 1.51$)[5]. This marked shielding effect can only be explained in terms of a strong 1,3-interaction between bromine atom and methyl group. This interpretation is supported by the ^{1}H-NMR spectrum of the isomeric allyl bromide **3**, in which the methyl signal once again appears in the "normal" position[1] at $\delta = 1.16$ because of the absence of the shielding effect. However, a shielding of the proton on C^1 is observed.

In the following reaction step, **2** is allowed to react with silver acetate in glacial acetic acid; **4** is obtained in 56% yield. Since this reaction ought to proceed by an S_N2 mechanism a product showing the methyl signal in the "normal" position[1] is to be expected; $\delta = 1.16$ is observed.

Subsequent catalytic hydrogenation of **4** should lead to the *trans*-hexahydroindane framework. *Hajos* and other authors[1,6] reported that the hydrogenation of 5-oxo-5,6,7,7a-tetrahydroindanes, which are substituted at C-4 (cf. **1**), affords *trans*-hexahydroindanones. However, if **4** is hydrogenated in ethyl acetate with Pd–C (5%) at room temperature under normal pressure until 1 mol H_2 (per



mol **4**) has been taken up, four new compounds (**5**–**8**) are formed which are chromatographically separable (silica gel, diisopropyl ether). Their structures were elucidated on the basis of spectral data[7]. That **6**, in contrast to **5**, is present in the enolized form is supported not only by the fine structure of the ^{1}H-NMR signal of C^{3a}–H, but also by the fact that only **6** shows an Fe^{3+}-reaction. It follows from the NMR data that the hydrogenation of **4** does not exclusively afford *trans*-compounds (**5** and **7**) but also *cis*-isomers (**6** and **8**) (*trans/cis* ratio ≈ 4 : 1). The primary products **5** and **6** are readily decarboxylated[8], so that only the compounds **7** and **8** can still be detected after hydrogenation, separation of the catalyst, and heating of the filtrate for 1 hour on a water-bath.

We obtained products with *trans*- and with *cis*-hexahydroindane frameworks on hydrogenation of **4**, whereas *Hajos* and *Parrish*[1] did not observe the formation of prod-

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ucts with *cis*-hexahydroindane framework in the hydrogenation of **1**. This was explained in terms of hydrogenation of the 3,3a-double bond of the intermediary dienol and not of the 3a,4-double bond (see Scheme 1, analogue **A**). If this were true the formation of a dienol would lead to a planarization of the symmetry center at C-3. Thus, on addition of hydrogen the C^3-epimer of **5** should be formed. However, this inversion is not observed.

The acetate **7** obtainable from **1** is a molecule which exhibits the same relative stereochemistry at the centers **3**, **3a**, and **7a** as observed in the naturally occurring prostaglandins.

Experimental

2: A solution of **1** (11.1 g, 4.1 mmol) and NBS (10 g, 5.6 mmol) in CCl_4 (300 mL) was heated to boiling for 2.5 h. After cooling, succinimide was filtered off, the filtrate evaporated down in a vacuum, and the residue taken up in a little ether. 9.7 g of **2** (68%) crystallized out within about 12 h on cooling the filtrate in a refrigerator at ca. 0°C. Colorless crystals, m.p. 154°C; IR: 1750, 1640, 1605 cm^{-1} (CO); ^{1}H-NMR: $\delta = 1.18$ (s, 9H, *t*Bu), 1.52 (s, 3H, 7a-CH_3), 3.58 (dd, 1H, $J_{1,2} = 10.1$, $J_{1,2'} = 7.6$ Hz, C^1–H), 5.87 (dd, 1H, $J_{3,2} = 8.9$, $J_{3,2'} = 7.4$ Hz, C^3–H).

3: The isomeric bromide **3** can also be isolated (in smaller amounts than 10%) from the mother liquor on silica gel with ether. Colorless crystals, m.p. 132°C (ether/petroleum ether; IR: 1745, 1640 cm^{-1} (CO); ^{1}H-NMR: $\delta = 1.16$ (s, 1H, 7a-CH_3), 1.24 (s, 9H, *t*Bu), 4.28 (dd, 1H, $J_{1,2} = 10.0$, $J_{1,2'} = 6.3$ Hz, C^1–H), 6.04 (dd, 1H, $J_{3,2} = 5.0$, $J_{3,2'} = 1.2$ Hz, C^3–H).

4: A solution of **2** (3.4 g, 1 mmol) and silver acetate (2 g, 1.2 mmol) in glacial acetic acid (100 mL) was heated to boiling for 3.5 h. After cooling, silver bromide was filtered off, the solvent removed in a vacuum, and the residue crystallized from ether/petroleum ether (1:1); yield 1.8 g (56%). Colorless crystals, m.p. 131–132°C; IR: 3300–2400 (br.), 1750, 1710, 1690 cm^{-1} (CO); ^{1}H-NMR: $\delta = 1.19$ (s, 9H, *t*Bu), 1.21 (s, 1H, 7a-CH_3), 2.03 (s, 3H, acetate), 3.90 (dd, 1H, $J_{1,2} = 11.5$, $J_{1,2'} = 6.5$ Hz, C^1–H), 6.24 (dd, 1H, $J_{3,2} = 8.5$, $J_{3,2'} = 2$ Hz, C^3–H).

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[1] Z. G. Hajos, D. R. Parrish, *J. Org. Chem. 38* (1973) 3239.

[2] All compounds were characterized by elemental analyses as well as IR and NMR data. All NMR spectra were recorded in $CDCl_3$ on a 200-MHz instrument, all IR spectra in KBr.

[3] L. Horner, E. H. Winkelmann, *Angew. Chem. 71* (1959) 349.

[4] **2** can be esterified with diazomethane in ether. **2**-Me-ester: colorless crystals, m.p. 121°C (ether/petroleum ether), ^{1}H-NMR: $\delta = 1.18$ (s, 9H, *t*Bu), 1.44 (s, 3H, 7a-CH_3), 3.77 (s, 3H, ester), 3.56 (dd, 1H, $J_{1,2} = 10.5$, $J_{1,2'} = 7.5$ Hz, C^1–H), 5.06 (dd, 1H, $J_{3,2} = 9$, $J_{3,2'} = 7$ Hz, C^3–H).

[5] We thank Dr. K. Pachler (Analytisches Zentrallabor, E. Merck Darmstadt) for recording and discussing the ^{1}H-NMR spectra.

[6] Z. G. Hajos, D. R. Parrish, E. P. Olivek, *Tetrahedron 24* (1968) 2039; U. Eder, H. P. Lorenz, DOS 2320285 (7. 11. 1974), Schering AG; T. C. McKenzie, *J. Org. Chem. 39* (1974) 629; R. L. Augustine, D. C. Migliorini, R. E. Foscante, C. S. Sodano, M. J. Sisbarro, *ibid. 34* (1969) 1075.

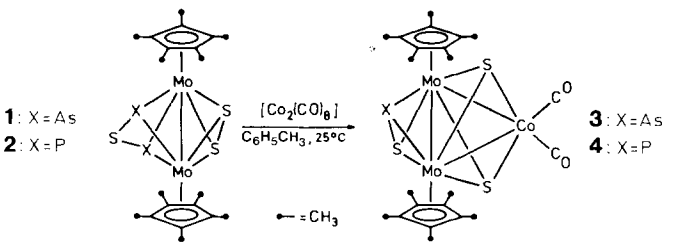
[7] Overall yields for all four compounds: quantitative. The product distribution is variable(CO_2-cleavage!).—**5**: colorless crystals, m.p. 118.5°C (ether), IR: 3300–2500 (br), 1740, 1650, 1603 cm^{-1} (CO); ^{1}H-NMR: $\delta = 1.04$ (s, 3H, 7a-CH_3), 1.14 (s, 9H, *t*Bu), 1.97 (s, 3H, acetate), 3.73 (dd, 1H, $J_{1,2} = 7.9$, $J_{1,2'} = 9.2$ Hz, C^1–H), 5.04 (ddd, 1H, $J_{3,2} = 10.0$, $J_{3,2'} = 4.2$, $J_{3,3a} = 9.6$ Hz, C^3–H), 2.37 (dd, 1H, $J_{3a,3} = 9.6$, $J_{3a,4} = 13.1$ Hz, C^{3a}–H), 3.44 (d, 1H, $J_{4,3a} = 13.1$ Hz, C^4–H).—**6**: colorless crystals, m.p. 104°C (ether/petroleum ether), IR: 3400–2500 (br.), 1730, 1700, 1640, 1595 cm^{-1}; ^{1}H-NMR: $\delta = 0.98$ (s, 3H, 7a-CH_3), 1.17 (s, 9H, *t*Bu), 1.94 (s, 3H, acetate), 2.85 (d, 1H, $J_{3a,3} = 6.8$ Hz, C^{3a}–H), 3.66 (dd, 1H, $J_{1,2} = 6.7$, $J_{1,2'} = 6.7$ Hz, C^1–H), 5.46 (m, 1H, C^3–H).—**7**: colorless crystals, m.p. 94°C (ether/petroleum ether), IR: 1740, 1720 cm^{-1} (CO); ^{1}H-NMR: $\delta = 1.03$ (s, 3H, 7a-CH_3), 1.14 (s, 9H, *t*Bu), 1.9 (m, 1H, C^{3a}–H), 2.02 (s, 3H, acetate), 3.66 (dd, 1H, $J_{1,2} = 7.8$, $J_{1,2'} = 9.2$ Hz, C^1–H), 4.88 (ddd, 1H, $J_{3,2} = 9.8$, $J_{3,2'} = 4.3$, $J_{3,3a} = 9.2$ Hz, C^3–H).—**8**: colorless crystals, m.p. 77°C (ether/petroleum ether), ^{1}H-NMR: $\delta = 1.14$ (s, 3H, 7a-CH_3), 1.16 (s, 9H, *t*Bu), 1.94 (s, 3H, acetate), 2.3 (m, 1H, C^{3a}–H), 3.81 (dd, 1H, $J_{1,2} = 6.2$, $J_{1,2'} = 5.4$ Hz, C^1–H), 5.31 (ddd, 1H, $J_{3,2} = 6.1$, $J_{3,2'} = 3.4$, $J_{3,3a} = 5.7$ Hz, C^3–H).

[8] The methyl esters of **5** and **6** can be prepared by esterification with diazomethane: **5**-Me-ester: colorless crystals, m.p. 119–121°C (petroleum ether), ^{1}H-NMR: $\delta = 1.05$ (s, 3H, 7a-CH_3), 1.14 (s, 9H, *t*Bu), 1.98 (s, 3H, acetate), 3.7 (s, 3H, OMe).—**6**-Me-ester: colorless oil, ^{1}H-NMR: $\delta = 0.97$ (s, 3H, 7a-CH_3), 1.16 (s, 9H, *t*Bu), 1.91 (s, 3H, acetate), 3.74 (s, 3H, OMe). Positions and couplings of the remaining protons as in **5** and **6** [7].

Synthesis of $[(C_5Me_5)_2Mo_2XS_3Co(CO)_2]$ Clusters (X = P, As) and Structural Characterization of a μ_2,η^2-AsS Ligand

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Spectroscopic investigation of the complexes **1** and **2**, which were synthesized from $[C_5Me_5(CO)_2Mo]_2$ and As_4S_4 or P_4S_3, revealed the possible presence of an unusual μ,η^2-XSX-structural unit[1]. Since it has so far proven impossible to confirm the presence of such a unit by single-crystal X-ray structural analyses, we attempted the preparation of clusters via a secondary reaction with $Co_2(CO)_8$ in the hope that their mode of synthesis might throw some light on the structure of **1** and **2**.



However, according to elemental analyses and mass spectra, the diamagnetic clusters **3** and **4**[2] formed on reaction of **1** and **2** respectively with $Co_2(CO)_8$ surprisingly contained one X-atom less than expected. An X-ray structure analysis carried out on **3** showed the presence of

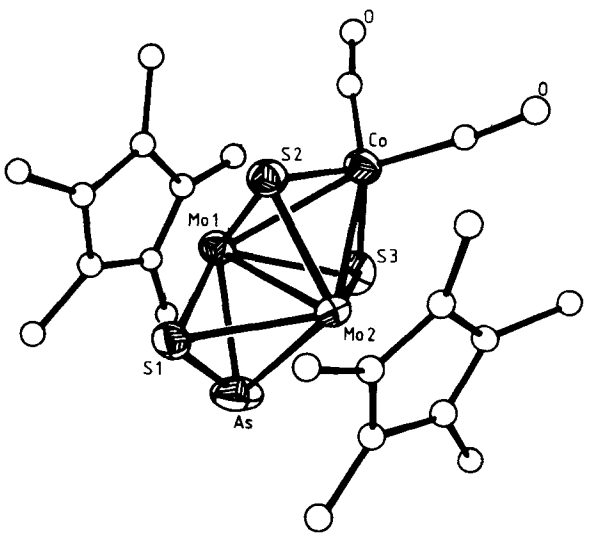


Fig. 1. Molecular structure of **3** in the crystal (ORTEP diagram). Selected bond lengths [Å] and angles [°]: Mo1–Mo2 2.610(1), Mo1–Co 2.722(2), Mo1–As 2.533(2), Mo1–S1 2.517(2), Mo1–S2 2.406(3), Mo1–S3 2.416(4), Mo2–Co 2.725(2), Co–S2 2.178(3), Co–S3 2.165(4), As–S1 2.237(3); Mo2–Mo1–Co 61.4(0), Mo2–Mo1–As 58.7(0), Mo2–Mo1–S1 58.6(1), Mo2–Mo1–S2 57.3(1), Mo1–Co–S2 57.5(1). The As and S1 positions are each 50% statistically occupied by arsenic and sulfur.

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an Mo_2Co-triangle bridged by two μ_3-sulfur ligands and a new structural unit, an η^2-AsS ligand as bridge between two Mo atoms. The AsS-ligand, the two S-bridges and the Co-atom lie in a plane bisecting the molecule. The carbonyl groups are located in the plane of the three-membered ring of metal atoms (Fig. 1). Hence, **3** constitutes the first example of a molecule containing complex-stabilized arsenic monosulfide, which, in the free state, is unstable. With the proviso that there is a 50% statistical distribution of arsenic and sulfur at the As and S1 sites, the As–S1 distance in **3** can be said to be 2.237(3) Å, a value which corresponds to the average length of the As–S single bond in α-As_4S_4[4]. We conclude, therefore, that the new ligand has a bond order of 1 and functions as a 5e-donor. Furthermore, if we consider the μ_3-S atoms as 4e-donors and the remaining ligands as 5e-donors (C_5Me_5-moieties) and 2e-donors (CO groups), then each metal atom acquires noble-gas configuration by formation of M–M single bonds. The experimentally determined metal-metal distances lend support to this conclusion.

Remarkably, the $Co(CO)_2$-fragment is incorporated exclusively in the η^2-S_2-group of **1** and **2**, even though there are several sites open to attack in the ligand sphere of the starting complex. The S_2-bridge over the Mo atoms is thereby enlarged to an SCoS unit, while elimination of X from the XSX-bridge leads to formation of the bridging XS-ligand. This apparent lability of an Mo–X bond is confirmed by the sensitivity of **1** towards oxidation: Only the previously reported arsenic-free complexes $[(C_5Me_5)_2Mo_2O_2S_2]$ and $[(C_5Me_5)_2Mo_2OS_3]$ can be isolated from toluene solutions of **1** in presence of air.

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1, 90790-24-2; **2**, 94570-20-4; **3**, 94570-21-5; **4**, 94570-22-6; $[(C_5Me_5)_2Mo_2OS_3]$, 94570-23-7; $[(C_5Me_5)_2Mo_2O_2S_2]$, 94570-24-8; $[Co_2(CO)_8]$, 10210-68-1.

[1] I. Bernal, H. Brunner, W. Meier, H. Pfisterer, J. Wachter, M. L. Ziegler, *Angew. Chem. 96* (1984) 428; *Angew. Chem. Int. Ed. Engl. 23* (1984) 438.

[2] a) A mixture of 0.60 mmol **1** or **2** and 0.64 mmol $Co_2(CO)_8$ in 50 mL toluene is stirred for 1 h (**1**) or 2.5 h (**2**) at room temperature. Chromatographic purification on SiO_2 with toluene/petroleum ether (1:1) afforded the red-brown complexes **3** and **4** in 60 and 28% yield, respectively. The complexes can be recrystallized from toluene/pentane (5:2).—b) IR (KBr, [cm^{-1}]): **3**: ν(CO) = 1975 (vs), 1927 (s); **4**: ν(CO) = 1982 (vs), 1932 (s). ^{1}H-NMR ($\delta(CH_3)$, $CDCl_3$): **3**: 1.88; **4**: 1.90.

[3] $P2_1/n$, $a = 11.529(7)$, $b = 15.348(9)$, $c = 15.588(5)$ Å, $\beta = 107.28(3)°$, $V = 2633.75$ Å^3, $Z = 4$, Syntex P3 diffractometer ($Mo_{K\alpha}$), $3° \leq 2\vartheta \leq 55°$, 2490 observed reflections with $I \geq 2.5\sigma(I)$, Patterson (Co, Mo, As, S) and Fourier methods, anisotropic refinement to $R_w = 0.04$. Further details of the crystal structure investigation are available on request from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2, on quoting the depository number CSD 51104, the names of the authors, and the full citation of the journal.

[4] D. J. E. Mullen, W. Nowacki, *Z. Kristallogr. Kristallgeom. Kristallphys. Kristallchem. 136* (1972) 48.

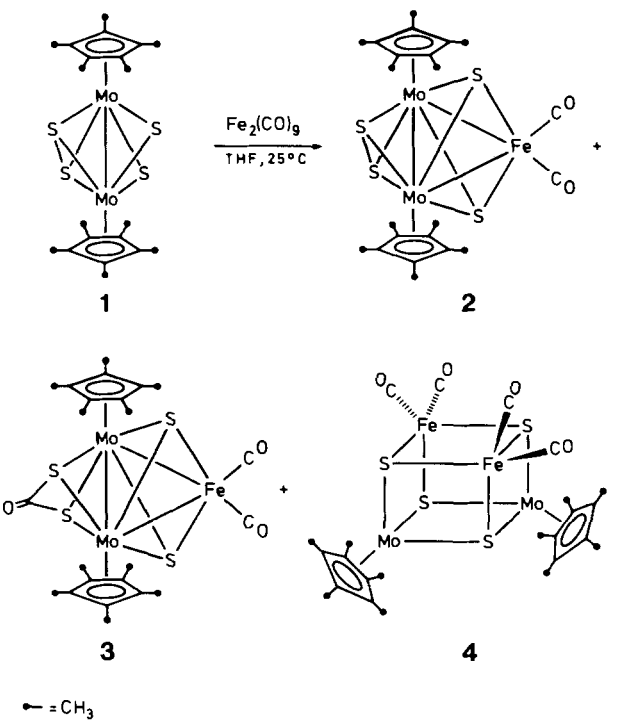
[5] If a solution of **1** in toluene is stirred for 48 h in presence of air, subsequent chromatographic work-up enables isolation of $[(C_5Me_5)_2Mo_2OS_3]$ (green, 46% yield; IR (KBr, [cm^{-1}]): ν(Mo=O) = 900 (vs), ν(Mo=S) = 482 (s); ^{1}H-NMR ($\delta(CH_3)$, $CDCl_3$): 2.03, 1.96) and $[(C_5Me_5)_2Mo_2O_2S_2]$ (orange, 39% yield; IR (KBr, [cm^{-1}]): ν(Mo=O) = 898 (vs), ν(Mo=S) = 451 (w); ^{1}H-NMR ($\delta(CH_3)$, $CDCl_3$): 2.00.

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Novel MoFeS Clusters from $[(C_5Me_5)_2Mo_2S_4]$ and $Fe(CO)_5$ or $Fe_2(CO)_9$

By *Henri Brunner, Norbert Janietz, Joachim Wachter*, Thomas Zahn,* and *Manfred L. Ziegler*

Thio-transition-metal clusters containing various metal atoms serve as model compounds, both in the catalysis of industrially important desulfurization reactions as well as in the deciphering of bioinorganic reactions. Of particular importance is the coupling of Mo and Fe with sulfur to give "heterocubanes", among which, compounds with a $Mo_2Fe_2S_4$ core are still very poorly represented in the literature. The first such cluster to be prepared and spectroscopically characterized was $[(C_5Me_5)_2Mo_2Fe_2(NO)_2S_4]$[1]. But "mixed" trinuclear clusters with a trigonal pyramidal $M_2M'S_2$ core and a μ_2,η^2-di-(main group element) ligand are also still relatively rare[2].



The three new diamagnetic MoFeS clusters **2**–**4** are formed on reaction of the complex **1** with $Fe_2(CO)_9$ in tetrahydrofuran (THF) (molar ratio 1:1.3). **2** and **4** are also formed in the photochemical reaction of **1** with $Fe(CO)_5$ (in the molar ratio 1:2) in THF[3a]. The composition of each product has been confirmed by elemental analysis and mass spectra. The ^{1}H-NMR and IR spectra[3b] are consistent with the results of the X-ray structure analysis.

Characteristic of the structures of **2** and **3**[4] (Figs. 1 and 2) is a trigonal-bipyramidal Mo_2FeS_2 core; the $Mo_2Fe(CO)_2$ moiety is perpendicular to the plane of the sulfur ligands. As 48e-clusters, **2** and **3** each contain three metal-metal single bonds, consistent with the observed

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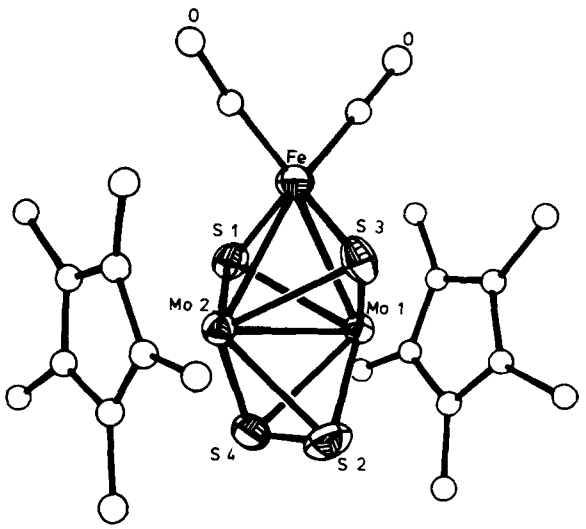


Fig. 1. Molecular structure of **2** (ORTEP diagram). Selected bond lengths [Å] and angles [°]: Mo1–Mo2 2.592(0), Mo1–Fe 2.778(1), Mo1–S1 2.432(1), Mo1–S2 2.437(1), Mo1–S3 2.436(1), Mo1–S4 2.440(1), Mo2–Fe 2.776(1), Fe–S1 2.153(1), S2–S4 2.071(1); Mo2–Mo1–Fe 62.1(0), Fe–Mo1–S1 48.3(0), S1–Mo1–S4 76.5(0), S2–Mo1–S4 50.3(0), S1–Mo1–S3 89.1(0), Mo1–Fe–S1 57.4(0).

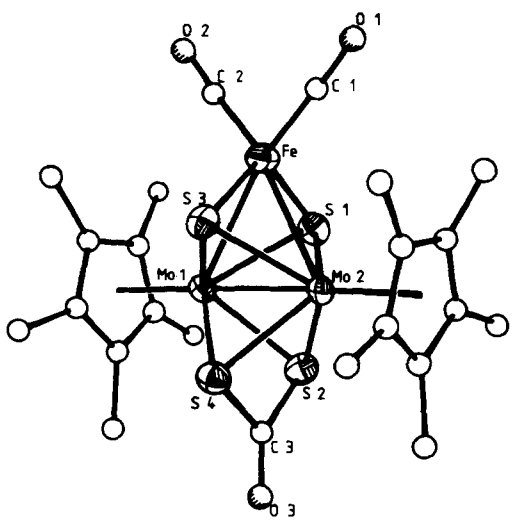


Fig. 2. Molecular structure of **3** (ORTEP diagram). Most important bond lengths [Å] and angles [°]: Mo1–Mo2 2.574(0), Mo1–Fe 2.830(1), Mo1–S1 2.467(1), Mo1–S2 2.470(1), Mo1–S3 2.448(1), Mo1–S4 2.467(1), Mo2–Fe 2.819(1), Fe–S1 2.130(1), S2–C3 1.800(4), S4–C3 1.817(4), C3–O3 1.196(5); Mo2–Mo1–Fe 62.7(0), Mo2–Mo1–S1 58.1(0), S1–Mo1–S2 69.8(0), S1–Mo1–S3 87.1(0), S2–Mo1–S4 68.2(0), Mo1–S4–C3 89.2(1), S2–C3–O3 130.7(3).

M–M distances. Thus, in both cases the relatively short Mo–Mo distance is ascribable to a "bracketing effect" of the bridge ligands. **2** can be regarded as an $Fe(CO)_2$-adduct of **1**[5], whereas **3** unexpectedly contains a dithiocarbonato-ligand as structural element bridging the two Mo atoms.

The X-ray structure analysis of **4**[4] confirms the presence of a $Mo_2Fe_2S_4$-cubane with relatively small differences (up to 0.09 Å) between the Mo–S and Fe–S bond lengths. In **2** and **3**, however, these differences are up to 0.44 Å. There are five metal-metal bonds of equal length (on average 2.803 Å) as opposed to one Fe–Fe distance of 3.334 Å (Fig. 3). A qualitative confirmation of this finding is obtained from the distribution of the 62 valence electrons over the cluster. A similar situation is found in the

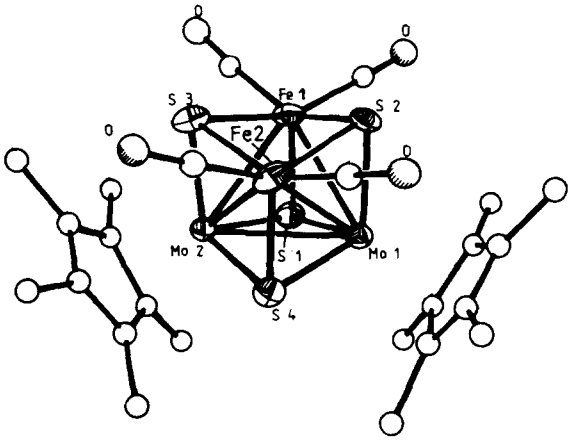


Fig. 3. Molecular structure of **4** (ORTEP diagram). Selected bond lengths [Å] and angles [°]: Mo1–Mo2 2.761(1), Mo1–Fe1 2.832(4), Mo1–Fe2 2.792(3), Mo1–S1 2.357(2), Mo1–S2 2.333(2), Mo1–S4 2.320(2), Mo2–Fe1 2.813(3), Mo2–Fe2 2.815(4), Mo2–S1 2.342(2), Mo2–S3 2.282(2), Mo2–S4 2.303(2), Fe1–S1 2.214(3), Fe1–S2 2.271(5), Fe1–S3 2.330(4), Fe1···Fe2 3.334; Mo2–Mo1–Fe1 60.4(1), Mo2–Mo1–Fe2 60.9(1), Fe1–Mo1–Fe2 72.7(1).

complex **5**, which is isoelectronic with **4** and is accessible from **6** and $Ni(CO)_4$[6]. However, in contrast to **1**, **5** is only able to incorporate $Fe(CO)_5$ or $Fe_2(CO)_9$ in a 66e-cluster **7** with planar metal framework[7]. The 62e-complex **8** obtainable from **1** and $Mo(CO)_6$ in boiling toluene should, on the other hand, be isostructural with **4**.

$[(C_5H_5)_2Mo_2Ni_2(CO)_2S_4]$	$[(MeC_5H_4)_2Mo_2(SH)_2S_2]$
5	**6**
$[(MeC_5H_4)_2Mo_2Fe_2(CO)_6S_4]$	$[(C_5Me_5)_2Mo_4(CO)_6S_4]$
7	**8**
$[(MeC_5H_4)_2V_2S_4]$	$Hg[Fe(NO)(CO)_3]_2$
9	**10**

The clusters **2**–**4** are formed in different ways: **2** and **3** can be synthesized by stepwise substitution of CO in the carbonyliron complexes by the two μ-S bridges in **1**, whereas transformation of the η^2-S_2-ligand into two μ_3-S-bridges requires a redox reaction with participation of the carbonyliron compounds. This reaction behavior essentially conforms with that of the vanadium complex **9**, which gives a similar reaction sequence with the iron complex **10**, resulting in a 58e-cluster with a $V_2Fe_2S_4$ core[2b]. However, the extraordinarily mild carbonyl transfer from $Fe_2(CO)_9$ to the η^2-S_2-ligand warrants further investigation.

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CAS Registry numbers:
1, 82167-40-6; **2**, 94598-08-0; **3**, 94598-09-1; **4**, 94619-63-3; $Fe_2(CO)_9$, 15321-51-4; $Fe(CO)_5$, 13463-40-6; Mo, 7439-98-7; Fe, 7439-89-6.

[1] H. Brunner, H. Kauermann, J. Wachter, *Angew. Chem. 95* (1983) 567; *Angew. Chem. Int. Ed. Engl. 22* (1983) 549.
[2] Examples known to us are a) $[(MeC_5H_4)_2V_2Fe(CO)_3S_4]$ (C. M. Bolinger, T. B. Rauchfuss, S. R. Wilson, *J. Am. Chem. Soc. 104* (1982) 7313); b) $[(MeC_5H_4)_2V_2Fe(NO)_2S_4]$ (T. B. Rauchfuss, T. D. Weatherhill, S. R. Wilson, J. P. Zebrowski, *ibid. 105* (1983) 6508; c) $[(C_5Me_5)_2Mo_2Co(CO)_2AsS_3]$

(H. Brunner, H. Kauermann, U. Klement, J. Wachter, T. Zahn, M. L. Ziegler, *Angew. Chem. 97* (1985) 122; *Angew. Chem. Int. Ed. Engl. 24* (1985) 132.

[3] a) The blue solution of **1** (290 mg, 0.50 mmol) and $Fe_2(CO)_9$ (240 mg, 0.66 mmol) in THF (100 mL) was stirred for 17 h at room temperature. Column chromatographic separation of the greenish-brown mixture (SiO_2, toluene/pentane 2:1) afforded green **4**, then brown **3**, followed by brown **2** (in yields of 33, 11 and 21%, respectively). The photolytic reaction with $Fe(CO)_5$ (THF, 125W Hg-lamp) afforded **4** in 10% yield and **3** in 38% yield. All the compounds can be recrystallized from CH_2Cl_2.—b) IR (KBr, [cm^{-1}]): **2**: ν(CO) = 1918, 1855; **3**: ν(CO) = 1937 (vs), 1883 (s), 1872 (s) (CH_2Cl_2 1943, 1879), $\nu(S_2C{=}O)$ = 1734 (s); **4**: 1995 (s), 1962 (vs), 1934 (s), ^{1}H-NMR ($\delta(CH_3)$, $CDCl_3$): **2**: 1.89; **3**: 1.80; **4**: 1.80.

[4] The structures of **2**—**4** were determined on a Syntex diffractometer ($Mo_{K\alpha}$), $3° \leq 2\vartheta \leq 60°$, Patterson (Mo, Fe, S) and Fourier methods. $P2_1/n$, $a = 11.476(3)$, $b = 15.259(4)$, $c = 15.589(4)$ Å, $\beta = 107.39(2)°$, $V = 2605.05$ Å^3, $Z = 4$. 4854 observed reflections, anisotropic refinement to $R_w = 0.026$. **3**: $P2_1/c$, $a = 11.540(5)$, $b = 15.235(5)$, $c = 15.303(7)$ Å, $\beta = 99.14(4)°$, $V = 2656.29$ Å^3, $Z = 4$. 5877 reflections, anisotropic refinement to $R_w = 0.028$. **4**: Cc, $a = 21.338(5)$, $b = 8.795(2)$, $c = 20.431(4)$ Å, $\beta = 130.75(1)°$, $V = 2904.68$ Å^3, $Z = 4$. 3319 observed reflections, anisotropic refinement to $R_w = 0.025$. Further details of the crystal structure investigation are available on request from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2, on quoting the depository number CSD 51103, the names of the authors, and full citation of the journal.

[5] H. Brunner, W. Meier, J. Wachter, E. Guggolz, T. Zahn, M. L. Ziegler, *Organometallics 1* (1982) 1107.

[6] M. D. Curtis, P. D. Williams, *Inorg. Chem. 22* (1983) 2661.

[7] B. Cowans, J. Noordik, M. Rakowski DuBois, *Organometallics 2* (1983) 931.

[8] IR (KBr, [cm^{-1}]): ν(CO) = 2000, 1975, 1932, 1883, 1870; ^{1}H-NMR ($\delta(CH_3)$, $CDCl_3$): 1.88.

Diamminebis(1,5-cyclooctadiene)(μ-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane-N^7,N^{16})dirhodiumbis(hexafluorophosphate): An Example of Simultaneous First and Second Sphere Coordination**

By *Howard M. Colquhoun, Simon M. Doughty, Alexandra M. Z. Slawin, J. Fraser Stoddart**, and *David J. Williams*

Previously, we have observed several examples[1] of second sphere coordination[2] of transition-metal complexes by crown ethers. Although numerous cases of first sphere coordination of transition metals to macrocyclic polyether ligands containing nitrogen atoms have been described[3], we now report a remarkable example of simultaneous first and second sphere coordination of rhodium by 1,4,10,13-tetraoxa-7,16-diazacyclooctadecane **1**[4].

cyclo-[(O−CH_2CH_2)$_2$NH−CH_2CH_2]$_2$ **1**
[Rh(cod)$(NH_3)_2$][PF_6] **2**
[{Rh(cod)$(NH_3)_2$}$_2$ · **1**][PF_6]$_2$ **3**

The fortuitous discovery[5] of [{Rh(cod)$(NH_3)_2$}$_2$ · **1**][PF_6]$_2$ (cod = 1,5-cyclooctadiene) **3** followed an unsuccessful attempt to isolate a crystalline adduct between [Rh(cod)$(NH_3)_2$][PF_6] **2**[6] and **1**. Elemental analysis[5] indicated the formation of a 2:1 covalent complex with loss of 2 NH_3[7]. X-Ray analysis[8] not only confirmed the constitution of the complex **3** but also revealed several interesting conformational features (Fig. 1). The complex contains a

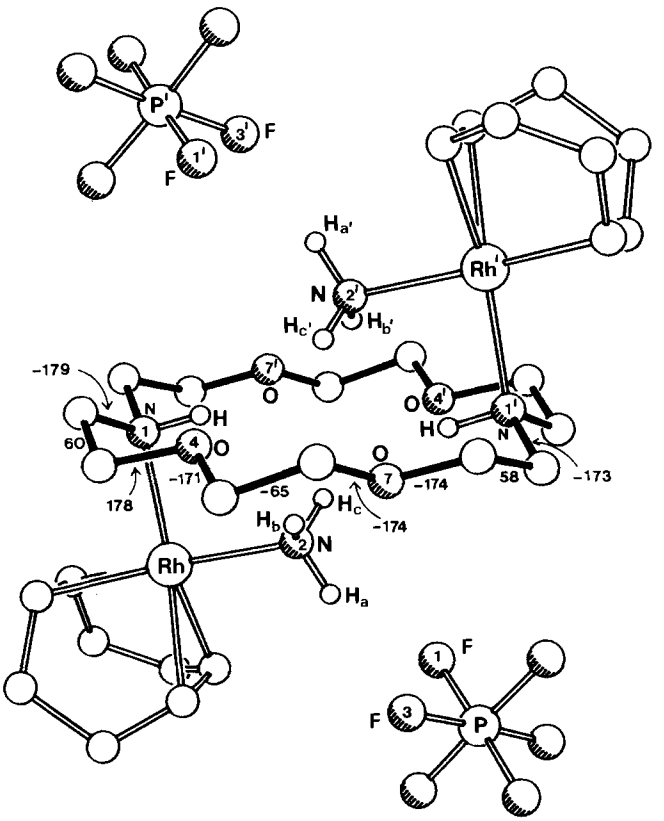


Fig. 1. Structure of **3** in the crystal. **3** is monoclinic, $a = 11.445(3)$, $b = 11.329(3)$, $c = 15.192(5)$ Å, $\beta = 90.45(2)°$, $V = 1970$ Å^3, space group $P2_1/n$, $Z = 2$, $\rho = 1.71$ g cm^{-3}, $\mu Cu_{K\alpha} = 86$ cm^{-1}, 2213 independent reflections with $[|F_o| > 3\sigma(|F_o|), \theta \leq 55°]$, $R = 0.101$. Torsional angles [°] associated with the 18-membered ring are shown beside the relevant bonds. Selected bond lengths [Å]: Rh−N(1) 2.17(1); Rh−N(2) 2.14(1). Selected bond angles [°]: Rh−N(1)−C(2) 117(1); Rh−N(1)−C(9') 116(1); C(2)−N(1)−C(9') 111(1). Intramolecular contact distances from N(2) to O(4), O(4'), O(7), O(7'), F(1), F(3): 3.22, 3.50, 3.45, 3.45, 3.22, 3.13 Å. Distance of N(2) from the mean plane of the ring heteroatoms: 1.92 Å. N(2)···N(2') distance: 3.97 Å. The PF_6^- ions have two orientations of estimated occupancies 0.65 and 0.35. Only the orientation of the major occupancy is illustrated.

crystallographic center of symmetry at the center of the 18-membered ring[9]. Despite the torsional freedom around the N(1)−Rh bonds, the ammine ligands [N(2)] are oriented directly over the faces of the macrocycle. There is also an appreciable flattening of the expected tetrahedral geometry at N(1), which is confined to the Rh−N−C angles (117 and 116°), enabling a closer approach of the ammine ligands to the faces of the macrocycle. However, the resulting N(2)···O distances are still rather long with only N(2)···O(4) (3.22 Å) lying within what would conventionally be considered a hydrogen bonding distance. In this instance, the contact is to an oxygen atom [O(4)] on the opposite face of the macrocycle, i.e., a nesting arrangement[10] analogous to that observed in [$(Ph_3PMe)_2$ · [18]crown-6][PF_6]$_2$[11]. The associated H_b···O(4) distance and N(2)−H_b···O(4) angle are 2.41 Å and 142°, respectively. The other H···O distances are 2.60 Å for H_b···O(7) and 2.59 Å for H_c···O(4'). The associated N(2)···O distances are given in the Figure caption[12].

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To our knowledge, this is the first example[13] of a crown ether containing nitrogen atoms acting as both a first and second sphere ligand towards a transition metal. Clearly, an extensive range of such complexes should exist[14]. This report could herald the preparation of a wide range of novel compounds, including polymers, in which transition-metal complexes and aza-crown ethers are covalently bonded.

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[2] A. Werner, *Neuere Anschauungen auf dem Gebiete der anorganischen Chemie*, 3rd Edition, Vieweg, Braunschweig 1913; J. Bjerrum, *Adv. Chem. Ser. 62* (1967) 178.

[3] For two recent examples, see J.-P. Lecomte, J.-M. Lehn, D. Parker, J. Guilheim, C. Pascard, *J. Chem. Soc. Chem. Commun. 1983*, 296; P. K. Coughlin, S. J. Lippard, *J. Am. Chem. Soc. 106* (1984) 2328.

[4] B. Dietrich, J.-M. Lehn, J.-P. Sauvage, *Tetrahedron 29* (1973) 1647.

[5] Experimental: **3**: 27.3 mg (0.07 mmol) **2** was dissolved in CH_2Cl_2 containing 18.4 mg (0.07 mmol) **1**. Dull yellow prisms, suitable for X-ray investigation were obtained by vapor diffusion using Et_2O (P. G. Jones, *Chem. Br. 17* (1981) 222). After 48 h, the crystals were filtered off and dried. Yield 20 mg (42%); m.p. = 216–219°C; IR (Nujol): 3350, 3330, 3290, 3270, 3230, 3190 (all νNH), 1620, 1610 (both δNH) cm^{-1}; ^{1}H-NMR (CD_3COCD_3): $\delta = 1.87$ (8H, m, $CH_{ax}H_{eq}$-cod), 2.46 (8H, bs, $CH_{ax}H_{eq}$-cod), 2.60–3.10 and 3.63–4.05 (32H, broad multiplets, OCH_2, NCH_2, NH, NH_3), 4.20 (8H, bs, CH-cod).

[6] **2**, m.p. 209–215°C, was prepared from $[Rh(cod)Cl]_2$ (R. B. King, *Organomet. Synth. 1* (1965) 132).

[7] The reaction between **1** and **2** is slow in CD_2Cl_2. ^{1}H-NMR data indicates that a non-covalently bonded adduct is formed initially.

[8] Nicolet R3m diffractometer, ω-scan, $Cu_{K\alpha}$ radiation (graphite monochromator). Empirical absorption correction based on 360 azimuthal measurements. Structure solution by heavy-atom method; anisotropic refinement. The ammine hydrogen atoms were located in a ΔF map and the NH_3 group refined as a rigid body. Four complete analyses using different crystals all resulted in R values of ca. 0.10. In all cases, the relatively high magnitude of these values was a result of disorder both in the PF_6^- ions and in the cyclooctadiene portion of the complex. Further details of the structural investigation can be obtained from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW (England). Any request should be accompanied by the full literature citation for this communication.

[9] The conformation of the macrocycle with alternating (+)- and (−)-*gauche* helicities for the C–C bonds and inward directing N–H bonds is similar to that observed in uncomplexed **1** (M. Herceg, R. Weiss, *Bull. Soc. Chim. 1972*, 549).

[10] D. J. Cram, K. N. Trueblood, *Top. Curr. Chem. 98* (1981) 43; K. N. Trueblood, C. B. Knobler, D. S. Lawrence, R. V. Stevens, *J. Am. Chem. Soc. 104* (1982) 1355.

[11] B. L. Allwood, H. M. Colquhoun, J. Crosby, D. A. Pears, J. F. Stoddart, D. J. Williams, *Angew. Chem. 96* (1984) 806; *Angew. Chem. Int. Ed. Engl. 23* (1984) 824.

[12] There are also bifurcated hydrogen bonds of 2.40 and 2.23 Å, respectively, between H_a and F(1) and H_a and F(3) of the major occupancy PF_6^- ion.

[13] The closest analogue is the macrocyclic aquo complex of a carbonyl(bisphosphino-ether)rhodium complex (N. W. Alcock, J. M. Brown, J. C. Jeffery, *J. Chem. Soc. Chem. Commun. 1974*, 829; *J. Chem. Soc. Dalton Trans. 1976*, 583). In $[RhCO(H_2O)\{Ph_2P(CH_2CH_2O)_3(CH_2)_2PPh_2\}][PF_6]$, the metal is coordinated by the H_2O molecule which is hydrogen bonded to two of the oxygen atoms in the polyether chain.

[14] Compare with the reactions between crown ethers and $AlMe_3$ (J. L. Atwood, R. D. Priester, R. D. Rogers, L. G. Canada, *J. Inclusion Phenom. 1* (1983) 61).

BOOK REVIEWS

The Analysis of Gases by Chromatography. By *C. J. Cowper* and *A. J. DeRose*. Pergamon Press, Oxford 1983. xii, 147 pp., bound, DM 114.00.

P. G. Jeffery writes in the foreword that he hopes that this book will be received with the same enthusiasm that greeted his contribution "Gas Analysis by Gas Chromatography" more than ten years ago. This book by *Cowper* and *DeRose*, which is published as Volume 7 of the "Pergamon Series in Analytical Chemistry" and which really ought to be entitled "The Analysis of Gases by *Gas* Chromatography" is long overdue; since the publication of the 2nd edition of *P. G. Jeffery* and *P. J. Kipping's* book in 1972, this field of application of gas chromatography has undergone immense development, which is documented in countless publications. However, a comprehensive review of this particular area has been lacking for a long time, apart from a company brochure entitled "Fundamentals of Gas Analysis by Gas Chromatography" by *B. Thompson*.

The present volume has certainly succeeded in largely closing this gap. A short introduction devoted to the problems and peculiarities of gaseous samples as compared with those of liquids is followed by an account of the apparatus required for such analyses. Alongside the equipment for regulating and controlling the flows of carrier gas and auxiliary gases and for sample introduction the main emphasis is on the detectors used in gas analysis. The focal point of this book lies in the three chapters that follow, in which there is a 43 page-long detailed discussion of the normal separating materials, the choice of carrier gas in connection with the detector of choice for a particular problem, the possibilities of multi-column operation and specific operating methods. Arrangements for two and three column operation with valve switching and "valveless" according to *Deans*, the techniques of fore and back flushing, heart cutting, and other techniques are discussed with the aid of a large number of operating strategies.

A chapter devoted to examples of applications follows, in which suggestions for the separation of the components of air, of noble gases, of natural gas, of refinery, synthesis and fuel gases are illustrated with numerous chromatograms. Neither is stimulation lacking concerning the separation of gaseous sulfur, nitrogen and halogen-containing compounds, nor the separation of isotopes and the seldom analyzed gaseous compounds of boron, silicon, germanium, phosphorus and arsenic. In all this, account is taken of the circumscribed size of the book and, in the main, the reader is referred back to the literature.

Chapter 7 is devoted to the analysis of liquified gases and to gases dissolved in liquids. Emphasis is laid on the devices used for sampling, handling and dosing. Head-

space analysis is deliberately omitted and the reader is referred to the book by *Hachenberg* and *Schmidt*. The authors devote the last two chapters to the quantification and evaluation of chromatograms and to the preparation of standard gas mixtures. For the latter they limit themselves to a brief review of the various methods and techniques for the preparation of mixtures of gases and their critical assessment.

The book includes an extensive reference list in order of authors' names (172 references), which includes publications up to 1981. Additionally an appendix includes publications from the years 1981 and 1982 (19 references).

A point worthy of criticism is the plethora of units quoted. With Anglo-American nonchalance and uninfluenced by IUPAC recommendations or even SI regulations, pascals, pounds per square inch, atmospheres and metric and imperial units of length are quoted alongside each other. This will, however, not present any difficulty to the analyst who practises gas chromatography every day.

This book is written for the man at the bench. It is easy to read, comprehensibly laid out, and easy to understand even for the reader whose native language is not English. There are almost no printing errors. Within its compass of 140 pages the book contains a wealth of information, which will be of great use to the reader who is acquainted with the basic principles and practice of gas chromatography in helping him in his choice of apparatus and in the analysis of complex mixtures of gases.

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Atomabsorptionsspektrometrie. By *B. Welz*. 3rd completely revised edition. Verlag Chemie, Weinheim 1983. xiii, 527 pp., bound, DM 128.00.

Almost every new edition of a scientific or technical book is offered to the reader as being "completely revised". During the period of eight years between the publication of the second edition[*] and the present third edition atomic absorption spectroscopy has undergone a great deal of development. The basic principles of AAS remain unaltered, but general knowledge has been greatly augmented through the large increase in the application of this analytical technique. A really "new" book must combine the old basic knowledge with the new developments, additional fields of application, and also a critical description of the method. *Welz* has attempted this in the new edition and seems to have succeeded well. The wealth of material has almost doubled the size of the book; the number of figures has been enlarged from 73 to 140, the number of tables has only been slightly increased from 46 to 51. The real extent of the enlargement of knowledge, however, is best seen in the additional 1103 references; the total is now 2491. The increase demonstrable in these numbers is sufficient alone to justify the publisher's claim of "complete revision" of this book.

The additional figures are particularly welcome, both in the sections covering the basic principles and in those dealing with interferences. The clarity is significantly improved in both cases. The beginner receives an easier entry into the basics of the subject. Those who are already familiar with the problems of AAS can estimate the real extent of interferences much better with the aid of the diagrams.

The methodic layout of the volume is very similar to that of the previous edition. The chapters are naturally somewhat longer, but neatly tailored to accommodate the newer methods. A short introduction is followed by a brief, but adequate, description of the radiation sources in use nowadays (e.g. HCL, EDL). The chapter on atomization techniques includes the flame technique, the graphite furnace technique, the hydride and cold vapor techniques. The author deals both with the basic theory and with the current design of apparatus for each method. The historical outline of the techniques and further reference to specific techniques convey not only topical hints but a general picture to the reader with a greater interest in AAS. Concisely constructed chapters on optics and detection and output give an insight into spectrometer structure. Since most users of AAS do not wish to rebuild their instruments a short treatment here is appropriate. A great deal of space is devoted to interferences in AAS. They are described in a separate chapter, but also in the detailed section "Techniques of atomic absorption spectroscopy". This indication of the many possibilities of interference can be of great help to the practitioner in avoiding systematic errors in his determinations. A great deal of space in this context is devoted to the hydride and cold vapor techniques, where even today the interferences often constitute unresolved problems. The third edition too contains the indispensable descriptions of the individual elements. For each element the description of the standard conditions is followed by allusion to the various sources of interference. Although only a minority of possible interferences can be covered in such a section, it will certainly be of help in avoiding a multiplicity of the more usual errors.

No matter what its length the chapter devoted to specific applications is, considering its aims, of necessity too short. This deficit is made up for here by the large number of references to specific applications in the original literature.

"Welz" is the only German-language book dealing with atomic absorption spectroscopy. The 3rd edition can be understood both as a textbook and as a laboratory handbook. It can provide both the interested laboratory technician and the experienced practitioner of AAS with a profusion of practical advice and a deeper understanding of the method.

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Transition Metal Carbene Complexes. With contributions by *K. H. Dötz, H. Fischer, P. Hofmann, F. R. Kreissl, U. Schubert*, and *K. Weiss*. Verlag Chemie, Weinheim 1983. xiii, 264 pp., bound, DM 120.00.

This book is dedicated to Professor *E. O. Fischer* and is written by some of his more recent senior co-workers in honor of his 65th birthday (November 10, 1983). The theme of the book relates to an area discovered by the dedicatee in 1964, and has been a principal preoccupation of his group in the intervening years. Hence, the appropriateness of the topic and the selection of the contributors is to be commended.

The book is attractively produced. Details of its chapter headings are as follows. 1. The Synthesis of Carbene Complexes *(H. Fischer)*, 66 pages, 476 refs.; 2. Spectroscopic Properties of Transition Metal Carbene Complexes *(H. Fischer* and *F. R. Kreissl)*, $1\frac{1}{2}$ pages, 12 refs.; 3. Solid State

[*] Cf. *Angew. Chem. Int. Ed. Engl. 15* (1976) 447.

Structures of Carbene Complexes *(U. Schubert)*, 37 pages, 159 refs.; 4. Electronic Structures of Transition Metal Carbene Complexes *(P. Hofmann)*, 35 pages, 55 refs.; 5. Metal Complexes from Carbene Complexes: Selected Reactions *(F. R. Kreissl)*, 37 pages, 174 refs.; 6. Carbene Complexes in Organic Synthesis *(K. H. Dötz)*, 34 pages, 88 refs.; 7. Carbene Complexes as Intermediates in Catalytic Reactions *(K. Weiss)*, 18 pages, 75 refs.; 8. Mechanistic Aspects of Carbene Complex Reactions *(H. Fischer)*, 16 pages, 76 refs. It is somewhat unexpected that there should be no subject index.

In the Preface, the authors indicate that their aim is to identify principles rather than to attempt to provide a comprehensive coverage of the field. No doubt it is right that they should concentrate their attention on what are now known generally as Fischer-type carbenemetal complexes, that is to say, they devote the majority of their detailed attention to complexes of the type $[M(CO)_5(CRR')]$, in which M = Cr or W, R is an alkyl or aryl group, and R′ is a π-electron-donor group such as methoxy or amino. In most chapters there is no indication of the literature cut-off date; but Professor Schubert, who incidentally does provide a comprehensive table of data on structures (150 in all), states that his bibliography coverage ends with September 1982.

The authors are, of course, experts in their fields. Therefore, it is not unexpected that they write with authority. Two chapters seem less good than might have been anticipated. To cover spectroscopy in $1\frac{1}{2}$ pages and in so doing ignore a topic such as the rotational barrier around the metal-carbon bond is surprising; and, moreover to have references, which with two exceptions (1974, 1977) terminate in 1972 is also curious. The section dealing with carbene complexes as catalytic intermediates could quite well have been omitted, in the light of the rather low level at which the discussioni is pitched, and the existence of superior reviews of this topic.

This book is clearly to be welcomed, particularly as a useful summary of some of the major achievements in this field of the Munich group. It will be of considerable value to other workers elsewhere; although they might well have preferred a more comprehensive coverage, with perhaps a somewhat different balance.

E. O. Fischer's achievements in organometallic chemistry are, of course, outstanding. This book gives readers an opportunity to reflect how, in only one of his major areas, a vast amount of current chemistry can be directly traced back to his initiatives. Furthermore his skill as a teacher has obviously been transmitted to many of his coworkers.

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New Books

The following books have been received by the editor. All the publications listed are available through W & P Buchversand für Wissenschaft und Praxis, Boschstrasse 12, D-6940 Weinheim (Federal Republic of Germany). Tel. (06201) 606-0, Telex 465516 vchwh d, Telefax (06201) 602328.

Immuno Enzyme Techniques in Cytochemistry. By *W. D. Kuhlmann*. Verlag Chemie, Weinheim 1984. xiii, 170 pp., bound, DM 128.00.—ISBN 3-527-26078-1

Forschung, Lehre und Erziehung. Aufsätze aus der Zeit des Wiederaufbaus der deutschen Hochschulen. By *K. Zierold*. A publication of the Deutsche Forschungsgemeinschaft. Acta humaniora, Weinheim 1984. viii, 97 pp., paperback, DM 28.00.—ISBN 3-527-17010-3

Wachstum von Mikroorganismen. Experimente und Modelle. 2nd revised edition. By *F. Bergter*. Verlag Chemie, Weinheim 1984. 161 pp., bound, DM 78.00.—ISBN 3-527-26109-5

Theory, Practice, and Process Principles for Physical Separations. Proceedings from the October 30—November 4, 1978 Conference, Pacific Grove, California. By *M. P. Freemann* and *J. A. Fitzpatrick*. American Institute of Chemical Engineers, New York 1984. 750 pp., bound, $ 50.00 (reduction for members of the American Institute of Chemical Engineers: $ 40.00).—ISBN 0-8169-0204-6

Biomembrane Structure and Function. Topics in Molecular and Structural Biology. Vol. 4. Edited by *D. Chapman*. Verlag Chemie, Weinheim 1984. x, 414 pp., bound, DM 160.00.—ISBN 3-527-26134-6

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Monoclonal Antibodies: Their Chemistry, Functions, and Possible Uses

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Dedicated to Professor Rolf Sammet on the occasion of his 65th birthday

In December of last year the Nobel Prize for Medicine or Physiology was awarded to the natural scientists *N. K. Jerne, C. Milstein,* and *G. Köhler.* These three immunologists have contributed fundamentally to our understanding of antibody synthesis by the individual immune cell. They confirmed the rule, established in the sixties, that *only one antibody comes from each type of immune cell,* thus giving it the status of a dogma. *Jerne* worked out the basic understanding of the great variety of antibodies, and his Jerne-Plaque-Test (1963) has enabled us to describe and analyze a single antibody-producing immune cell in vitro. Thus, the study of immune cell interaction and the cooperation of lymphocyte subpopulations, which leads to the formation of antibodies, received decisive impulses and important methodological prerequisites. In 1975 *Köhler* and *Milstein* succeeded in permanently stabilizing, i.e., *immortalizing,* the antibody production of an already immunologically specifically primed mortal immune cell by means of cell fusion *(hybridization)* with an immortal, cancerous immune cell (myeloma cell). The hybrid cell and the hybrid cell clone grown from it in cell culture produced a homogeneous antibody, having the desired constant binding specificity, in a practically unlimited fashion and independently of an animal organism, a *monoclonal antibody.* This scientific breakthrough was the beginning of a tremendously stimulating new biotechnological development, which very quickly spread to laboratories in diverse fields and which today enables us to take up, and in part even solve, scientific, technical, and medical problems that would otherwise not have been analyzable at present.

1. Introduction

Emil von Behring was the first (1890) to discover antibodies as the carriers of immunity in the serum of an organism immune against a toxic agent[1]. He was awarded the first Nobel Prize for Medicine in 1901 for his therapeutic success with immune serum won from previously specifically vaccinated animals. Not until long after his discovery, however, between 1950 and 1970—when protein structure chemistry and immune chemistry had been inspired by many new analytical and preparative methods, the use of immunodiagnosis with antibodies had become established, and immunological research had been challenged by new medical problems, for instance graft rejection—could the structure of the antibody molecules be explained and a better understanding of the extent of their functions be obtained.

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In 1972 *G. M. Edelmann*[2] and *R. R. Porter*[3] were awarded the Nobel Prize for their contributions to explaining the structure of antibodies. The analysis of pathologically occurring myeloma proteins also proved useful in their work. These turned out to be monoclonal antibody molecules, partial molecules, or fragments thereof produced in an uncontrolled way by a degenerate immune cell clone and appearing in unusually high concentrations in the serum or the urine of patients. For the immunologists, however, the *myeloma cells*, the malignant cells producing these proteins pathologically, were important aids in achieving their aim of developing *immortalized immune cell hybrids* and producing *monoclonal antibodies* in vitro. Thus the honor afforded last year to the work of *N. K. Jerne*[4] and of *C. Milstein* and *G. Köhler*[5] with the Nobel Prize logically follows upon nearly one hundred years of development in the field of antibodies.

This review of monoclonal antibodies does not intend to cover the immense and still growing flood of publications in this new field. Its intention, rather, is to stress the particular properties of *monoclonal* antibodies and to compare them to *heteroclonal* and *polyclonal* antibodies in order to illustrate how monoclonal antibodies can provide us with a new and deeper understanding of the great variety of antibodies and their functions. We intend to show how a monoclonal antibody can emerge from an antibody family, which previously was only generally understood as a group with structures and properties that varied within certain limits, and how it thus suddenly acquires its own determination, significance, and use. Above all, attention will be directed towards the new technical and medical uses known at present or envisioned for the future.

2. Antibody Formation

2.1. Antibody Formation in vivo

When foreign substances or infectious pathogens invade the body of a vertebrate or when organs are transplanted from a donor to a recipient, the body defends itself, by means of its immune apparatus, with protective reactions, which normally lead to the elimination of the foreign substances from the body. The white blood corpuscles, the immune cells, are the vehicles of the immune system. These are, on the one hand, phagocytosing cells, such as *granulocytes* and *macrophages*, and, on the other, lymphocytes, which can be divided into two groups—*T-lymphocytes* (thymus-determined) and *B-lymphocytes* (bone-marrow-derived). In the course of an immune response, resting B-lymphocytes finally form, after several stages of development, mostly under the influence of T-lymphocytes and their hormone-like immune factors, differentiated *plasma cells*, whose only function is antibody synthesis. Antibodies are protein molecules and belong to the large group of immunoglobulins (see Section 3). They are capable of binding with partial structures (determinants) on the surface of foreign substances, the *antigens*, in a highly specific manner, and thus of initiating the expulsion of the antigens from the body[6, 7].

Antibodies are coded by the V-genes (variable part; see Section 3) and by the C-genes (constant part) of DNA. Both gene groups are situated on *one* chromosome, but separated by an intron which plays no part in synthesis. For their biosynthesis, the complete DNA section, together with the intron, is first transcribed into RNA. The intron is then cut out and the shortened RNA strand appears as mRNA. This mRNA codes for the sequence of an amino acid chain of the antibody molecule, which is synthesized at the ribosome. After the linking of usually two heavy and two light chains by disulfide bonds and the glycosylation of the heavy chains, the completed antibody molecule is secreted out of the plasma cell.

One important functional characteristic of an antibody molecule is its specificity for only *one* determinant on *one* antigen. This also means that an immunologically determined maturated B-cell as its succeeding antibody producer, the plasma cell, only produces one antibody type of one specificity, a *monoclonal antibody* as it were. However, in response to an antigen stimulus the organism always produces an antibody family with related specificity and reaction patterns, namely, *heteroclonal antibodies*. In this way it is more able to protect itself and is safeguarded in a number of ways. The family includes antibodies against different determinants on one antigen as well as those which differ in form and strength of binding. Thus it is almost impossible to isolate a monoclonal antibody from a heteroclonal serum, since these antibody molecules with their related specificities are, as a rule, too alike in their protein chemical properties. It is likewise not possible to isolate a plasma cell and cultivate a clone from it in order to produce monoclonal antibodies, since these cells cannot survive in a culture medium.

2.2. Antibody Formation in vitro

It was the pioneering work of *G. Köhler* and *C. Milstein*[5] that first made the in-vitro synthesis of a monoclonal antibody with the desired specificity and in almost any amount possible. They obtained B-lymphocytes from the spleen of mice specifically immunized against sheep erythrocytes, a cellular antigen, and then brought them into close contact with a mouse myeloma cell line (X63-Ag8) along with a fusion-promoting agent (Sendai virus; polyethylene glycol 4000; dimethylsulfoxide), thus achieving cell fusion *(hybridization)*. The fusion mixture was cultivated in a selective culture medium (HAT medium, containing hypoxanthine, aminopterine, and thymidine), in which only *hybridoma cells* are able to grow[8, 9].

Although the myeloma tumor cell is immortal and grows in a culture medium, it does not have the enzyme hypoxanthine-guanine phosphoribosyltransferase (HGPRT) and cannot survive in a HAT medium. Only those cells can multiply in a HAT medium which contain the enzyme HGPRT, which enables exogenously supplied hypoxanthine to be used for the salvage pathway of purine nucleotide synthesis. Aminopterine, an antagonist of folic acid reductase, blocks the main synthesis pathway for thymidine. Hybridoma cells are HGPRT+ and also contain the enzyme thymidine kinase (they are TK^+); thus, they can make use of exogenously supplied hypoxanthine and thymidine. This is also of significance for myeloma cell line

variants, selected on account of a thymidine kinase defect[8, 10].

The hybrid cells are not all useful producers of monoclonal antibodies at first, since they contain chromosomes of both parental lines and can, in principle, produce two types of both heavy and light antibody chains. A monoclonal antibody, however, only consists of one type of heavy and light chain, which should only be coded by spleen cell chromosomes, for antibody specificity is selected via the specificity of the fused spleen cells. Hybrid cells lose chromosomes during the first cell divisions; the number of chromosomes is reduced from about 112 (40 from the B-lymphoblasts and 72 from the myeloma cell) to a more stable number of about 70 to 80. Thus, the proteins that are coded on the lost chromosomes cannot be synthesized. A purging process therefore takes place at this stage of cloning. The useful clones must then be especially carefully selected, so that the desired hybridomas and monoclonal antibodies are obtained. Finally, after the elimination and destruction of all undesired cells and unusable hybrid cells, the selected and stabilized clones are continuously multiplied in tissue culture or in the peritoneum of the mouse (higher antibody yield). In order to maintain the stock, parts are frozen in liquid nitrogen; they can thus be stored for a practically unlimited period of time and reintroduced into the cell culture at will.

3. Antibodies: Basic Structure and Function

The understanding of the structure of antibody molecules, from the primary structure up to an exact three-dimensional structure[11–13], afforded insights into their biosynthesis and genetic determination and made possible a further understanding of their biological significance and function.

All antibody molecules are built up according to the same scheme and have four structural features in common (Fig. 1)[14, 15]:

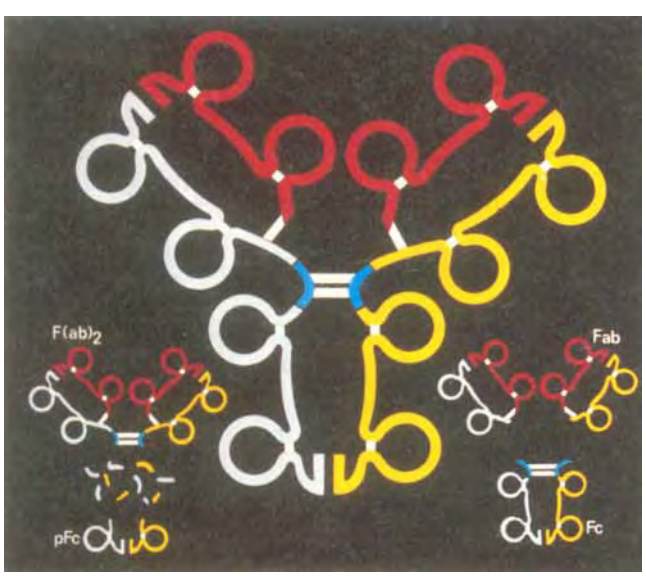


Fig. 1. Model of an immunoglobulin G molecule. Red: light chains (L-chains); light blue and yellow: heavy chains (H-chains); dark blue: hinge (hinge region); white: disulfide bonds. Bottom left: the results of cleavage with pepsin [F(ab')$_2$ and pFc]. Bottom right: the results of cleavage with plasmin or papain [Fab and Fc]. For further details see text.

- Antibodies are symmetrical and consist, in the case of immunoglobulin G (IgG), of two heavy (H) chains (50 kDa) of equal length and of two light (L) chains (25 kDa) of equal length. The L-chains flank the H-chains from their amino end onwards; L- and H-chains are joined by a number of different chemical bonds. Thus they constitute two antigen-binding moieties of the molecule, the Fab parts *(fragment antigen binding)*. The two still free halves of the H-chains link together and form the stem of the molecule (Fc moiety; *fragment crystallizable*). The overall structure therefore has the T- or better known Y-form (Fig. 1).
- The basic structural component of both the H- and the L-chains is a polypeptide chain folded in about the same way in each unit (pleated sheet structure) and with ca. 110 amino acids and a molecular weight of about 12 kDa. L-chains are always composed of two such basic components *(domains)*, the H-chains of IgG and IgM of four and five domains, respectively. The domains are connected over short, mobile polypeptide pieces *(switch region)*, which contain the functionally important hinge *(hinge region)* of the antibody molecule in the area where the H-chains are linked by disulfide bonds. This region allows great mobility of the Fab arms during interaction with the antigen and is particularly exposed to attack by proteases. Thus the enzymes plasmin and papain and certain leukocyte proteases cleave the IgG molecule into an Fc and two Fab fragments (Fig. 1, bottom right). Pepsin and certain tissue cathepsins cleave IgG into pFc and still bivalently binding F(ab')$_2$ fragments (Fig. 1, bottom left).
- In each of the first *N*-terminal domains of the H- and L-chains there are variable sequences (V-domains), whereas all the other domains of a particular immunoglobulin class have largely constant amino-acid sequences (C-domains). The C-domains thus ensure the structural and functional uniformity of an Ig class, whereas the V-domains, with their three or four hypervariable regions, are responsible for the diverse specificity for the binding of all possible antigens. In order to bind an antigen the V-domains of H- and L-chains are joined together to act, as it were, as a hand of the antibody molecule which seizes the antigen and holds on to it.
- The disulfide bonds are an essential and stabilizing structural feature. Each domain contains an interchain bond in the vicinity of the pleated sheet. The L-chains are linked to the H-chains, and the H-chains to one another in the hinge region, via interchain disulfide bonds. The number of bridges between the H-chains varies within the subclasses. Carbohydrates are found in the C_H2 domain; they prevent an intensive protein-protein interaction in this domain area.

3.1. Human Immunoglobulins

Despite the great uniformity in the structures of the immunoglobulins, there are also clear differences, as can be seen from the arrangement of human immunoglobulins in Fig. 2: in the number of H-chain domains, the number and position of the disulfide bonds, and in the assembly of the

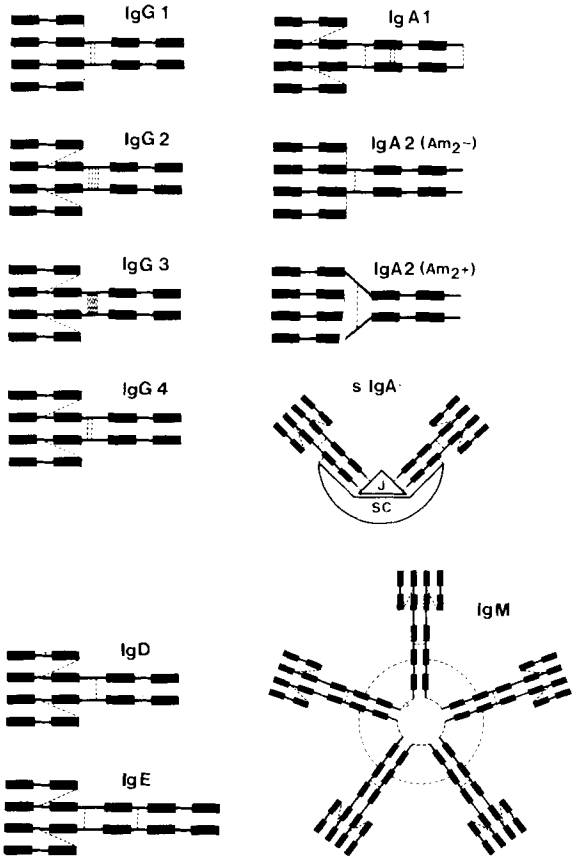


Fig. 2. Model structures of the classes of human immunoglobulins and the subclasses of IgG and IgA. The chains are composed of linearly arranged components of the same type, the domains (▬); these are linked by switch peptides (—) and disulfide bonds (----). J: J-chain; SC: secretory components. For further information see text.

basic molecules, for instance as dimers (IgA) or pentamers (IgM). The immunoglobulin classes are defined as IgG, IgA, IgM, IgD, and IgE according to their differently constructed H-chains and therefore their different overall structures. The H-chains are named according to their corresponding Greek letters (γ-, α-, μ-, δ-, and ε-chains). There are only two variations for the L-chains of all immunoglobulin classes and subclasses (e.g., IgG1 to IgG4), kappa and lambda chains (κ and λ).

The five immunologically and biochemically easily distinguishable classes of antibody molecules appear in an organism in greatly varying quantities and fulfill different functions. Apart from their different molecular weights, their different half-lives, etc., the following immunological features of the individual Ig classes should be stressed: IgE is the main mediator of allergies, IgD is probably an important receptor on lymphoid cells in the early phase of differentiation, IgM is a natural antibody in the first phase of immune resistance, the so-called primary reaction, with special significance for the lysis of bacteria, IgA is the main carrier of immune resistance in secretions and on mucous membranes and is conspicuously active against viruses, and secretory IgA is the most important antibody in colostrum. There are several structural variants of IgA which also have functional significance. The dimer of IgA, bound by a *J*-chain and equipped with a *secretory piece*, constitutes the acid-resistant form of IgA. IgG, which exhibits almost all the functional characteristics of antibodies, fulfills, moreover, the task of passive immune protection in the fetus, since it is the only immunoglobulin that is able to pass the placental barrier. IgG constitutes about 75 to 80% of the immunoglobulins in an organism: approximately 180 g blood with 80 g cell-free plasma contains about 1.3 g immunoglobulins; of this, about 1 g is IgG.

Besides structural variants of IgA, there are also four subclasses of IgG, which differ mainly in the number and position of their disulfide bonds. No noteworthy distinguishing functional characteristics are at present known to us. IgG1 constitutes about 60% and IgG2 about 30% of total IgG, whereas the share of IgG3 and IgG4 is only about 5% each.

3.2. Mouse Immunoglobulins

Due to difficulties in the production of human monoclonal antibodies (see Section 5.4.4), the major role is still played by mouse antibodies. A summary of mouse IgG subclasses that occur as monoclonal antibodies is given in Figure 3 (IgM is not included). It can be assumed that the knowledge of human antibodies can, in principle, be applied to those of the mouse on account of their structural similarity; however, there are large differences in their secondary functions, which are governed by the Fc fragment of the antibody, as is also the case within the human Ig classes. The reactivity of the Fc fragment with human receptor structures plays an important role in the in-vivo human use of mouse immunoglobulins.

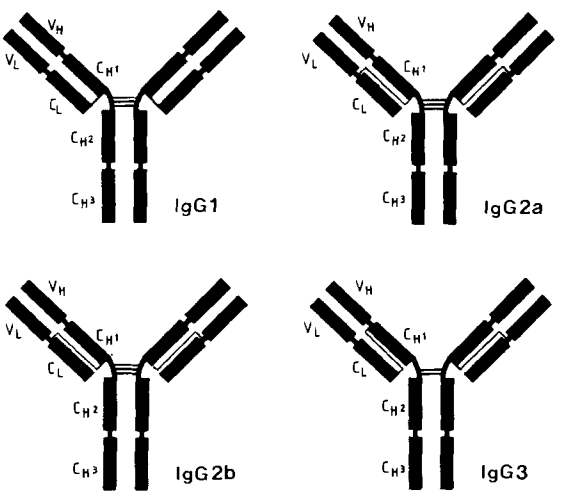


Fig. 3. Model structures of mouse IgG subclasses. Compare also with Figure 2.

Fc-mediated Antibody Effects

Formerly, antibodies were thought of predominantly in connection with specific resistance towards and control of infectious pathogens and poisons. Nowadays subsequent reactions, which are predominantly Fc-mediated, must also be considered. These reactions have controlling and regulatory functions (Table 1). Moreover, antibodies are not only humorally active, but also mediate between cellular and humoral immunity via Fc-dependent mechanisms.

Table 1. Fc-mediated reactions and functional features of IgG that are generally induced upon antigen-antibody interaction.

Bindung to Fc receptors in an organism
Regulation of IgG synthesis: positive/negative feedback
Complement activation via C1q (classical)
Phagocytosis (if via Fc receptors)
Platelet activation and aggregation
Antibody-dependent cellular cytotoxicity (ADCC)
Biological half-life of the antibody (mediated by carbohydrate of the C_H2 domain)
Placental transfer (passive immunity of the fetus)

The induction of Fc activity requires first either the binding of the antibody to the corresponding antigen, which normally leads to cross-linking or polymerization of the antibody-antigen complex, or an antigen-independent, artificial, in-vitro aggregation, which can normally take place during the routine process for the isolation of IgG from serum. In any case, the Fc fragments of several immunoglobulin molecules must come together in order to initiate the subsequent reactions.

The Fc stem binds to the Fc receptor, which can be found in very different parts of the body. Its best known location is on the surface membranes of various cells. Certain lymphocyte populations, for example, granulocytes, macrophages, thrombocytes, and mast cells, have been well investigated.

The Fc receptor, and thus the Fc part of the antibody, plays an important role in the regulation of antibody formation. A negative feedback effect on IgG synthesis has been shown.

One of the important secondary functions resulting from antibody binding to the antigen is the activation of the complement system. This is a plasma protein system consisting of now well-characterized single components (ten to twenty, depending on the point of view); included are proenzymes and enzymes, activators, and inhibitors, which, after the activation of the starter components (C1 or C3) and in the course of the cascade-like reaction, play a number of important biological and physiological roles. These can be either of a humoral nature (especially via the anaphylatoxins C3a and C5a) or of a cellular nature (reviews in [6, 7]). The most important is usually the lytic destruction of the relevant cells, cellular organisms, or bacteria.

The activation of the complement system takes place either via the *classical pathway*, in which C1 is activated and C1q must first bind to the Fc portions (e.g., of immune complexes), or via the *alternative pathway* ("properdin pathway"), which begins with the cleavage of C3 into C3b and C3a, is not Fc-dependent, and can also be regarded as a cell-bound mechanism in connection with macrophages[16, 17]. Thus the classical pathway joins the alternative one via its own specific starter reaction sequence (C1→C4→C2). C3 can also be cleaved, and thus the alternative pathway activated, by enzymes such as plasmin, thrombin, and tissue and bacterial proteases, as well as by various other substances.

A simplified and still very temporary summary of some Fc functions of mouse IgG subclasses is given in Table 2. Only very little information from comparable studies is available on the reaction of mouse IgG with human cells that carry Fc receptors; therefore, this information should be considered as being only schematic. Fc functions have been selected which are important for the technical and medical uses discussed below.

Table 2. Fc-dependent functions of mouse immunoglobulin subclasses.

Subclasses	Complement-dependent Cytolysis (Rabbit C)	Staphylococcus Protein A Binding	Staphylococcus Protein A Elution at pH	Fc Receptor (human)
IgG 1	−	+	6.0	+/−
IgG 2a	++	++	4.5–5.0	+
IgG 2b	++/+++	+++	3.0–3.5	+/−
IgG 3	+	++	4.0–4.5	+

4. Purification and Fragmentation

4.1. The Isolation of Monoclonal Antibodies

The hybrid cells that produce monoclonal antibodies are either grown in special culture media, containing essential amino acids, vitamins, and salts as well as the serum protein albumin or fetal calf serum, or they are grown in the peritoneal cavity of mice. Whereas antibody concentrations of usually 1–20 μg/mL can be achieved in cell culture supernatants, the results achievable in the serous fluid of the peritoneal cavity (ascites fluid) are up to 1000 times better. Since very large volumes must be handled for antibody isolation from cell culture supernatants, the second method of in-vivo cultivation is sometimes preferred, despite difficult separation problems, on account of the much greater production capacity. For the production in the ascites fluid the monoclonal antibodies have to be isolated from a protein mixture having a composition similar to that of serum (Fig. 4). To this end, methods are successfully applied which have proved of value in the purification of polyclonal antibodies[18].

Due to the fact, however, that established procedures have been optimized for polyclonal immunoglobulin mix-

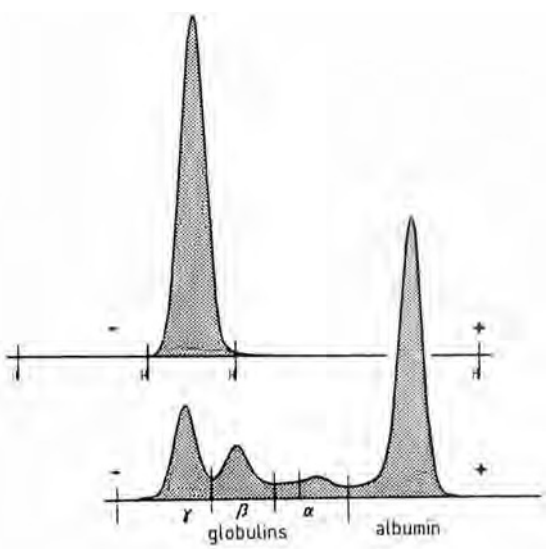


Fig. 4. Microzone electrophoresis of mouse ascites fluid (lower profile) and the IgG fraction isolated from it (upper profile).

tures, particular problems may arise with monoclonal antibodies when the product of one clone has protein chemical properties considerably different from the average properties of a heteroclonal mixture. In order to isolate a monoclonal antibody it is therefore advisable to select methods and conditions of separation on the basis of its particular properties and to adjust them accordingly[19]. Gel filtration, based on molecule size as the separation principle, is frequently a more suitable purification procedure than anion exchange chromatography, which uses the quite variable charge of the antibody molecule for purification. Fractional precipitation with the aid of a neutral salt, such as ammonium sulfate, or the use of carrier-bound staphylococcus protein A in the case of monoclonal antibodies of the class IgG, has similarly proved to be useful. The IgG subclasses often show such a great affinity for protein A that separation from other proteins in the ascites fluid can take place in an elegant one-step procedure (see also Table 2)[20-22].

Since the ascites fluid has a protein composition similar to that of serum, and thus also contains polyclonal immunoglobulins of the "producing" mouse, further problems can arise. The specific activity of the monoclonal antibody fraction in a clone of only moderate productivity is decreased by the non-separable polyclonal immunoglobulins. These products are less suitable for the production of so-called *immunotoxins* (see Section 5.4.2).

4.2. The Enzymatic Fragmentation

In the production of certain antibody fragments using proteases such as pepsin, plasmin, or papain, the subclass to which they belong (Fig. 1) plays an important role. Thus, in general, the classical method, according to which $F(ab')_2$ fragments are produced by pepsin fermentation of human polyclonal IgG with a natural subclass composition[23], is also successful with mouse antibodies of the subclass IgG2.

An $F(ab')_2$ preparation can be produced from the subclass IgG1 with previously activated papain in a thiol-free reaction medium after optimization of the amount of enzyme and the fermentation period, parameters which can differ from one antibody to another[19]. The absence of SH-agents (cysteine, mercaptoethanol, dithiothreitol, etc.), which are usually used to activate papain, is recommended on account of the otherwise possible heterogeneity of the reaction products after the partial cleavage of the three disulfide bonds that link the heavy chains. Monovalent Fab' fragments can now be easily produced from $F(ab')_2$ preparations by reductive cleavage of the hinge-region disulfide bonds. A combination of anion exchange and gel permeation chromatography normally makes possible a satisfactory separation of reaction mixtures containing IgG, $F(ab')_2$, Fab', Fc, and papain.

What has been said above about the isolation and enzymatic cleavage of monoclonal antibodies shows quite clearly that there is no standard procedure which can be used under all circumstances, but that individual methods have to be used which are adjusted to the given protein chemical properties of the relevant monoclonal immunoglobulins.

5. Uses of Monoclonal Antibodies

5.1. Use in Biochemistry and Biotechnology

Monoclonal antibodies are available for a large number of different purposes in research. Apart from their direct medical uses (Section 5.4) such as, for example, the production of antibody-drug conjugates (e.g., immunotoxins; Section 5.4.2), the analytical possibilities in all scientific fields, which we can only deal with in part (Sections 5.2 and 5.3), have been greatly increased.

In affinity chromatography, monoclonal antibodies bound to a solid phase continue to be a suitable aid in isolating certain antigens from a heterogeneous mixture. The isolation of interferon or other immune factors can be taken as an example here[24]. Monoclonal antibodies are also used for this purpose in gene technology. Thus, it is possible, with their aid, to isolate DNA fragments via gene banks cloned in E. coli or λ-phages. These code seemingly interesting epitopes (antigenic determinants) of viral coat proteins[25].

The combination of monoclonal antibodies of differing specificities often permits the differentiation and classification of antigens, owing to their characteristic reaction patterns. Here, too, one must mention the possibility of characterizing diverse cell subpopulations (see Section 5.3)[26,27].

Changes in conformation are often discussed in protein chemistry as the triggering principle for certain reaction sequences. An example of this is the activation of the first complement component, the C1 complex, in the classical pathway. This activation process can be triggered off by interaction of the C1q subcomponent with antigen-antibody complexes. The subcomponents undergo a change in conformation, in the course of which an epitope is exposed, which has only recently been detected with the aid of monoclonal antibodies[28].

Not only changes in conformation but also enzymatic cleavage are a necessary precondition for many cascade-like reaction processes (complement activation, blood coagulation, etc.). During such processes a reactive partner without enzymatic activity *(zymogen)* is normally cleaved by a specific protease, which is located one step ahead of it in the activation cascade. Via this process, the zymogen becomes an enzyme which is able to continue the reaction sequence. The process is shown schematically in Fig. 5: the zymogen is a typical protein with a number of different antigenic determinants (A, B, C, and D), which can be indi-

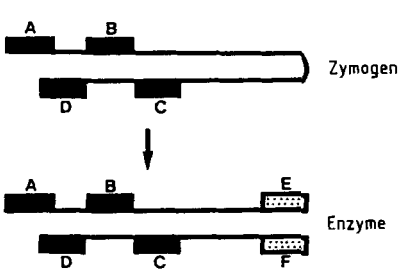


Fig. 5. Above: Schematic representation of a polypeptide chain with four different epitopes (A, B, C, and D). Below: Enzymatic cleavage of the chain causes the appearance of two new antigenic determinants (E and F).

vidually well detected and identified with the relevant monoclonal antibodies. After enzyme cleavage and the changes in structure involved, new epitopes (E and F) arise, against which monoclonal antibodies can be produced. With their aid the new enzyme can then be selectively and specifically detected. With polyclonal antibodies, this would often not have been possible, or only with considerable difficulty.

Antibodies can, as normally bivalent molecules, form precipitating immune complexes with antigens having sufficient size and a sufficient number of antigenic determinants. The influence of molecular parameters, such as concentration, affinity, or the heterogeneity of the antibody populations involved in precipitation, which have somewhat different specificities, can only be investigated to a certain extent with heteroclonal antibody mixtures. In this case, definable reaction conditions and monoclonal antibodies and combinations of them can also help in dealing with unanswered questions.

Monoclonal antibodies will also make possible the study of antibody structure and variety, of the variability of the antigen-binding sites, as well as of special areas of the molecule (e.g., the Fc part) to which various effector functions are linked. Thus relationships between structure and function, as well as genetic determination and individual-specific significance, can be better investigated.

These examples are only intended to give an impression of the many possible uses of monoclonal antibodies and thus to show what a valuable instrument has been made available to natural scientists of all disciplines.

5.2. General Diagnostic Uses

5.2.1. The Advantages of Monoclonal Antibodies in Immunoassay Systems

Polyclonal antisera are characterized by their heterogeneity. The use of highly purified antigens for immunization, the special selection of animals, and immune adsorption techniques have already allowed the development of sensitive test systems of high specificity and reproducibility. However, the problems relating to these antisera remain: serum batches obtained from different animals or groups of animals, or from one animal at different times, have different antibody contents and do not usually show an identical reaction pattern. Moreover, the small share of specific antibodies (ca. 1—15%) is often a disadvantage.

On account of their great specificity, identity, and unlimited availability, monoclonal antibodies are nowadays an obvious choice as diagnostic reagents. They have numerous advantages, especially in immunoassay systems. The most frequently employed test systems are competitive binding assays (RIA, EIA; Fig. 6a) and the "Sandwich" assays (IRMA, ELISA; Fig. 6b). Whereas labeled antigen is used in the competitive tests, labeled antibodies are used in the Sandwich test systems. So far both systems have a number of important disadvantages. The competitive assays require pure antigen, which has to be labeled without altering its immune reactivity; the reference curve is not linear; and the reaction cannot take place in the presence of an excess of reagent.

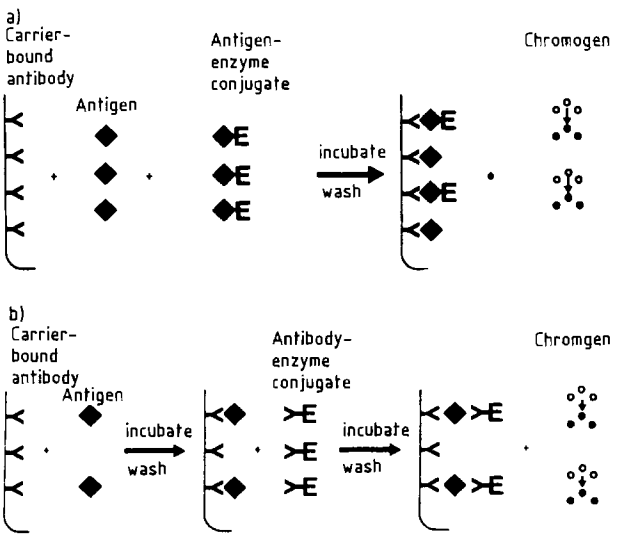


Fig. 6. a) The principle of the competitive immunoassay: RIA = radioimmunoassay; EIA = enzyme immunoassay. The antigen labeled with enzyme E and the unlabeled antigen react competitively with the carrier-bound antibody, so that the unknown amount of antigen can be determined if, for comparison, a reaction with pure antigen of known concentration is carried out. An excess of reagent is to be avoided. b) The principle of the Sandwich immunoassay: IRMA = immunoradiometric assay; ELISA = enzyme-linked immunosorbent assay. The antigen to be determined is bound by the carrier-bound antibody and quantitatively determined by an enzyme-labeled second antibody. These test systems require large amounts of purified (highly specific) antibody and can take place with an excess of reagent.

The Sandwich assays require large amounts of antibodies purified by affinity chromatography. Since a mixture of antibodies with different affinity constants is present, the standard calibration curve is linear only within narrow test limits. One advantage over the competitive tests is the possibility of using solid phase and labeled antibodies in excess, which allows a higher reaction rate in the test. IRMA and ELISA are thus test systems that can make full use of the advantages of monoclonal antibodies; namely, specificity, identity, and unlimited availability.

In the Sandwich assay (Fig. 6b) the solid phase (microtiter plates, tubes, beads) is coated with monoclonal antibodies. In the first stage of the reaction, the antigen reacts with the antibodies bound to the solid phase. In the second incubation step, an isotope-labeled or enzyme-labeled monoclonal antibody reacts with the antigen-antibody complex on the solid phase. The samples are evaluated in a γ-scintillation counter, or a substrate solution is added to the samples and the enzyme activity determined. The antigen concentration is determined by means of a reference curve.

The advantages of monoclonal antibodies can be summarized as follows:

- Uniform affinity constants and homogeneity of material usually make shorter incubation times possible.
- Very high standardization of reagents allows a better reproducibility.
- The solid phase is optimally used, due to the homogeneous affinity of monoclonal antibodies. False determinations (high-dose hook effects), which can arise with large amounts of antigen in test samples are, in part, avoided.

- When two monoclonal antibodies have been found which recognize two epitopes of an antigen and cooperate in a Sandwich assay, *one* incubation step is sufficient, since the antibodies bound to the solid phase and the labeled antibodies do not compete for the binding sites.
- The calibration curves are linear over a large measuring range so that the number of standardization points can be reduced.
- The sensitivity and the measuring range of the test systems can be varied using monoclonal antibodies with different affinity constants[29].

5.2.2. *Examples of Uses*

Drug Monitoring

The first immunoassay for a drug was described for digoxin, a heart glycoside, approximately 15 years ago. Nowadays it is possible to demonstrate the presence of substances in nanomolar ranges, and the active form of a drug can be distinguished from closely related metabolites. There are already numerous publications describing the use of monoclonal antibodies for *drug monitoring*. Digoxin was again the first examined, since it is an uncharged and chemically well-defined hapten. *Margolis* et al. and *Mudgett* et al.[30,31] obtained highly affine monoclonal antibodies, which, unlike conventional digoxin-specific antisera, made the differentiation of molecules possible.

Kato et al.[32] have produced monoclonal antibodies against the antitumor drug methotrexate (MTX). Competitive binding RIAs showed that the specificity patterns of monoclonal and conventional antibodies for MTX and structural analogues were similar, although the monoclonal antibodies cross-reacted less strongly with folic acid and other derivatives. *Hoebeke* et al.[33] were able to produce highly affine monoclonal antibodies against β-adrenergic ligands and tricyclic antidepressive drugs (alprenolol, nortriptyline). Apart from the use of these antibodies for the study of receptor-ligand structure relationships, the antibodies could also be used for a quantitative determination of these substances in biological fluids.

Tumor Marker Diagnosis

Monoclonal antibodies are particularly suited for the diagnosis of tumors and for the demonstration of the presence of tumor-associated antigens (Section 5.3). Numerous monoclonal antibodies have been produced against the presently existing markers, such as the carcinoembryonic antigen (CEA), α-fetoprotein (AFP), chorionic gonadotropin (human chorionic gonadotropin, HCG), β_2-microglobulin (β_2M), ferritin, and the acid prostate phosphatase, and there are good indications that a higher specificity and sensitivity can be achieved with monoclonal antibodies in tumor diagnosis and monitoring (see also Section 5.4.1)[34–36].

Further, new antigens will most likely be brought to light with monoclonal antibodies (see also Sections 5.3.3, 5.3.4, and 5.4). *Koprowski* et al. described a monoclonal antibody that reacts specifically with a surface antigen on colorectal tumor cells[37]. This antigen was later described as "carbohydrate antigen" CA 19-9. Using an inhibition RIA, the authors were able to show that increased levels of CA 19-9 only appear in the sera of patients with tumors in the colorectal area, in the stomach, and in the pancreas. Thus CA 19-9 could be a useful tumor marker. This is also the case for CA 125, another carbohydrate antigen. *Bast* et al. have described a monoclonal antibody against this antigen, which is found on most non-mucous, epithelial ovarial carcinomas[38].

Polypeptide Hormones

The specific detection of polypeptide hormones is a further important area of use. The pituitary hormones thyroid-stimulating hormone (TSH), follicle-stimulating hormone (FSH), and luteinizing hormone (LH), as well as HCG, are complex molecules with a large number of antigenic determinants. These glycoproteins have the same α-subunits and differ only in parts of their β-subunits. Due to the problems of producing specific antisera against them, it has so far been very difficult to develop good immunodiagnostic test systems.

Nowadays there are monoclonal antibodies with specificity for the α- or β-subunit[39] and for conformation epitopes[40], which only react with the intact molecule. By combining these three types of antibodies, test systems can be developed in which either only the intact molecule or only the free subunit is specifically detected.

Earlier investigations with monoclonal antibodies led to the expectation of some disadvantages in precipitation and agglutination. However, in recent years monoclonal antibodies have also been described which are very much able to precipitate and agglutinate[41]. *Rahamim* et al. obtained a monoclonal antibody against the β-subunit of HCG, which agglutinates HCG-coated erythrocytes. Due to the sensitivity, specificity, and affinity, this monoclonal antibody is very well suited for detecting HCG in biological fluids. Further interesting monoclonal antibodies have also been developed against L-thyroxin, *T4*, and L-triiodothyronine, *T3*[42]. They have an improved specificity and are more quickly bound.

Microbiological Diagnosis

Monoclonal antibodies have become important for the differential diagnosis of viral, bacterial, and parasitic infectious diseases, since the pathogen can be thereby specifically detected. New diagnostic possibilities have, in some cases, been found. *Wiktor* et al.[43], for instance, were able to reliably recognize animals infected with rabies by means of brain cell smears. The diagnosis of sexually transmitted diseases, such as *herpes, Chlamydia trachomatis, Neisseria gonorrhoeae,* has also been made easier[44]. Not so very long ago a direct demonstration of chlamydia infections was not possible. With monoclonal antibodies and using the immunofluorescence technique, urethral and cervical smears produce characteristic reaction patterns for chlamydia infections even after only 30 min. These results have been confirmed by *Ruijs* et al.[45], who compared the rapid detection of *C. trachomatis* in urethral smears and urine sediments using monoclonal antibodies with conventional culture methods.

As *Nowinski* et al.[44] also showed using immunofluorescence studies with monoclonal antibodies specific to herpes simplex virus (HSV) I and II, the classification of HSV into two subgroups produced complete correlation with the results of the restriction endonuclease analysis of viral DNA. *Franze*[46] also successfully showed a differentiation of HSV I and II in an ELISA test.

Sometimes the specificity of monoclonal antibodies is too high for a viral or bacterial infection, especially when, with a large number of strains, no common antigenic determinant is present. In such cases a mixture of monoclonal antibodies can often be used successfully for immunodiagnosis. *Nowinski* et al., for example, used a mixture of three monoclonal antibodies for their studies of *Neisseria gonorrhoeae*[44]. This mixture identified 99.6% of the tested samples without cross-reaction with 17 other Neisseria-related species.

Monoclonal antibodies continue to be used in IgM antibody tests: the determination of virus-specific IgM antibodies is often more advantageous for demonstrating fresh virus infections than the measurement of the IgG antibody titer increase (see Section 3.1). The antibodies are used as antihuman-IgM catcher antibodies on the solid phase[47].

Using highly affine monoclonal antibodies, *Wands* et al.[48] improved the determination of hepatitis-B surface antigen (HBsAg) in human sera. *Richman* et al.[49] were able to demonstrate influenza viruses in cell cultures which had been infected with clinical samples from sick patients. With monoclonal antibodies, it should be possible to demonstrate antigen variations on influenza virus molecules; this would be of very great epidemiological interest.

5.2.3. Heterobispecific Antibodies

Heterobispecific antibodies (hybrid antibodies) are characterized by two binding sites, issuing from two different immunoglobulins. These two binding sites can be directed against different epitopes of an antigen, or they can demonstrate similar specificity with different H-chains, due to their being composed of different subclasses. Hybrid antibodies can have very great advantages in immune tests, immunohistochemistry, and immunotherapy.

Until recently hybrid antibodies could only be produced using chemical methods. Disulfide bonds were selectively cleaved by means of careful reduction, and the dissociated half molecules of two different immunoglobulins were then carefully oxidatively coupled.

A new and elegant method was made possible by the hybridoma technique. When cells of two hybridoma clones are fused, the hybrid hybridomas thus created are capable of producing hybrid antibody molecules, the synthesized immunoglobulin chains being determined by the genes of the two fusion partners[5,50]. One use of these techniques for a special immunohistochemical method was described by *Milstein* and *Cuello*[51], who were able to produce a bispecific, antisomatostatin antiperoxidase antibody.

Hybrid antibodies could be used in many ways. For example, they make possible a one-step immunoassay in which the bispecific antibody binds the antigen on the one hand and the indicator molecule (peroxidase, phosphatase) on the other. Heterobispecific antibodies could also have special advantages as immunotoxins (Sections 5.4.2), and antigen-bound toxins could be transported to the target of the second antibody binding site[52]. Further examples for the production of hybrid antibodies by cell fusion were described by *Martinis* et al.[52].

5.2.4. Perspective

By means of the special selection of two or three monoclonal antibodies, which react with closely located antigenic determinants, the absolute epitope specificity of monoclonal antibodies can open up completely new possibilities for immunoanalysis; for instance, on the basis of fluorescence excitation through energy transfer[54]. Two monoclonal antibodies recognizing neighboring epitopes are conjugated with two indicator molecules, rhodamine and fluorescein being used for fluorescence quenching. The use of two enzymes is also conceivable, whereby the first enzyme must produce the substrate for the second.

5.3. Cell Diagnosis

There is no doubt that cell diagnosis is at present undergoing profound changes due to the use of monoclonal antibodies. Access has been gained to biological structures whose presence could only be detected with great difficulty, or not at all, using the classical biochemical and immunological methods. Fig. 7 shows schematically that, for example, it is possible, on the one hand, to discover new structures expressed on the surface of the cell membrane, to demonstrate their presence in a highly specific way, and to characterize them biochemically and, on the other hand, with the relevant number of different antibodies, to inspect and describe anew the surface of a cell. Thus structures can be described which are only expressed in connection with cell activation, cell growth, or cell differentiation. With immune cells, it will soon be possible to characterize and, where necessary, to re-catogorize all the cell populations and subpopulations between the original stem cell in the bone marrow and the final functionally determined immune cells (see Sections 5.3.1 and 5.3.2). With this extremely effective instrument for differentiation of the cell populations of the immune system, we hope to be able to obtain information from which valuable conclusions about the immune reactions may be drawn[55].

Similarly, attempts are now being made to find and characterize specific growth, differentiation, and activation markers on tumor cells, to comprehend their structure and function, and thus perhaps to gain new insights into the formation and spread of tumors and of regulatory and possible counterregulatory mechanisms (see Sections 5.3.3 and 5.3.4).

5.3.1. Methods and Areas of Use

Antibodies bind to surface determinants on cells and in tissues. In order to detect the antibodies, they can be directly labeled, or they can be indirectly labeled by fluorescent dyes or enzyme-labeled second antibody (immunohis-

tochemistry; see Fig. 6–9). Complement-activating monoclonal antibodies are also suitable for complement-mediated cytolytic assays, which play a part as a micromethod in histocompatibility testing (Fig. 7).

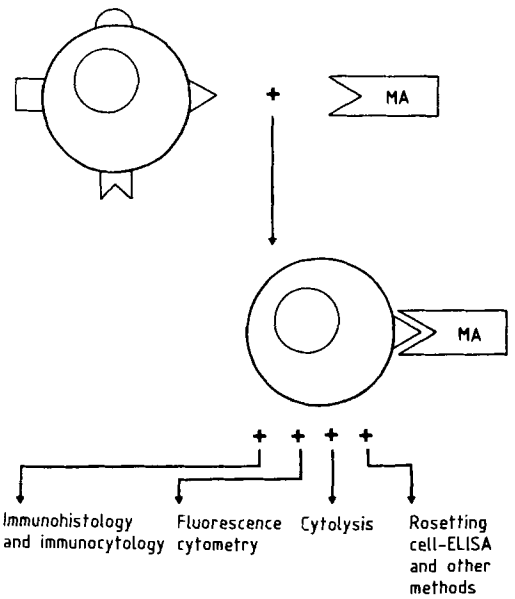


Fig. 7. Schematic representation of methods of testing monoclonal antibodies against cell-bound antigens: a cell, which, in this example, schematically expresses four different antigens on the cell surface, of which (for instance) only one antigen is cell population specific, is recognized by a specific monoclonal antibody (MA) and bound, and can thus be quantified: the antigen as a cell surface determinant thus allows the determination of the number of cells bearing the antigen. The MA is either directly labeled *(direct method)*, or an unlabeled second antibody, in this case an *anti-MA*, binds additionally to the already bound MA *(indirect method)*. Since the MA is usually a mouse IgG, the second antibody is, e.g., a rabbit-anti-mouse IgG. Rosetting means a ring-like adhesion of several erythrocytes around one leukocyte.

For the direct detection of cellular antigens via immunofluorescence, fluorescein- or rhodamine-labeled monoclonal antibodies are used. In indirect immunofluorescence this is achieved by means of labeled second antibodies, which, in the case of monoclonal antibodies, are usually anti-mouse immunoglobulins. Evaluation takes place by counting under a microscope, or, nowadays, with increasing automation, by flow cytofluorimetric analysis.

In immunohistology and immunocytology, monoclonal antibodies are applied to cryostatic sections, cytocentrifuge and smear preparations, and paraffin sections. It is remarkable that all known monoclonal antibodies are suitable for use on cryostatic sections, a number can be used in cytocentrifuge and smear preparations, but only a few are suitable for use on formalin-fixed, paraffin-embedded sections. Rosetting, cell-ELISA, and cell-RIA are very time-consuming and elaborate methods, which cannot yet be recommended as routine procedures (Fig. 7).

Monoclonal antibodies allow the observation of structures in living cells and, at the same time, the recognition of their function in the immune system. This had not been possible before with other methods. With monoclonal antibodies, human lymphoid and myeloid cell populations can also be identified in lymphatic tissues and, after infiltration, in diseased organ regions. For pathology and histology this therefore means a simplified evaluation of histological sections, since judgment no longer has to be made on the basis of morphology and staining alone.

Numerous systemic diseases result from faulty regulation of the immune system or accompany disturbances in cellular immunity. These include primary immune deficiency, acquired immune defects, e.g., "aquired immune deficiency syndrome" (AIDS), autoimmune diseases, leukemias, lymphomas, and infectious diseases. Dysfunctions in the immune system are usually linked to changes in the different lymphocyte populations. Both the activation of the lymphocytes as well as their effector functions can be impaired to the same extent.

The phenotype characterization of thymocytes, bone marrow cells, and peripheral lymphocytes with monoclonal antibodies makes a better definition of these complex disorders now possible for patients with primary immune deficiencies. In immune deficiency and autoimmunities the relationship of T-helper cells (T4) to T-suppressor cells (T8) is often disturbed. In AIDS, for instance, the population of T-helper cells is greatly diminished and, in the case of autoaggressive diseases, often that of the T-suppressor cells.

The diagnostic significance of monoclonal antibodies therefore lies in the field of cell characterization. Cells that had been difficult or impossible to recognize and categorize morphologically can now be found and defined. With T-lymphocyte markers (Table 3), it has become possible to follow the maturation process of T-lymphocytes from the bone marrow to the peripheral blood and to categorize exactly the stages of differentiation. In analogy, it would be very nice to observe the differentiation and growth of tumor cells and other cellular differentiation systems. B-cell markers will gain in significance for hematologists, since a large number of malignant lymphatic disorders in human beings derive from the unregulated proliferation of B-lymphocytes at various stages of development. Cell-surface membrane-bound immunoglobulin has always been, and still is, considered as a marker for mature B-lymphocytes. Early developmental stages of B-lymphocytes in the bone marrow, in which surface immunoglobulin is not yet expressed, can nowadays be identified using monoclonal antibodies. Apart from the B-lymphocytes circulating in the blood, those in the peripheral lymphatic organs, especially in their germinal centers, can be detected. As a result, further differentiation antigens, of especial importance for lymphoma research, have become recognizable (Fig. 8).

Due to hybridoma technology, a completely new picture has emerged, especially for the characterization of myelomonocytic cells. Today, we have at our disposal a large number of monoclonal antibodies against myeloid differentiation antigens. Here, a rough distinction can be made between antibody groups: antibodies that react with granulocytes *and* monocytes, those that react *only* with granulocytes, and those that react *only* with monocytes (see also Table 3).

With monoclonal antibodies, thrombocyte antigens can also be used today in the characterization of immature blasts. Thus it has become possible to identify immature and atypical thrombocyte precursors, which until now could only be recognized using an electron microscope, if at all.

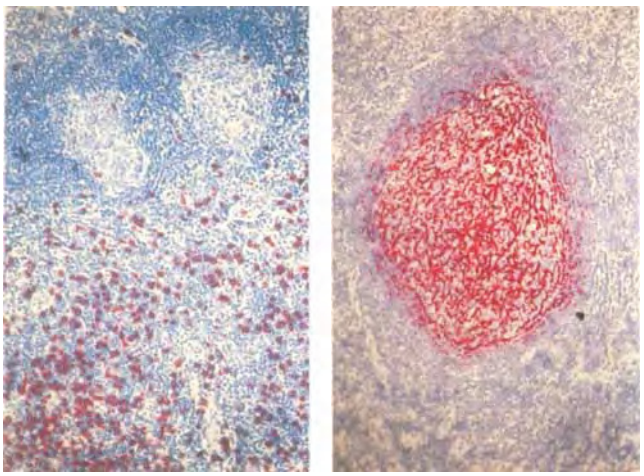


Fig. 8. Alkaline-phosphatase anti-alkaline-phosphatase reaction (APAAP) with a monoclonal anti-alkaline-phosphatase antibody and an unconjugated rabbit-anti-mouse immunoglobulin bridge antibody (red-blue Fast-Red/Haemalaun method). Cryostatic section of a human tonsil: left: T-8-positive suppressor T-lymphocytes in the interfollicular area; right: dendritic reticulum cells in the germinal center of a follicle (enlargement ca. 250 times; preparation: Institute of Pathology, University of Kiel, FRG).

5.3.2. *Lymphocytes and Immunology*

The activation of the immune system as a response to confrontation with a natural immunogen is an extremely complex reaction. Even under in-vitro conditions an effective stimulation of the cellular components of the immune system is only possible when all the parameters necessary for the cascade-like sequence of an immune reaction are considered. On the one hand, the cellular interactions both on the induction and differentiation level and in the effector phase are dependent on the structures coded in the major histocompatibility complex and are thus genetically controlled. On the other hand, essential signals for differentiation of immune reactive cells are only transmitted by various immune mediators[56, 57].

Both the knowledge of the genetic control of cellular immune reactions and the demonstration of the immune factors involved in an immune reaction have enabled some basic immune mechanisms to be explained. A large number of elaborate experimental systems have made possible a definition of the experimental cell populations involved as well as a description of their functions. By the use of the conventional methods of leukocyte differentiation, however, it was normally not possible to attribute functions to individual cells on the basis of cell morphology. Thus the description of lymphocyte populations was limited for T-cells to functional systems (induction of DNA synthesis by the mitogens phytohemagglutinin (PHA) and Conconavalin A, and by antibody-mediated cellular cytotoxicity (ADCC), natural killer cells (NK), and cytotoxic T-lymphocytes (CTL)) or to phenotypical markers. The determination of the extent of B-lymphocyte differentiation was analogously based on the interaction with various activators (e.g., lipopolysaccharide (LPS), pokeweed mitogen (PWM), *Staphylococcus aureus*, Convan I (SAC)) and the demonstration of cytoplasmatic or cell-surface-bound immunoglobulin. However, not until the relevant monoclonal antibodies were available was it possible to clarify the relationship between a phenotype of a lymphocyte and its function[58-60]. In the meantime it has often been shown that the antigen recognized by the monoclonal antibody is not only a marker structure for the relevant function of the cell, but that it itself is involved in the cell function (e.g., as a receptor)[61-64].

In order that monoclonal antibodies, which can be used to differentiate human leukocytes, may be internationally compared, the *First International Workshop for Human Leukocyte Differentiation Antigens* in Paris in 1982 undertook to assign monoclonal antibodies to characteristic differentiation antigens[65]. The subsequent congress in Boston in 1984 continued the work of characterizing the various stages of differentiation with monoclonal antibodies, and produced newly formulated *differentiation clusters* (Table 3).

The specificity of an antileukocyte antibody, and thus its belonging to defined *clusters*, only considers in part the de-

Table 3. Monoclonal antibodies for classification of human leukocytes [a, b].

Cluster of Differentiation (CD)	Cell Type and Antigen	Characterized Cell Population	Selected antibodies with cluster-defined specificity
CD 1	Thy, p45-12 [c]	cortical thymocytes	T6; M241; SK9/Leu 6
CD 2	T, p50	E-rosette-forming T-lymphocytes	T11; 9.6; S2/Leu 56
CD 3	T, p19-29	mature T-lymphocytes	T3, BW 264/56 (BMA 030); SK7/Leu 4
CD 4	T, p55	T-cell subpopulation; predominantly T-helper lymphocytes	T4; BW 264/123 (BMA 041); MT321 (BMA 040)
CD 5	T, p67	Pan T-lymphocytes; B-cell subpopulation	T1; T101; UCHT2
CD 6	T, p120	mature T-lymphocytes; B-cell subpopulation	T12.1; T411; 12.1.5
CD 7	T, p41	Pan T-lymphocytes	3A1A; 4A; 4H9/Leu 9
CD 8	T, p32-33	predominantly T-suppressor cells and cytotoxic T-lymphocytes	T8; BW 135/80 (BMA 081); UCHT4
CD 9	nT-nB, p24	Monocytes	BA2
CD 10	nT-nB, p100	Pre-B-cells, polymorphonuclear cells (CALLA)	J5; VIL-A1
CD 11	M, G	Monocytes, granulocytes; some bone marrow cells	Ki-M5 (BMA 0350); VIM-12
CD 15	G	Granulocytes	VIM-C6 (BMA 0200)
CD 16	G, NK	Granulocytes, NK-cells (Fc receptor)	BW 243/41; VEP13 (BMA 070); BW 209/2
CD 25	T	activated T-lymphocytes	TAC; T1A

[a] Modified according to [65]; partially supplemented: results of the 2nd Int. Workshop and Conference on Human Leukocyte Differentiation Antigens, Boston 1984. [b] Abbreviations: Thy = thymocytes; T = T-lymphocytes; nT-nB = nonT-nonB cells; M = monocytes, macrophages; G = granulocytes; NK = natural killer cells, p = protein. Abbreviations in the last column represent the original, individual nomenclature of laboratories, institutes, or firms, which is still in use and to be found in the literature. All the clones listed were selected and catalogued by the workshop committee. [c] Molecular weight in kDa.

mands made upon monoclonal antibodies for therapeutic purposes (see Section 5.4.3).

Monoclonal antibodies that bind to the T3 complex have been described as activating T-lymphocytes[66] if they are also able to bind to the Fc receptors of *monocytes*[67-69]. However, we were able to isolate four monoclonal antibodies against the T3 complex, of which only the antibodies BW 264/56 (CD3b) and BW 242/55 (CD3a) are capable of activating human T-cells, whereas BW 239/347 (CD3b) and BW 242/412 are not able to do so (Table 4). The specificity of these antibodies was determined with isolated cell populations, using double labeling and comodulation experiments and by means of competitive binding tests. T-cell activation leads to modulation of the T3 complex, induction of DNA synthesis, release of immune mediators such as interleukin-2 and γ-interferon, and to IgM synthesis in vitro (Table 4). All test systems showed that only the binding of anti-T3 antibodies of the isotypes IgG2a and IgG3 led to a T-cell activation, whereas the corresponding antibodies of the isotype IgG2b were not able to induce a T-cell activation[70].

Table 4. The activation of T-lymphocytes by monoclonal CD3 antibodies [a].

Antibody [b]	Isotype	Mitogenicity		Induction of IgM Synthesis		Modulation of the T3-Antigen	
		R	NR	R	NR	R	NR
Leu 4	IgG 1	+	−	+	−	+	−
BW 264/56	IgG 2a	+	+	+	+	+	+
OKT3	IgG 2a	+	+	+	+	+	+
BW 239/347	IgG 2b	−	−	−	−	−	−
BW 242/412	IgG 2b	−	−	−	−	−	−
BW 242/55	IgG 3	+	+	+	+	+	+

[a] Peripheral blood lymphocytes of healthy blood donors are classified as reactive (R) or non-reactive (NR) according to their reactivity with CD3 antibodies (anti-T3) of subclass IgG 1 [146]. [b] BW: Behring-Werke; Leu4: Becton Dickinson; OKT3: Ortho.

Thus, during the therapeutic use of monoclonal mouse antibodies, Fc-mediated immune reactions also have to be considered. When using monoclonal antibodies of the cluster type CD3, which activate T-cells, these reactions must at least be taken into consideration if the monoclonal antibodies are to be used for immune suppression (e.g., in organ and bone marrow transplantation) (see Section 5.4.3).

5.3.3. Leukemias and Lymphomas

Comparative phenotype characterization of normal and malignant cells of the hemotopoietic system with the aid of monoclonal antibodies is a decisive step forward in the search for the cellular origin of lymphatic diseases and their classification and thus also signifies a step forward for prognosis and therapy. Malignant lymphatic diseases are due to an uncontrolled expansion of a neoplastic lymphatic cell clone which has remained at a certain stage during its maturation process. The cells of such a clone express the surface markers of the corresponding normal cell type, and can therefore be easily identified with monoclonal antibodies. Only rarely do additional markers of foreign cell lines appear.

Acute lymphatic leukemias (ALL) are divided, according to the differentiation state of the cell types involved, into five main groups: 1. undifferentiated ALL, 2. common ALL (cALL), 3. pre-B-ALL, 4. B-ALL, and 5. T-ALL. 60–70% of all cases of ALL can be attributed to *Common ALL*. Using monoclonal antibodies (the best known presently seems to be VIL-Al), a differentiation antigen with a molecular weight of about 100 kDa has been demonstrated on the membrane of the blasts of this form of leukemia. This was first called the *Common Acute Lymphatic Leukemia Antigen* (CALLA) in 1975 (Table 3). This is not leukemia specific, but a normal differentiation antigen which can also be found on normal bone marrow lymphocytes.

No CALLA is expressed in undifferentiated ALL; the cells of pre-B-cell leukemia are characterized by the demonstration of intracytoplasmatic immunoglobulin chains (μ-chains). Acute leukemias of the B-cell type are rare (1—5%). B-lymphocyte antigens, the same as those found on mature B-cells, are found on the blasts along with additional cell-surface membrane-bound immunoglobulin, mostly of the IgM isotype.

With about 20%, T-ALL is the second largest group of acute lymphatic leukemias. By the use of monoclonal antibodies, typical markers of T-cell differentiation can be found on the blasts of this form of leukemia, such as the T-11 antigen, the E-receptor, or in the case of the corticothymocytic form, the normal cortical thymocyte marker, T6. In addition, the markers T9 (transferrin receptor) and T10 (hemopoietic precursor cell) can be demonstrated.

Chronic lymphocytic leukemias (CLL) result from the malignant proliferation of B-lymphocytes that have been held up in their further development. Only 5% of all CLL cases derive from the peripheral T-cell compartment; they bear the markers T3, T10, and either T4 or T8.

The so-called Non-Hodgkin Lymphomas can be divided according to their surface makers into a heterogeneous group of lymphoblastic lymphomas, which express thymus antigens, or, for example in the Burkitt lymphoma, they clearly belong to the B-cell type with cell surface IgM and an Epstein-Barr-Virus-specific membrane antigen. T-lymphomas of the skin and the Sezary syndrome are due to the malignant proliferation of helper T-lymphocytes (T4).

Myeloid leukemias are judged according to morphological criteria. An intensive search is still going on for monoclonal antibodies able to recognize immature myeloblasts. At present it is still necessary to work with a combination of antibodies, e.g., the antibodies VIM C6 and VIM 2, with which all myeloid leukemias can be detected. The antibodies VIM C6 and VIM D2 can already be used today to differentiate between the monocytic and granulocytic forms of leukemia (see Table 3).

5.3.4. Immune Histochemistry and Solid Tumors

The histological diagnosis of tumors from solid tissues is largely dependent on the pathologist's interpretation of tissue sections. Discrepancies arise between various observers, when using conventional histomorphological methods

for classification, if only little biopsy material is available. However, in routine examinations, too, especially in the case of lung carcinomas of different histology, questionable interpretations are possible[71]; in such cases, markers enabling a differentiation between adenocarcinomas of the lung and mesotheliomas could be of great help[72].

Reagents for classifying metastases, which derive from undiscovered primary carcinomas, sarcomas, or melanomas of different origins, would make the choice of an adequate patient-specific therapy easier[73]. A precondition for the development of such reagents is the selective distribution of antigens or antigenic determinants (epitopes) on those tissue types to be differentiated. Monoclonal antibodies are ideal reagents for the immune histochemical demonstration of marker epitopes if they react with structures that are very strongly expressed on certain tumor types but not at all, or only to a small extent, on others.

The indirect immunoperoxidase method[74] and the avidin-biotin peroxidase method[75] are the most frequently employed techniques for judging the tissue distribution of epitopes that are defined by monoclonal antibodies. Especially when working with formalin-fixed tissue sections, these techniques have resulted in a very precise histochemical staining reaction in a well-preserved tissue structure. The distribution of the dye enables the determination of qualitative differences in reactivity within defined compartments of the tissue sections, e.g., in tumor cell regions, stroma components, or non-malignant structures.

The method allows the fine specificity of monoclonal antibodies to be tested on all available human tissues, since undesired reactivities are revealed. Extensive specificity analyses have so far only been carried out with a small number of monoclonal antibodies that recognize formalin-resistant epitopes[76–80]. With such antibodies, indirect immunoperoxidase tests on formalin-fixed, paraffin-embedded tissues, can be carried out. One example is shown in Figure 9, in which the monoclonal antibody BMA 130b (Behring Diagnostics) reacts with a pancreas carcinoma (brown staining in the region of the tumor cells), but not at all with the tissue of a chronic pancreatitis. Monoclonal antibodies that recognize formalin-sensitive epitopes cannot be tested in the same way, since fresh or frozen human tissue is only available to a limited extent[81–83].

The majority of the presently existing monoclonal antibodies, raised and selected using cell lines, bind to formalin-sensitive epitopes, which means that fine specificity analysis can hardly be carried out on many human tissues[84–87]. These antibodies are especially suited for finding out the physiological functions of cell surface antigens; e.g., the receptors for growth factors, for hormones, and for attachment factors[88–90]. Similarly, antigen distribution on cell surface membranes or the heterogeneity of cell populations can be examined[91–93].

Together with macrophages and killer cells, monoclonal antibodies of different isotypes, which recognize glycoproteins or glycolipid molecules on tumor cell surface membranes are able to lyse target cells to very different extents[94,95]. Monoclonal antibodies coupled with isotopes, toxins, cytostatic drugs, or immunogenic molecules, will probably play an important role in the in-vivo demonstration and therapy of tumor illnesses (see Section 5.4.1 and 5.4.2).

5.4. Medical Uses

5.4.1. Tumor Localization: Radioimmunoscintigraphy of Tumors

For several decades attempts have been made, more or less unsuccessfully, to incorporate scintigraphical methods into the in-vivo diagnosis of malignant tumors. Gamma-emitting substances are administered to the patient intravenously, in the hope that these will be transported in the blood stream to the tumor, will accumulate there, and will be detectable with a radiation detector. Elaborate techniques, using so-called gamma-cameras, are available for this radiation detection.

Pressman first had the idea of using the specificity of antibodies for in-vivo accumulation of radioactivity in the relevant tumors. He found that the antibody molecule can be labeled with radioactive iodine without losing its binding capacity[96] and that, after "radio-iodine labeling" and in-vivo application, the antibodies directed against individual organs accumulated in the relevant organs, for instance, in the kidneys[97]. The way seemed open for the evaluation of this principle for tumor detection. An obsta-

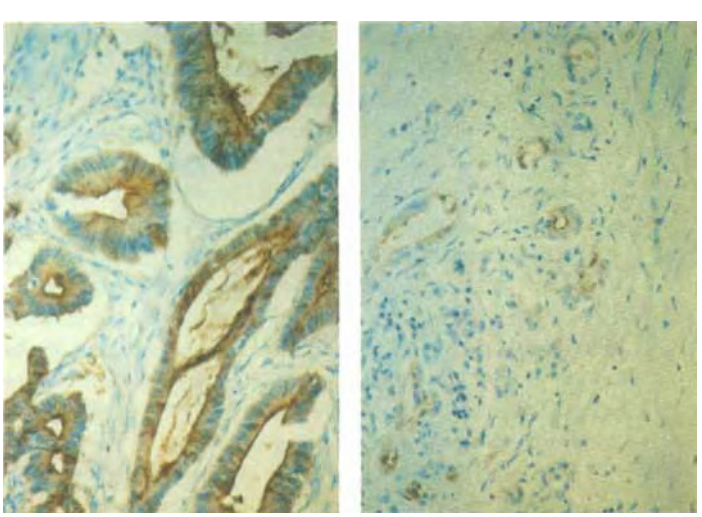


Fig. 9. Left: Indirect immune peroxidase staining of formalin-fixed, paraffin-embedded tissue sections from a pancreatic carcinoma. The brown staining shows the reaction with the tumor cell areas. Right: No reaction with the tissue from a chronic pancreatitis. Slight counter staining with hematoxilin (enlargement ca. 250 times).

cle was raised, however, by the then insurmountable problem of nonspecific binding of antibodies to tissue not belonging to the tumor. Moreover, accumulation was mainly due not to the tumor antigens but to fibrin, which had been increasingly deposited in the tumor region owing to the inflammatory processes taking place there. This observation gave rise to the idea of using specific antifibrin antibodies[98], which, however, did not provide the hoped for breakthrough in tumor imaging.

It was clear, even then, that one of the most important conditions for successful immunoscintigraphy is the purity of the antibody used. Until then, however, only hyperimmune sera had been available, whose immunoglobulin fraction always contained, at most, 1% of the specific antibody, even after separation from the other serum proteins.

An important step forward was made with the use of antibodies against a series of so-called tumor-associated antigens. These proteins are frequently produced in large quantities by certain types of tumors and released into the blood, where they can be detected by means of sensitive diagnostic methods[119]. They can be isolated from blood serum or tumor tissue and then used in affinity chromatography for the purification of the relevant antibodies from xenogenic immune sera.

Table 5. Heteroclonal antibodies (purified by affinity chromatography) already used in clinical studies for radioimmunodetection of solid human tumors.

Antigen	Site of Tumor	Number of Cases (positive/total)	Ref.
Carcinoembryonal antigen (CEA)	Colon	1/2	[99]
	Breast	3/23	
	Medullar thyroid gland	0/5	
	Colon, rectum; also lung, larynx, medullar thyroid gland	28/31	[100]
	Colon, rectum, pancreas various other organs	22/53	[101]
	Colon, rectum	35/41	[102]
	Ovary	21/24	
	Lung	12/17	
	Pancreas	4/8	
	Breast	9/14	
	Uterus	28/31	
	Stomach	5/6	
	Various other organs	25/39	
	Colon, rectum (primary)	10/12	[103]
	Colon, rectum (metastases)	49/53	
	Colon, rectum (primary)	4/5	[104]
	Colon, rectum (metastases)	8/11	
Human chorionogonadotropin (HCG)	Lung, pelvis, abdomen (Chorion Carcinoma)	9/14	[105]
	Brain, lung, abdomen (Teratoma)	3/7	
α-Fetoprotein (AFP)	Testes (Teratoma)	8/12	[106]

The most important systematic investigations of this kind (antigens, tumors, findings) are shown in Table 5. This summary clearly shows that not all the research groups obtained results as convincing as those of *Goldenberg*[102, 103]. One objection to the carcinoembryonic antigen (CEA), which is mentioned most frequently here, is that it cross-reacts with a number of similar proteins which are widespread in the organism, so that the condition of tumor specificity is only unsatisfactorily fulfilled.

Monoclonal antibodies should play the decisive role in solving the specificity problem; moreover, their many qualitative advantages may allow the standardization and use of radioimmunodetection on a wide scale. Unfortunately, the tumor antigens known to date can, at best, be called tumor-associated, since they can also be found in smaller quantities in normal tissue.

Table 6. Monoclonal antibodies already used in clinical studies for radioimmunodetection of solid human tumors.

Antibody	Antigen	Tumor Type	Number of Cases (positives/total)	Ref.
17-1A	Colon carcinoma cell line	Colon carcinoma	3/9	[107]
			31/59	[108]
			22/38	[109]
19-9	Monosialoganglioside	Colon carcinoma	10/13	[107]
791T/36	Osteosarcoma cell line	Colon carcinoma	8/11	[110]
		Rectum carcinoma	5/12	
LICR-LON-M8	Membrane of milk fat globules	Breast carcinoma	11/14	[111]
Anti-p97	p97 (cell membrane antigen of melanoma)	Melanoma	22/25	[112]
MAb VII 23	Carcinoembryonal antigen	Colon carcinoma	14/28	[113]
MAb 35, $[F(ab')_2]$	Carcinoembryonal antigen	Colon carcinoma	18/24	[114]
HMFG1 HMFG2	Membrane of milk fat globules	Ovarial carcinoma	11/12	[115]
		Colon carcinoma	4/6	
		Ovarial carcinoma	35/40	[116]

Table 6 shows that, under clinical conditions, it has so far been possible to use only a few monoclonal antibodies on a limited number of tumor types (with varying degrees of success). Far more experience has been gathered, however, with animal models, using, in most cases, xenogenic tumor transplants on athymic nude mice[117]. This test regimen is considered an important preclinical test system, even though, for several reasons, it makes the in-vivo behavior of antibodies often appear in a more favorable light than is the case in human beings.

Antibody binding in the transplanted tumor (xenograft) is judged using either external scintigraphy with the gamma-camera or by calculation of the localization indices (L. I.)[118], as the examples in Fig. 10 and 11 show[79]. Figure 10 shows the time-dependent accumulation of radioactivity in the tumor and the simultaneous decrease in the central region of the mouse quite clearly. Fig. 11 shows increased L. I. values and thus specific antibody accumulation in the tumor alone. This procedure utilizes the double labeling method first described by *Pressman* et al.[120] for the in-vivo determination of tumor-imaging antibodies.

There is no clear answer to the question as to how large a tumor has to be before it can be discovered with the aid

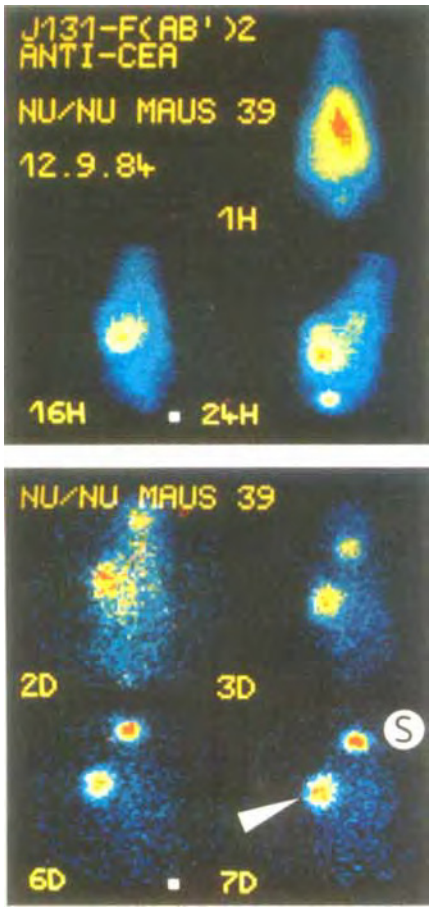


Fig. 10. Radioimmunoscintigram of a nude mouse with a colon-carcinoma xenograft on the left side (white arrow); monoclonal antibody BW 431 ($F(ab')_2$ fragment of a monoclonal antibody against carcinoembryonal antigen) radioactively labeled with ^{131}I; gamma-camera pictures after 1 h, 24 h, 2 d, 3 d, 6 d, and 7 d. The thyroid gland of the animal (S) was not blocked, thus radioactivity could also accumulate there. (Pictures by *A. Schwarz* et al., Hoechst AG.)

of radioimmunoscintigraphy, owing to the numerous influencing parameters. Even for monoclonal antibodies, the sensitivity limit in human beings, under favorable conditions, is a minimum diameter of about 1 cm, or a minimum

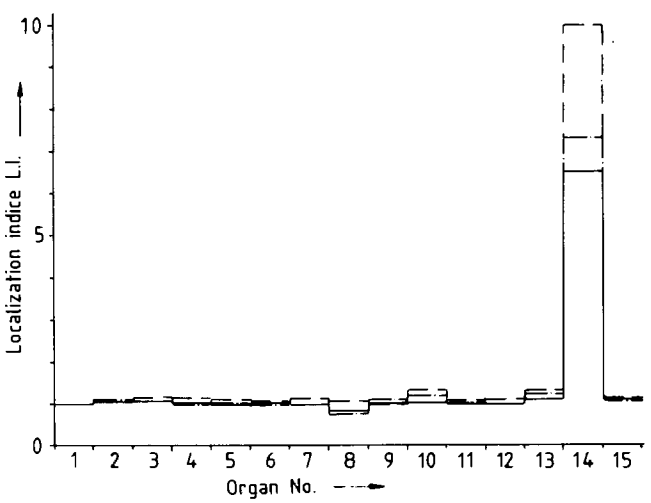


Fig. 11. Accumulation of the monoclonal antibody BW 431 in a colon-carcinoma-bearing nude mouse after 3 d (three animals: ––, -·-, and —). L.I. > 1 means specific accumulation of the monoclonal antibody. Organs: blood (1), bladder (2), heart (3), intestine (4), kidneys (5, 6), liver (7), spleen (8), lung (9), thyroid gland (10), head (11), muscles (12), stomach (13), tumor (14), the rest of the body (15).

mass of 0.1 g[121]. In animal models, however, tumor diameters of 1 mm have been reported[122].

The results of scintigraphy are strongly dependent on the relationship of radioactive absorption in the tumor to that in the surrounding tissue. Substraction procedures, in which other chemical substances are used to label the blood pool (e.g., ^{99m}Tc-human serum albumin) or to represent the nonspecific absorption in the reticulo-endothelial system (e.g., ^{99m}Tc-colloidal sulphur), often lead to false-positive results[99]. If this principle is to be used at all, a nonspecific antibody preparation should be employed as a control and be labeled with a radioisotope of the same chemical element according to the same method[120]. The consideration that Fc-mediated binding to Fc receptors of the cellular immune system could be partly responsible for nonspecificity led to the use of the antibody fragments $F(ab')_2$ and Fab instead of the complete molecule. These have the advantage that they are much quicker than the complete molecule to leave the circulation, penetrate into the tissue, and be excreted via the kidneys; the background activity in the blood dies down more quickly (clearance) and the tumor therefore emerges more rapidly from the background. It seems at present unclear which of the two fragments should be given preference. On account of its quick and direct clearance, Fab seems to be responsible for an increased background radiation in the region of the kidneys[123]; however, reports have appeared on disturbing radioactivity accumulation in the kidneys and bladder with $F(ab')_2$, which is also metabolized more rapidly than complete IgG. The relative position of the tumor, of course, determines whether these effects impair tumor imaging. Nevertheless, tomographic visualization techniques can provide more clarity in this respect than simple scintigraphy.

In order to obtain optimal scintigrams, as many labeled antibody molecules as possible must reach the tumor and bind to the tumor cells. Therefore, vascularization of tumor tissue and antigen density on the cells are of great importance for the extent of antibody binding. Whereas it is hardly possible to influence vascularization, it is possible, in the case of an insufficient antigen density on the cell surface, to use several antibody types directed against different epitopes instead of one antibody. This procedure is also advantageous, since the antigen structure of tumor cell membranes not only varies from one patient to another, but also in one and the same patient depending on localization and clonal differentiation[109]. There is little scope for increasing the accumulation of radioactivity in the target tissue by means of a higher degree of antibody labeling. Higher labeling means a greater risk of damage to the antibody and a greater tendency to nonspecific binding and accelerated excretion due to metabolism. Here, often on account of their uniform structure, monoclonal antibodies are at a greater risk than heteroclonal ones.

Without going into the details concerning scintigraphy at this point, suffice it to say that the presently used gamma-cameras are not optimal for the most frequently employed radionuclide, ^{131}I (γ: 0.36 MeV, $t_{1/2}=8.0$ d). ^{123}I, with a gamma-emission of mainly 1.60 MeV, seems better suited; however, its short half-life often creates delivery problems. Short half-lives are still generally of interest, due to the lower level of radiation for the patient. However,

with radioimmunoscintigraphy, the fact that useful tumor/background relationships are generally only available after a period of two days must be taken into consideration, unless, as described above, Fab or $F(ab')_2$ fragments are used. For this reason there is little use for ^{99m}Tc (γ: 0.14 MeV, $t_{1/2}=6.1$ h), which was almost always used in classical organ imaging. More success can thus be expected with complex-forming radionuclides, such as ^{111}In (γ: 0.17, 0.25 MeV, $t_{1/2}=2.8$ d) or ^{67}Ga (γ: 0.09, 0.18, 0.30, 0.39 MeV, $t_{1/2}=3.3$ d), even though they have to be bound via a chelating agent, such as diethylenetriaminepentaacetic acid (DTPA), to the antibody molecule. It has already been shown how useful ^{111}In, in particular, is for the radioimmunoscintigraphy of tumors[100], although this radionuclide can often lead to problems of nonspecific accumulation in the liver, spleen, and kidneys.

In the course of the few years in which monoclonal antibodies have been available, they have proved their suitability for radioimmunodetection and have shown themselves to be at least as good as other competing detection methods, including X-ray computer tomography. In the near future we can expect important, if not spectacular breakthroughs, due to the finding of new antibody specificities, the testing of available antibodies with regard to their specificity and avidity (stronger antigen-antibody binding), the continuing standardization of antibody fragments, and the improvements in the adjustment of measuring techniques to the radiation properties of the radionuclides. This development will be followed by the first therapeutic applications with radioactively labeled antibodies (radioimmunotherapy), as is already being done in a few centers[124]. Moreover, localization experiments provide useful indications for the later use of immunotoxins or immunocytostatic drugs (see next section).

5.4.2. *Immunotoxins: Preparative Problems and Possible Uses*

The terms immunotoxins and, in certain cases, antibody-drug conjugates refer to cytotoxic agents[125–128] which, via a specific antibody binding site, are intended to reach specifically their target cell, for example, a tumor cell. There the toxic agent should interfere in the cell metabolism and cause its death.

Various problems, several of which are dealt with in part below, have to be solved during the preparation of such conjugates. First, a high-affinity antibody of the required specificity, in its pure and native form, has to be isolated (Table 7). Monoclonal immunoglobulins, mainly from the mouse at present, are an obvious choice. A later in-vivo use in human beings can therefore lead to problems of antigenicity.

Table 7. Immunotoxins: problems connected with the antibody.

Problem	possible solution
Specificity/affinity	monoclonal antibodies
Purity/nativity	special fractionation
Antigenicity	human monoclonal antibodies
Pharmacokinetics Enzymatic cleavage Chemical modifications	selection of suitable class or subclass

The question also arises as to which immunoglobulin class or subclass is especially suitable; for this choice also determines which biological and Fc-mediated activities the antibody will be able to perform (see Section 3.2) and which chemical modifications can be used. The problems arising in the use of enzyme cleavage for the production of certain antibody fragments and in their isolation have been discussed in Section 4.2.

In the selection of toxic compounds, a choice can be made between different working principles (Table 8). Various toxins, cytostatic drugs, or radionuclides are available. The toxins, such as ricin, abrin, or diphtheria toxin, are proteins that can inhibit protein synthesis. In these toxins two functionally differing molecular moieties can be distinguished: one containing the toxic activity (A-chain or A-fragment) and one on which the binding site for cell surface receptors is found (B-chain or B-fragment). In order, therefore, to avoid undesired interaction with cells other than those of the target tissue (target cells), either the B-chain (B-fragment) has to be removed from the complete molecule prior to binding the A-chain to the antibody or antibody fragment, or the relevant binding site for carbohydrates on the B-chain has to be inactivated or blocked. In general, toxin-antibody conjugates are quite useful for the case of low antigen density on the target cell since even a few toxin molecules can cause cell death.

Table 8. Immunotoxins: problems related to the toxic component.

Problem	possible solution
Selection of adequate toxic principle (toxin, cytostatic, radionuclide, etc.)	estimation of antigen density on the target cell surface
Undesired interactions	modification of toxic components
Low amount of toxic agent at the target site	carrier molecule

On the other hand, low molecular weight cytostatic drugs, such as adriamycin, which belongs to the group of anthracyclines, daunomycin, and methotrexate, can be used; these are compounds which can inhibit cell division. These cytostatic agents can, in principle, be directly linked to an antibody molecule. Since relatively large amounts are required, in comparison to toxins, to destroy a cell, a large number of toxic molecules are bound to the antibody; in general, however, this lowers the specific binding activity of immunoglobulin[127]. For this reason the use of carrier molecules is often considered; *one* carrier molecule is loaded with cytostatic drugs and then linked to *one* antibody molecule.

The problems confronting the biochemist (Table 9) when he couples the antibody (i.e., specific binding principle or the targeting unit) with the toxin (the toxic principle) to form a conjugate are summarized in Table 9. The linking strategy has to be selected in such a way that the activities of the two components are as little impaired as possible. The linking method and the spacer must be so chosen that stable conjugates are formed reproducibly and in good yield. These conjugates normally then have to be sep-

arated from excess starting components in a purification step. Otherwise there is a danger that the free antibody molecules not linked with a cytotoxic agent will compete in the later reaction and thus decrease the effectiveness of the conjugates. Moreover, in order for the toxic principle to be effective, it is especially important that the bond between antibody and toxin can be cleaved in the phagosome after endocytosis has taken place[129-131].

Table 9. Immunotoxins: problems associated with the synthesis of conjugates of antibodies with the toxic agent.

Problem	possible solution
Activity/stability Reproducible production Yield In-vivo cleavage of the conjugate bonds	selection of suitable coupling methods
Formation of homopolymers	heterobifunctional reagents
Pluridirectional bindings (statistical)	selection of specific binding sites
Antigenicity/solubility	selection of suitable coupling *principle*

Special problems arise, if, as in the case of toxin-antibody linkage, two proteins are to be linked (Fig. 12). Due to the more or less statistical distribution of the groups that are often used for linkage reactions (ε-amino group of lysine, carboxyl group of glutamic or aspartic acid), and their differing levels of reactivity, conjugate formation takes place at various sites on the molecule, including those located in the vicinity of the antibody binding site. This can result in inactivation of this site.

Heterobifunctional linkage reagents are preferred in all cases, since they help to prevent the formation of homopolymers, that is to say antibody-antibody and toxin-toxin conjugates. The level of substitution obtained is merely an average value. Thus there are both more and less substituted fragments, of which the more highly substituted have a better chance of taking part in the reaction. In many cases the specific antibody reactivity is lower for higher levels of substitution. This example also shows quite clearly that surplus unreacted groups may remain in the conjugates and thus create additional problems for the subsequent application.

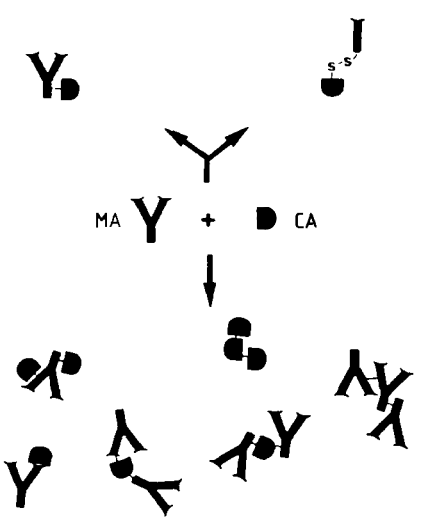


Fig. 12. Problems that can arise in the coupling of monoclonal antibodies (MA) to cytotoxic agents (CA) are shown in the lower half of the picture: Homopolymers can form or the antibody binding site can be blocked. Sought are conjugates via groups [e.g., the carbohydrate moiety in the Fc area (top left) or the SH groups of former inter-H-chain disulfide bonds in the Fab' fragment (top right)] that do not cause any impairment of the antibody binding site.

Thus the ideal methods of conjugate formation would be those using groups that, on account of their position in the molecule, do not result in impairment of the antibody binding site. The carbohydrate moiety, mainly found in the Fc domain of the molecule, or the SH groups of the former inter-H-chain disulfide bonds present mainly in the Fab' fragment fulfill these requirements. In this way SH groups can be converted into activated disulfide bonds with various reagents. These are then able to form the desired conjugate with the SH group of a ricin A-chain.

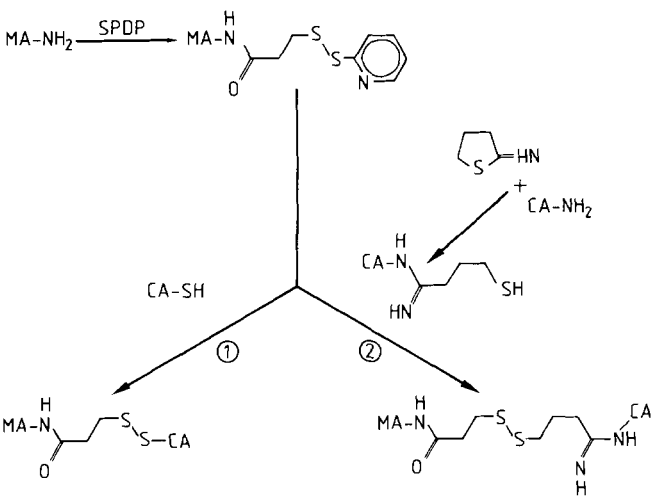


Fig. 13. Synthesis of conjugates from monoclonal antibodies (MA) and cytotoxic agents (CA): activated disulfide bonds can be introduced into monoclonal antibodies with the heterobifunctional reagent *N*-succinimidyl-3-(2-pyridyldithio)propionate (*SPDP*). The reaction leading to the desired coupling product takes place via SH groups that are either already present in the cytotoxic agent (reaction pathway ①) or have to be introduced (e.g., with iminothiolane; reaction pathway ②).

However, many methods cannot be employed on account of either the high losses during production of the Fab' fragments or the poor yields during the linking reaction. The possibility remains of introducing activated disulfide bonds via the amino groups of uncleaved immunoglobulin with the aid of special reagents (SPDP, etc.). These can then be similarly used for the synthesis of conjugates (Fig. 13). Thus, from a pragmatic point of view, compromises must always be sought.

Fig. 14 shows the dose-dependent effect of a ricin-antibody conjugate in an in-vitro cell system, in which protein synthesis was measured quantitatively via ^{14}C-leucine incorporation. Since the complete toxin molecule and not the ricin A-chain was coupled to the monoclonal antibody in this experiment, the nonspecific binding site on the B-chain for the ubiquitously appearing carbohydrate cell surface structures with terminal galactose had to be blocked by the addition of lactose (0.1 mol/L). The reactive immunotoxin has an effect comparable to that of free ricin,

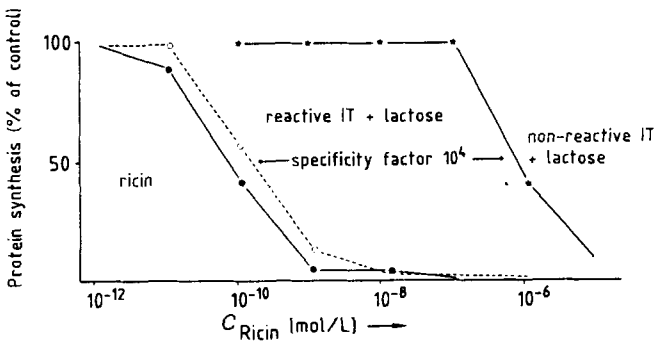


Fig. 14. The dose-dependent effect on protein synthesis in an in-vitro cell system of ricin-antibody conjugates. The immunotoxins (IT) were tested in the presence of 0.1 mol/L lactose in order to suppress nonspecific cell binding by ricin B-chain (for further information see text).

whereas an analogous conjugate with a non-reactive monoclonal antibody is less toxic by about four orders of magnitude *(specificity factor)*.

It is clear that, due to the lack of detailed knowledge, an empirical approach is still required in each individual case. The problems are still graver for the in-vivo use of antibody-linked cytotoxic agents. As is shown schematically in Fig. 15, it is expected that, in this case, the conjugate reacts first with a membrane-bound antigen on the target cell[132]. The correct antibody specificity on the one hand and the antigen stability on the other guarantee that the antigen-antibody complex forming on the cell surface is not only cleaved, but also taken into the cell via endocytosis. The cytotoxic principle will be subsequently released in the phagosome in order to inhibit finally protein synthesis or DNA replication. In tumor therapy this blockage must be able to inactivate and destroy more than 99.99% of the target cells in order to be effective[133, 134]. Variability in the target antigen, such as in primary tumors and metastases, reduces the effectiveness. Mechanisms that enable the nonspecific absorption of agents into non-target cells can lead to undesired side effects with all their negative consequences. The use of the relatively small monovalent antibody fragments with their shorter half-lives, even in the conjugate, will most likely be advantageous.

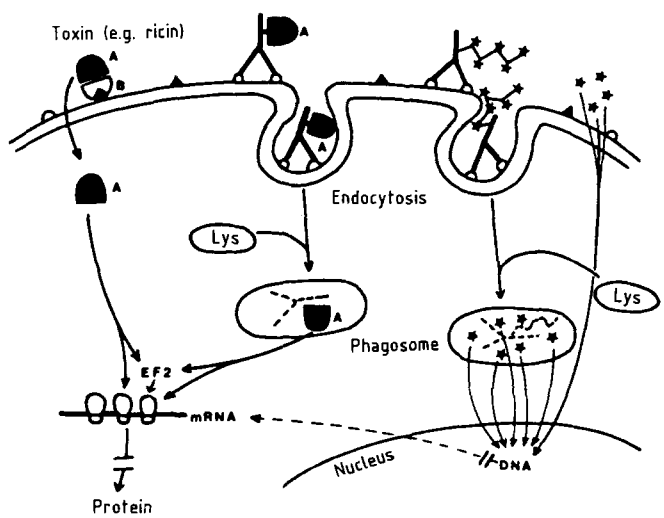


Fig. 15. Schematic representation of actual in-vivo mechanisms of immunotoxins and cytotoxic agents (for further information see text). ▲ = Receptor, ▭ = cell antigen, ✱ = cytostatic agent, EF = elongation factor, Lys = lysosome.

5.4.3. *Transplantation*

During the therapeutic use of mouse monoclonal antibodies, Fc-mediated immune reactions must be considered (see Sections 3.2 and 5.3.2). These also have to be considered when using CD3 monoclonal antibodies with T-cell-activating properties if such monoclonal antibodies are used for immune suppression (organ transplantation and bone marrow transplantation). At present clinical experience is available for only one type of T-cell-activating antibody (OKT3) with CD3 specificity. This antibody was principally used for treating kidney transplant patients, both prophylactically and, during acute rejection crises, therapeutically[135-137]. In allogenic bone-marrow transplantation, OKT3 was used to prevent "graft versus host" (GvH) reactions, both in vitro for the elimination of immune reactive T-cells and in vivo for the treatment of acute GvH reactions[138, 139]. Whereas an overwhelmingly positive therapeutic effect could be achieved with OKT3 for organ transplantation and allogenic bone-marrow transplantation in leukemia pateints, an in-vitro/in-vivo treatment with OKT3 in severe combined immune deficiencies (SCID) was not able to prevent GvH reactions[140].

Monoclonal antibodies with other specificities than that of CD3 have also been used in both organ transplantation and allogenic bone-marrow transplantation. The individual considerations and experiments underlying the choice of each monoclonal antibody cannot be discussed in detail here; however, some general examples will be given. Campath 1, a monoclonal rat antibody of the IgM class with wide reactivity on mononuclear cells, has been used in allogenic bone-marrow transplantation; it was chosen on account of its ability to effectively lyse target cells with the aid of human complement[141]. Mixtures of several antibodies are often preferred to avoid *escape* mechanisms and for a more exact definition of target cell populations. In this case either cell elimination takes place via complement-mediated cytolysis or the antibodies act directly as immunotoxins[142, 143].

For organ transplantation, the immune reactive T-lymphocyte, the target cell, is hit with an anti-T12-antibody, as was the case for OKT3[144]. A different target cell population is the basis of therapy with CBL1. This antibody could be capable of eliminating the B-lymphoblast clones activated during a transplant rejection reaction[145].

5.4.4. *Human Hybridomas*

Compared with conventional antisera, monoclonal antibodies of mouse origin have the decisive advantage of monospecificity. When judging their therapeutic value, however, the complete immunoglobulin molecule has to be taken into account since numerous Fc-mediated immune mechanisms are involved in complex immune reactions (see Section 3.2). Due to the polymorphism of human Fc receptors, mouse immunoglobulins of the subclass Ig1 or IgG2b cannot be processed analogously to human immu-

noglobulins, or only to a limited extent[67, 146]. Thus Fc-mediated immune reactions, such as antibody-dependent cellular cytotoxicity (ADCC), cannot take place as effectively as they can with rabbit or human antibodies. Moreover, mouse immunoglobulins are antigens for the human immune system, so that anti-mouse-Ig antibodies may be induced after the administration of mouse monoclonal antibodies. Such anti-mouse-Ig antibodies, at high titers, can impair therapy. This sort of difficulty is not to be expected when using human monoclonal antibodies[147].

In principle, human monoclonal antibodies can be produced by three basic methods:

- Epstein-Barr-Virus (EBV) transformation of B-lymphocytes[148-150],
- cell fusion, in analogy to the mouse system, and
- via heterohybrids, mouse-human (mouse myeloma cell line).

For the production of human antigen-specific monoclonal antibodies, the availability of appropriately stimulated human lymphocytes has often been a limiting factor. Whereas the mouse immune system can be activated, as a rule, by in-vivo immunization—only for extremely small amounts of antigen was in-vitro immunization occasionally preferable—the stimulation of human B-cells must be carried out in vitro for the majority of antigens. Not until improvements were made in culture conditions, for example, the use of serum-free Iscove's medium, and the T-cell help for stimulation of B-cells was optimized, was a more effective in-vitro induction of the human Ig synthesis possible for certain selected antigens.

The increasing understanding of the activation mechanisms in lymphocyte stimulation and the biochemical characterization of the factors involved have now also made it possible to interfere specifically in the differentiation and proliferation of B-lymphocytes[56, 151, 152]. If antigen-specific precursor cells can be expanded selectively with the aid of mediators produced by gene technology (B-cell growth factor (BCGF), B-cell differentiation factor (BCDF), interleukin-2, γ-interferon), the preconditions would be created for specifically producing human antibodies in high yields. The immortalization of B-lymphocytes (transformation or fusion) would then play a subordinate role.

Since *Olsson* and *Kaplan* described the first human monoclonal antibodies[153], many different approaches have been used for the isolation of activated B-lymphocytes. At first, monoclonal antibodies could mainly be isolated against antigens with which blood donors had been naturally or artificially immunized. Now, however, human monoclonal antibodies with specificity against tumors can be produced via the fusion of lymphocytes from tumor-draining lymph nodes. Table 10 is a summary of selected human monoclonal antibodies with different specificities.

It is noteworthy that xeno-hybrids based on human-mouse fusions can be produced in relatively good yields[159, 161, 164, 165]. The in-vivo use of human-mouse monoclonal antibodies has, to date, been limited to case studies of tumor patients[167]; however, new horizons, especially for tumor therapy, appear with the isolation of further human monoclonal antibodies having different specificities.

Table 10. Specificity of human monoclonal antibodies.

Binding specificity for	Ref.
Tetanus Toxoid [a]	[159, 160]
Diphtheria Toxoid [a]	[159]
Sheep erythrocytes	[156]
Thyrotropin Receptor	[158]
Hemophilus influencae B.	[159]
Keyhole Limpet Hemocyanin	[161]
Influenza virus	[154]
Pneumococcus	[155]
Human monoclonal antibody with reactivity against human tumors (colon, lung, breast, glioma, melanoma, and others)	[157, 162—166]

[a] A toxoid is a toxin that has retained its antigenicity but lost its toxic effect due to inactivation.

Human monoclonal antibodies would be very desirable for the production of hyperimmune sera, specifically against bacterial and viral pathogens for which suitable and well-tolerated vaccines are not available or difficult to produce.

5.4.5. *The Problems of Using Monoclonal Antibodies in Humans*

The in-vivo application of monoclonal antibodies, whether they are coupled to cytotoxically effective agents or not, gives rise to problems which, above all, have to be taken into account by the various health organizations when they authorize the use of such preparations. Up to now monoclonal antibodies have only been used to a limited extent for therapy on human beings, so that no general summary of tolerance and side-effects is available[168]. It is understandable that, for this new drug, all possible safety precautions are considered. Of course, depending on the purpose of the application (anti-tumor therapy, immune modulation, immune suppression, passive immunization, diagnosis, etc.), the possible damages must be weighed against the benefits. Experience gained over the course of time will certainly help to identify the criteria with real practical significance.

High demands are therefore made on the cells used for fusion (myeloma lines, B-lymphocytes), as well as on the cloned hybridoma line which produces the relevant monoclonal antibody, with regard to their being free from bacteria, viruses (especially lymphocytic choriomeningitis (LCM) and respiratory-enteric-orphan (REO) viruses type 3), and mycoplasmas.

The method of purification for monoclonal antibodies should guarantee, in a reproducible manner, the removal of viruses and undesired macromolecules, including DNA. Sterility, the absence of pyrogens, stability of the final product, and its biochemical (subclass, electrophoretic mobility, aggregate content, etc.) and functional (specific activity, titer information, etc.) characterization must also be guaranteed. Likewise, the safe use of the product for human beings must be assured by general and specific pharmacological and toxicological animal tests. All the investigations summarized in part here must, of course, be sufficiently documented.

6. Summary and Outlook

The success of immunological research over the past one hundred years lies in the establishment of antibody therapy, the discovery of many infectious pathogens, and the provision of numerous vaccines, as well as in the development of immunodiagnosis. Above all, in the last twenty years, immunology has studied the immune system more closely and thus enabled us to seize upon new forms of therapy.

Access to monoclonal antibodies has set a new milestone in the history of immunology: the discovery that they could be produced in vitro by means of immortalized hybrid cell clones has now become a matter of general interest, not only in the field of immunology but in many fields of science, technology, and medicine.

The particular advantages of monoclonal antibodies could be first and most easily shown for immunodiagnosis. The discussion concerning their superiority over conventional, heteroclonal antibody preparations, however, is still underway. There is no question about the advantages of monoclonal antibodies for the differentiation and the fine analysis of cell surface structures, e.g., for immune cells, parasites, bacteria, and viruses. The histological differentiation of tissue structures, too, is expected to make interesting progress.

However, as already shown in pilot studies, the new medical uses could become of greater importance. First signs of success have been recorded in the localization of tumors in a living organism using radioactively labeled monoclonal antibodies. The search, however, for suitable antibodies is still very costly and difficult. The aim is to discover specific or tumor-associated antigens for many types of tumor and to characterize them, showing at the same time that such substances cannot be found in normal tissue, or only in negligibly small concentrations. The next goal is tumor therapy, either directly with monoclonal antibodies or with antibody conjugates (with radionuclides in suitable doses, with tumor cytostatic drugs, or with toxins). Very encouraging initial successes have been achieved with a few sorts of tumors, but we shall have to await the results of further clinical trials.

In addition to the immune mediators now accessible by gene technology, monoclonal antibodies are receiving more attention with regard to immunoregulatory forms of therapy. The value of this type of treatment has been shown by the first clinical studies in organ and bone-marrow transplantation. Much hope has also been placed in antibodies that may enable us to treat the undesired immune reactions in autoimmune disorders by possibly inactivating or eliminating immune cells with immunologically wrongly primed recognition structures.

To what extent conventional immunosubstitution with homologous human antibody preparations can be replaced by specific monoclonal antibodies depends on the progress made in the field of human hybridomas. These systems do not work as well as the mouse systems. Further improvements are necessary, and, above all, methods of in-vitro immunization must be developed to specifically stimulate still unprimed B-lymphocytes with any desired antigen. In principle, this is possible, but still not to the required extent or in any direction.

Intensive research with and into monoclonal antibodies is being carried out worldwide, so that the many still unsolved problems will presumably be quickly solved and improved methods will most likely be developed. Interesting developments can also be expected from the use of the methods of gene technology in the production of antibodies or the occasionally more advantageous antibody fragments.

Unfortunately, this revolutionizing hybridoma technology is confronted with rather conventional production methods: modern cell culture methods are relatively underdeveloped and thus normally still very expensive. If one considers that ca. 100000 L of cell culture would have to be prepared to produce 1 kg of monoclonal antibody, an amount certainly necessary for an established therapy, then limits become apparent. However, there are also efforts here to produce the same quantity of antibody with only 1000 to 10000 L of cell culture. This unfavorable situation also exists for the production of recombinant protein from mammalian cell cultures. The demands of two modern biotechnologies will surely accelerate the urgently needed breakthrough in cell culture technology.

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Hexafluoropropene Oxide— A Key Compound in Organofluorine Chemistry

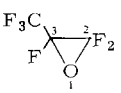
By Hans Millauer, Werner Schwertfeger, and Günter Siegemund*

Dedicated to Professor Rolf Sammet on the occasion of his 65th birthday

Of the important C_3-compounds in organofluorine chemistry, namely hexafluoropropene, hexafluoroacetone and hexafluoropropene oxide, the latter is chemically the most versatile compound. Hexafluoropropene oxide provides another example of the frequently observed change in reactivity when hydrocarbon compounds are converted into their perfluorinated derivatives. The overwhelming majority of the known reactions of hexafluoropropene oxide are initiated through attack by a nucleophile. The conversion of hexafluoropropene oxide into hexafluoroacetone in the presence of Lewis acids is the basis of further development of the chemistry of this synthetic chemical. Hexafluoropropene oxide is also regarded as a convenient source of difluorocarbene. In industrial chemistry it now plays a significant part in the manufacture of high-grade organofluorine products.

1. Introduction

In 1959 E.I. du Pont de Nemours & Co. filed a patent application on fluorocarbon epoxides as a new class of perfluorinated compounds, whose industrial importance for the manufacture of highly upgraded perfluorinated polymers was clear from the outset. In the 25 years since then the most important member of this new class of compounds has proved to be hexafluoropropene oxide (HFPO, 2,2,3-trifluoro-3-trifluoromethyloxirane).



HFPO

Various methods of synthesis and a multitude of reactions justify a survey of the extensive chemistry of HFPO. Reviews already published are either somewhat old[1,2] or are not readily accessible[3].

2. General Properties of HFPO

HFPO is a colorless, nonflammable gas with a slight odor and a boiling point of −27.4 °C/1013 mbar. Even when liquified under pressure HFPO is stable at room temperature in the dry state and in the absence of Lewis acids or bases. Spontaneous polymerization has not been observed. Marked thermal decomposition occurs only at a temperature of 150 °C or above[2].

The interatomic distances and bond angles of HFPO have been determined[4]; unlike the analogous hydrocarbon compound, propylene oxide, the perfluorinated compound has a shorter C–O distance and a lengthened C–CF_3 bond.

The ^{19}F-NMR spectrum has been described[5]. In the IR spectrum HFPO exhibits a strong band between 1480 and 1620 cm^{-1} with a maximum at 1550 cm^{-1}, which characterizes perfluorinated epoxides and in a number of instances can be employed for quantitative determination.

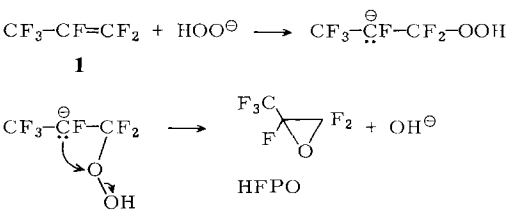
HFPO is a relatively non-toxic compound. In the test for acute inhalation toxicity a 4-hour LC 50 of 3700 ppm was recorded[6]. In the Ames test, HFPO displayed no mutagenic activity[7].

3. Preparation and Purification of HFPO

All known methods for the synthesis of HFPO are based on the reaction of hexafluoropropene **1** (HFP) — a commercially available fluoroolefin — with an oxygen donor. Depending on the type of oxidizing agent, epoxidation can be regarded as a nucleophilic, electrophilic or radical reaction.

3.1. Nucleophilic Syntheses

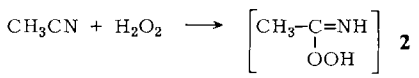
HFPO was first prepared, in about 35% yield, by reacting hexafluoropropene **1** with 30% hydrogen peroxide in aqueous-methanolic potassium hydroxide solution at −40 °C[8]. It is assumed that the hydroperoxide anion, which is a stronger nucleophile than the hydroxide anion, attaches itself preferably to the electron-deficient double bond. The resultant carbanion stabilizes with elimination of a hydroxide ion and ring-closure to the epoxide[2].

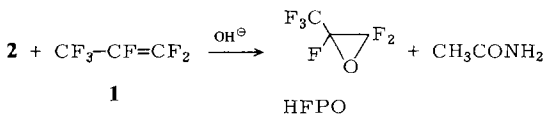


The reaction can also be carried out in other water-miscible organic solvents or in aqueous solution in the presence of sodium perfluorooctanoate[8]. Higher yields (54%) and a reduced consumption of feedstock are achieved by

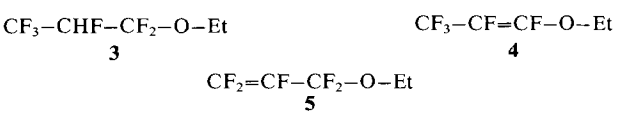
[*] Dr. G. Siegemund, Dr. H. Millauer, Dr. W. Schwertfeger
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slowly adding the potassium hydroxide solution to the reaction mixture[9]. Similarly, high yields (about 52%) are said to have been achieved by adding the reactants simultaneously and continuously to the reaction vessel[10]. Another continuous method employs an aqueous hydrogen peroxide solution at pH 7.5—8 in the presence of acetonitrile[11]. Oxygen is transferred by the intermediate acetoperoxyimidic acid **2** or by its anion. Stoichiometric quantities of acetamide are formed as a by-product.





Sokolov et al.[12] investigated the structure of the by-products formed in the reaction of **1** with alkaline, aqueous-ethanolic hydrogen peroxide solution. With a molar ratio of H_2O_2 : HFP greater than 4 : 1, the main products obtained are HFPO and trifluoroacetate, whereas with a molar ratio less than 1 : 1 the ethers **3**, **4** and **5** are formed.



HFPO is also produced by the action of hypohalites, especially sodium hypochlorite, on **1**. The reaction is carried out at pH 9—11 and 15—20°C in the presence of water-miscible aprotic solvents, e.g. acetonitrile or diglyme[13, 14].

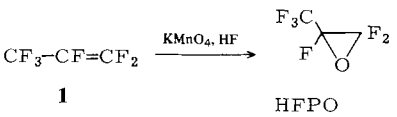
Other methods employ a two-phase system, consisting of an aqueous hypohalite solution and a water-immiscible organic solvent. The reaction in this case proceeds only in the presence of a phase transfer catalyst or a lipophilic alkali metal-ion chelating compound[15, 16]. Aliphatic and aromatic hydrocarbons, chlorinated hydrocarbons, and chlorofluoroalkanes, e.g. 1,1,2-trichloro-1,2,2-trifluoroethane, are suitable for the organic phase. Catalysts mainly mentioned are quaternary ammonium salts, whilst macrocyclic ethers are mentioned as complexing agents. Anionic and nonionic surface-active compounds, too, are described as activators[17]. The HFP conversions and the yields are generally higher in the hypohalite method than in the peroxide method.

One variant of the hypohalite method is the electrolysis of a two-phase mixture consisting of aqueous alkali chloride solution and organic solvent in an undivided cell in the presence of HFP and one of the above-mentioned catalysts or lipophilic complexing agents[18]. In this case the hypochlorite is produced and reacted continuously in the cell.

HFPO is produced, along with a considerable quantity of 1,2-dichlorohexafluoropropane, in the reaction of **1** with chlorine in the presence of aqueous bases at room temperature in the absence of light[19].

3.2. Electrophilic Syntheses

The epoxidation of hexafluoropropene **1** under electrophilic conditions has so far been observed in only a few instances. *Belen'kij* et al.[20] obtained HFPO in 30% yield on reaction of **1** with potassium permanganate in anhydrous hydrogen fluoride at −70°C.



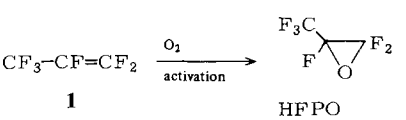
When chromium trioxide is used in fluorosulfuric acid, the yield is about 55%[21].

The anodic epoxidation of **1** can also be regarded as an electrophilic reaction. Suitable electrolytes are HFP-saturated, aqueous, aliphatic carboxylic acids or nitriles, and suitable conductive salts are nitrates, perchlorates or tetrafluoroborates. Platinum is a suitable universal anode material; in acetic acid/nitric acid electrolytes, a lead dioxide anode can also be used[22, 23]. The reaction is carried out in a tubular flow cell. The material yield is 92%, while the current yield is 55%[24, 25].

3.3. Radical Syntheses

3.3.1. Syntheses with Molecular Oxygen

Methods for the production of HFPO with molecular oxygen have been thoroughly investigated. In these reactions either thermal activation, the use of energy-rich radiation, or the addition of radical-forming agents is generally necessary; a combination of various methods has occasionally been used.



The main by-products formed are carbonyl difluoride, trifluoroacetyl fluoride and hexafluoroacetone. Depending on the reaction conditions, the different methods are carried out in the liquid phase or in the gas phase.

The syntheses in the liquid phase are usually carried out under pressure in an autoclave with oxygen being added to the HFP. The reaction temperatures are generally 100—200°C; the yields reach 76% with a conversion of 70%. Frequently, the liquid phase is diluted with a solvent (e.g. fluorocarbons or chlorofluoroalkanes)[26, 27]. By adding 5—500 ppm benzene or diphenyl ether the undesired rearrangement of HFPO to hexafluoroacetone is suppressed[28]. By using a reactor lined with Teflon® (du Pont), *Kartsov* et al.[29] achieved double the yields they obtained in a stainless steel reactor. According to a Japanese patent[30] very high yields (90% selectivity with 100% conversion) are said to be achieved by adding oxygen in small portions in the absence of other substances. Organic per-

oxides, too, such as benzoyl peroxide or *tert*-butyl perbenzoate[31], or oxygen difluoride[32] have been used as activators for oxygen.

The photoinitiated reaction of **1** with oxygen in the gas phase was investigated by *Heicklen* and *Johnston*[33]. Substantial quantities of COF_2 and CF_3COF were detected in addition to HFPO as reaction products at room temperature and with the use of UV light. Under similar conditions *Sianesi*[34] found only 1% HFPO in addition to 15% COF_2, 37% CF_3–COF and 47% higher-molecular compounds of the type **6**

$CF_3O(CF_2O)_n$–COF $CF_3O(CF_2O)_n$–CF_2–COF (n = 0–15)
6a **6b**

HFPO has also been obtained by the action of X-rays on an HFP/O_2 mixture rendered inert in the gas phase[35]. Several methods for the epoxidation of **1** with oxygen in the gas phase over solid catalysts at temperatures of 100–350 °C have been described in the patent literature. Catalysts claimed are either pretreated silicic acid[36,37], carriers consisting of silicic acid[38] or silicic acid/aluminum oxide mixtures[39] doped with copper compounds, zeoliths doped with transition metals[40], or catalysts prepared from barium compounds[41]. With conversions between 10% and 40%, selectivities between 30% and 80% are mentioned for the gas phase methods.

3.3.2. Syntheses with Other Oxidizing Agents

Organic hydroperoxides in the presence of catalysts are also suitable as oxygen donors in the epoxidation of hexafluoropropene **1**. With *tert*-butyl hydroperoxide and hexacarbonylmolybdenum as catalyst, the reaction proceeds in 1,1,2-trichloro-1,2,2-trifluoroethane at 70 °C with 39% conversion and a selectivity of 88%[42].

Ruff and *Merritt*[5] obtained HFPO together with other products on reacting oxygen difluoride with **1** in the gas phase under UV radiation at 35 °C. The same reaction has also been carried out with silver difluoride as catalyst[43,44].

3.4. Purification Methods

In most reactions for the preparation of HFPO, partial conversion of **1** is accepted as sufficient. Special methods are required for the separation of unreacted **1**, which boils at −29.4 °C. On the laboratory scale the HFPO/**1** mixture is allowed to react with bromine; in this reaction, **1** forms 1,2-dibromohexafluoropropane, which can be readily separated by distillation.

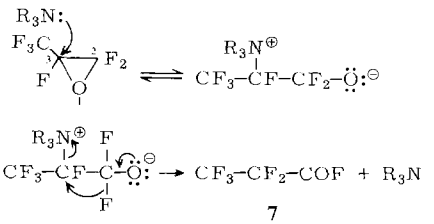
For industrial purposes extractive distillation is employed as the purification method[45–49]. The extractants used include dichloromethane, 1,2-dichloroethane, 1,2-dimethoxyethane, diisopropyl ether and toluene (for the solubility of HFPO and **1** in various organic solvents see [50]).

Very pure HFPO with <0.1 ppm HF, <1 ppm H_2O, <0.2% acid fluoride and <0.01% hexafluoroacetone is obtained by passing HFPO successively over potassium hydroxide and calcium hydride[51].

4. Reactions with Nucleophiles

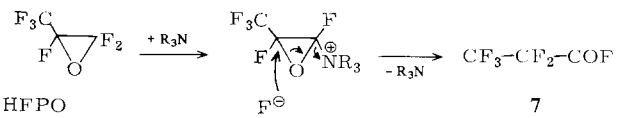
HFPO is highly sensitive to nucleophilic reagents. It reacts with strong nucleophiles even below room temperature. The attack usually takes place at C-3 and only rarely at C-2. The following mechanisms have been suggested for the reactions of HFPO with secondary or tertiary amines, which result in perfluoropropionic acid derivatives:

Sianesi et al.[52] and *Knunyants* et al.[53] assume that the attack by tertiary amines takes place at C-3,

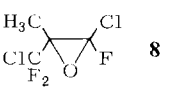


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whereas *Bekker* et al. postulate an attack by the amine at C-2 and substantiate this mechanism by reference to analogous reactions at the epoxide **8**[54].

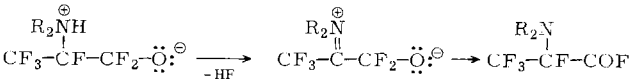


HFPO



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Evidence for attack at C-2 is also provided by the fact that secondary amines likewise give perfluoropropionic acid derivatives. Attack at C-3 would, however, lead to a betaine **9**, which should react further with elimination of HF.



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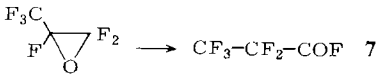
The explanation given in the literature[54] for the extraordinary behavior of secondary and tertiary amines with HFPO (NH_3 and primary amines usually react at C-3; see Section 4.7 and 4.8) is the increasing steric hindrance of the amines, which no longer permits "normal" attack but causes substitution of a fluoride ion at C-2 as an initial step.

4.1. Isomerization of HFPO to Perfluoropropionic Acid Fluoride

One of the most frequently observed reactions of HFPO with nucleophiles is the exothermic isomerization to perfluoropropionic acid fluoride **7**.

The following nucleophiles have been used for this reaction: tertiary amines (particularly triethylamine)[52,53,55–63]; secondary amines[52,53]; primary amines[64]; enamines[65];

Me_3SiOMe, $Me_2Si(OEt)_2$[66]; halide ions (particularly fluoride ions)[67-71].

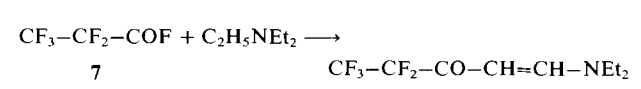


HFPO

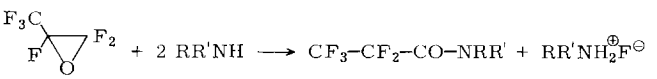
If the isomerization is carried out in the presence of tertiary amines the resultant **7** is usually not isolated but allowed to react further in situ. Thus, on allowing **7** to react with alcohols[52,58,63], thiols[58,61,63], ammonia[52], primary amines[58,60,61] and 1,2-bifunctional ethanes ($X-CH_2-CH_2-Y$; X, Y = OH, SH)[62] the corresponding derivatives of pentafluoropropionic acid are obtained (see also Section 4.8).

The reaction mixture consisting of **7** and NEt_3 is also used as a fluorinating agent in the preparation of carboxylic acid fluorides from the free carboxylic acids[57,59].

However, triethylamine itself also reacts with **7**; this yields the unsaturated ketone **10**[55,56].



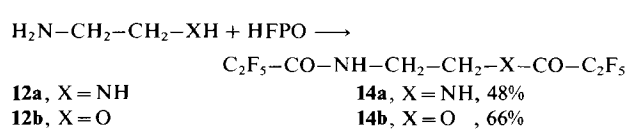
The reaction of HFPO with secondary amines yields pentafluoropropionic acid amides **11**[52,53].

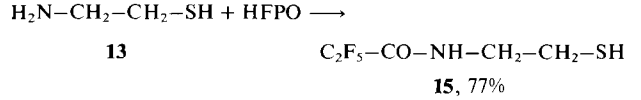


HFPO

Assuming the mechanism suggested by *Bekker* et al.[54], it is however unlikely that **7** occurs as an intermediate product in this reaction.

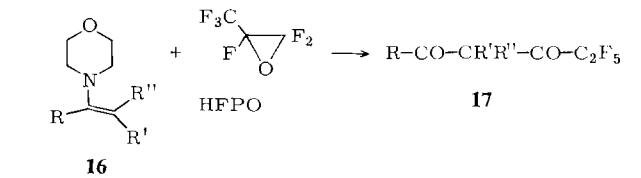
Whereas most primary amines react with HFPO by attacking the C-3 atom (see Section 4.7 and 4.8), the perfluoropropionic acid derivatives **14** and **15** are produced when the amines **12** and **13** are reacted under comparable conditions[64].

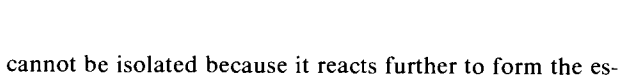




The reaction of *N*-(1-alkenyl)morpholines **16** with HFPO proceeds via **7** to give the diketones **17** in yields of up to 80%[65].

Even in the reaction of HFPO with the silanes **18** and **19** in the presence of activated carbon the initially formed **7** cannot be isolated because it reacts further to form the ester[66].

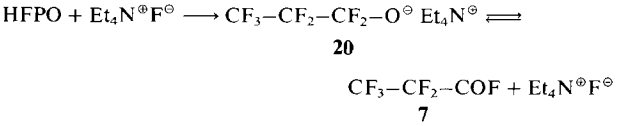


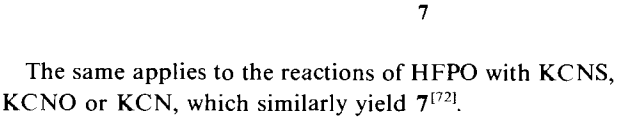


The fluoride-ion catalyzed rearrangement of HFPO to **7** is carried out both in the presence[67-70,72] and in the absence[71] of solvents. Thus, for example, by passing HFPO over KF/activated carbon the yield of perfluoropropionic acid fluoride **7** is >90%[71]. When solvents are used, the yield of **7** has been found to be highly dependent on the solvent[69].

It is not always necessary to employ fluoride ions for the isomerization; they are often formed in situ in a previous reaction.

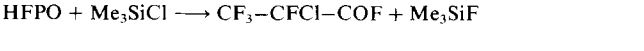
The action of $Et_4N^{\oplus}Cl^{\ominus}$ on HFPO in dichloromethane yields, for example, the propoxide **20**, which is in equilibrium with **7** and $Et_4N^{\oplus}F^{\ominus}$[67]. It is suggested that the chloride ion from $Et_4N^{\oplus}Cl^{\ominus}$ attacks HFPO nucleophilically and is bound irreversibly. The fluoride ion thus liberated then catalyzes the isomerization to **7**.



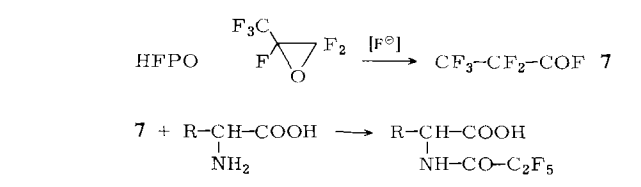


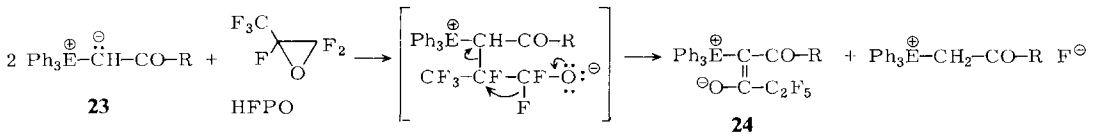
The same applies to the reactions of HFPO with KCNS, KCNO or KCN, which similarly yield **7**[72].

On the other hand, when HFPO is reacted with trimethylchlorosilane, the resultant fluoride ion is captured as trimethylfluorosilane, and so the formation of **7** is prevented[66].



Even in the reaction of amino acids **21** with HFPO, which leads to the acylated derivatives **22**, *Ishikawa* et al. assume catalysis by intermediary fluoride ions[70].





a, E = As, R = OMe; **b**, E = As, R = Ph; **c**, E = P, R = OMe; **d**, E = P, R = Ph

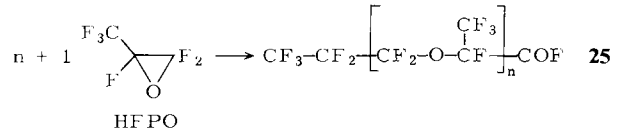
7 is quoted as an intermediate in the reaction of triphenylarsoranes **23a**, **b** or triphenylphosphoranes **23c**, **d** with HFPO to form the fluorinated ylides **24a**—**d**[74].

In this reaction the carbanion attacks at the C-3 of HFPO nucleophilically and initiates isomerization to **7**, which then reacts with **23** to form **24**.

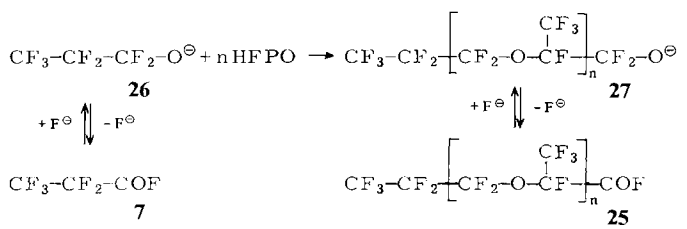
Recent investigations[75] have not been able to confirm the previously described thermal isomerization of HFPO to **7**[8].

4.2. Oligomerization of HFPO

HFPO can be converted by anionic polymerization into oligomers having the general formula **25**, where n can have values between 1 and > 100.



The initial oligomerization step is the isomerization of HFPO to perfluoropropionic acid fluoride **7** described in Section 4.1. The perfluoropropoxide ion **26**, which is in equilibrium with **7**, attacks one molecule of HFPO, giving rise to the alkoxide **27** (n = 1); this then continues to react in the same way (n > 1) or forms the acid fluoride **25** (n = 1) after elimination of one fluoride ion.



The degree of oligomerization depends on the catalyst system, the reaction conditions, and the purity of the HFPO. Acid fluoride mixtures are always produced whose molecular weight distribution can be kept within narrow limits only by using special measures. Numerous investigations have been carried out concerning the mechanism and kinetics of oligomerization and the influence of the catalyst system[69, 76–84].

Table 1 contains a list of catalyst systems and the degrees of oligomerization obtained. Many of the reactions given in Table 1 were carried out with an HFPO/HFP mixture[87–89, 91, 93, 96, 97] (for further catalyst systems for the oligomerization of HFPO see [90]).

Table 1. Degree of oligomerization of HFPO to **25** with different catalyst systems (see text).

Catalyst	n in **25** (Yield)	Ref.
Activated carbon	wide product range	[85]
CsF/tetraglyme	> 33 (≥ 85%)	[86, 87]
$AgNO_3$/acetonitrile, propionitrile	1 (86%), 2 (3%)	[88]
Activated carbon	mainly higher-oligomer material	[89]
Ph—NMe_2/tetrahydrofuran	1 (88%)	[90]
$(Me_2N)_3PF_2$/diglyme	1 (23%), 2 (34%), > 2 (10%)	[91]
$(Me_2N)_3PF_2$/diglyme	1 (12%), 2 (30%), 3 (17%)	[91]
Trialkylsulfonium salt/solvent	1–3	[92]
Tris(dialkylamino)sulfonium salt/solvent	1–3	[92]
Tris(dialkylamino)sulfonium salt · Me_3SiF/solvent	1–3	[92]
$(Me_2N)_2CF_2$/diglyme	1 (to 7%), 2 (to 59%), 3 (to 45%)	[93]
$(Me_2N)_2CO$/diglyme, tetraglyme	1 (to 77%), 2 (to 50%), 3 (to 40%), 4 (to 44%)	[93, 94]
$(Me_2N)_2CS$/diglyme	1 (13%), 2 (40%), 3 (22%)	[93]
KF/polyethylene glycol/glyme	1 (49%), 2 (17%)	[95]
CuCl/acetonitrile/acrylonitrile	1 (to ≈ 82%)	[96]
CuCl/$CuCl_2$/acetonitrile/acrylonitrile	1 (82.7%), 2 (3.8%), ≥ 3 (11.2%)	[97]
KF/diglyme	1 (53%)	[98]
CsF/diglyme/ $CF_3(CF_2)_2O$—$CF(CF_3)$—COF	1 (83%)	[99]
CsF/diglyme	1 (52%)	[99]
KF/[18]crown-6/diglyme	1 (41%), 2 (18%)	[100]

The dependence of the degree of oligomerization on the nature of the solvent was the subject of an investigation[69], in which cesium fluoride was reacted in various solvents with HFPO at 30 °C and 10^5 Pa and the concentration of the alkoxide ions **27** present was determined (see Table 2).

Table 2. Degree of oligomerization of HFPO to **25** in different solvents (see text). n and yields were determined for the alkoxide ions **27**.

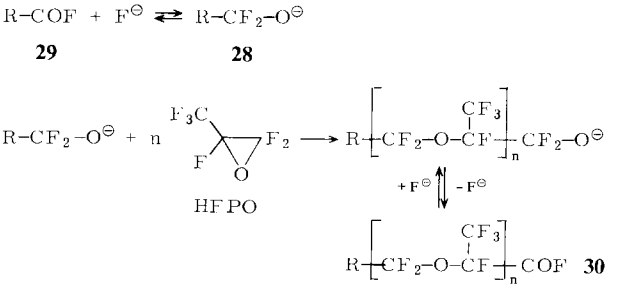
Solvent	Rel. yield [%]					
	n = 0	n = 1	n = 2	n = 3	n = 4	n = 5
Tetrahydrofuran	100					
Acetonitrile	88	9	3			
Glyme	71	20	9			
Diglyme	32	31	25	10	2	
Tetraglyme	16	17	21	20	16	10

The influence of the halide ion on the oligomerization of HFPO follows from Table 3.

Oligomeric material can also be obtained by irradiating HFPO using a Van de Graaff generator[101].

Table 3. Degree of oligomerization of HFPO to **25** in presence of different halides of potassium. Other components of the catalysts: CH_3CN as solvent; reaction conditions: autoclave, 6 h, 22°C.

KX X=	Yield [%] n=1	n=2	n=3	n=4	n=5
F	6.4	27.0	40.4	23.0	2.7
Cl	26.4	42.1	24.4	5.3	
Br	45.5	41.0	7.3	0.2	
I	75.1	16.9	0.2		



4.3. Reactions of HFPO with Fluorinated Alkoxides

4.3.1. Primary Fluorinated Alkoxides

Primary fluorinated alkoxides **28**, which are accessible by addition of a fluoride ion to a carboxylic acid fluoride **29**[102], can attack HFPO nucleophilically to form the addition products **30**.

The oligomerization of HFPO described in Section 4.2 is a special example of this reaction and differs from it only in that formation of a perfluoropropoxide ion **26** from HFPO occurs initially. It is therefore not surprising that the oligomerization of HFPO always occurs as a side reaction.

Suitable starting compounds are acid fluorides **29** with very different structures. The yield of addition products **30**

Table 4. Reactions of acid fluorides **29** with HFPO to give (partially oligomeric) addition products **30**.

29 R	Molar ratio **29** : HFPO	Catalyst	n in **30** (Yield)	Ref.
F		Activated carbon	1 (33%)	[103]
	1:0.5	CsF(AgF, Me_4NF)/diglyme	1 (70.7%) [a]	[103, 104]
		$CN^⊖$ or $CNS^⊖$	1 (74–82%)	[105]
CF_3	1:0.7	Activated carbon	1 (89%) [a]	[104]
	1:1	Tris(4-methylpiperidino)sulfonium fluoride·Me_3SiF/CH_3CN	1	[106]
C_2F_5	1:1	Activated carbon	1 (44.8%)	[103]
	1:2.36 [b]	$(Me_2N)_3PF_2$/diglyme	1 (57%), 2 (30%)	[91]
$(CF_3)_2CF$	1:0.93	CsF(AgF, Me_4NF)/diglyme	1 (10.1%) [a]	[103]
$CF_3(CF_2)_3$	1:0.98	$(Me_2N)_3S^⊙F^⊖ \cdot Me_3SiF$/acetonitrile	1–3	[106]
$H(CF_2)_6$	1:1.17	CsF/triglyme	1 (22%)	[107]
$CF_3–CHF–CF_2$	1:1.69	CsF/tetraglyme	1 (48%), 2 (23%)	[108]
	1:3.03	CsF/tetraglyme	1 (29%), 2 (38%), 3 (12%)	[108]
$CF_3–O–CF_2$	1:1.11	CsF/diglyme	1 (97%)	[110]
$CF_3(O–CF_2)_2$	1:0.8	CsF/diglyme	1 (53.6%) [a]	[109]
$CF_3(O–CF_2)_4$	1:0.94	CsF/diglyme	1 (47.5%) [a]	[109]
$CF_3(O–CF_2)_5$	1:1.02	CsF/diglyme	1 (61.1%)	[109]
$C_2F_5–O–CF_2$		CsF/diglyme	1 (92%)	[110]
$CF_3(CF_2)_2–O–CF(CF_3)$	1:3.58 [b]	$(Me_2N)_3PF_2$/diglyme	1 (36%)	[91]
$C_6F_5–O–CF_2CF_2$	1:1.16	CsF/tetraglyme	1 (39%) [c]	[111]
CF_2Cl	1:1.1	CsF/tetraglyme	1 (75%)	[112]
$CFCl_2$	1:1.1	CsF/tetraglyme	1 (71%)	[112]
CCl_3	1:1.06	CsF/tetraglyme	1 (42%)	[110, 112]
CF_2Br	1:1.26	CsF/diglyme	1 (76%)	[113]
CF_2I	1:1.05	CsF/diglyme	1 (18.1%)	[114, 115]
$ClCF_2–CFCl$	1:1.2	CsF/diglyme	1 (13.6%)	[116]
$ICH_2CH_2(CF_2)_3$		CsF/tetraglyme	1 (72%)	[117]
$CF_3–CF(CN)$	1:0.98	CsF/tetraglyme	1 (86.3%) [a]	[118]
	1:2.04	CsF/tetraglyme	1 (13%), 2 (75%), 3 (4%)	[118]
$CF_3(CF_2)_2–O–CF(CF_2N_3)$	1:2	KF/adiponitrile/tetraglyme	1 (34%), 2 (4%)	[119]
$FSO_2–CF_2$	1:1.08	CsF/diglyme	1 (56%)	[120]
	1:1.85	$(Me_2N)_3S^⊙F^⊖Me_3SiF$/acetonitrile	1–3 (ratio 1:2.54:1.22)	[106]
[d]	1:0.7	KF/CsF	1 (80%)	[121]
$FSO_2(CF_2)_2$	1:1.1	KF/diglyme	1 (56.8%)	[122]
	1:1.9	KF/diglyme	1 (23%), 2 (50%)	[122]
$MeS(CF_2)_2$	1:1.22	CsF/tetraglyme	1 (35%)	[123]
$EtS(CF_2)_2$	1:1	CsF/tetraglyme	1 (38.9%)	[123]
	1:2	CsF/tetraglyme	1 (11.1%), 2 (19.3%)	[123]
$EtSO_2(CF_2)_2$	1:1.16	CsF/tetraglyme	1 (29.6%)	[123]
$MeOOC–CF_2$	1:0.98	CsF/tetraglyme	1–3; 1 (23%), 2 (7%)	[124]
	1:2.1	CsF/tetraglyme	1–6; 1 (9%), 2 (7.5%), 3 (12%)	[124]
	1:1.47	KF/adiponitrile/butyrolactone	1 (50.5%), 2 (28.1%)	[125]
	1:1.98	KF/adiponitrile/tetraglyme	1 (20%), 2 (46.5%)	[125]
$MeOOC(CF_2)_2$	1:1.12	CsF/diglyme	1 (56%)	[126]
$EtOOC(CF_2)_2$	1:1.17	CsF/tetraglyme	1 (57%)	[126]
	1:2.2	CsF/tetraglyme	2 (56%)	[126]
$MeOOC(CF_2)_3$	1:3.8	CsF/tetraglyme	2 (27.6%), 3 (22.4%)	[127]
$MeOOC(CF_2)_4$	1:1.12	CsF/diglyme	1 (71%)	[126]

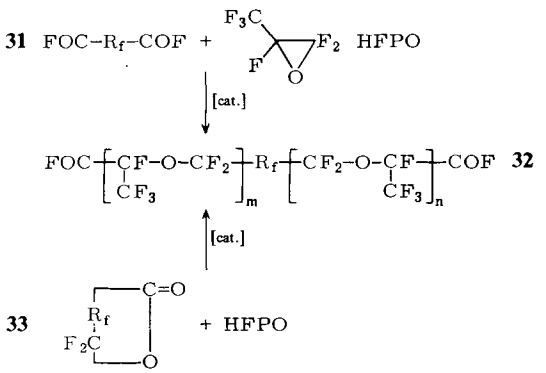
[a] Calculated on HFPO used. [b] Hexafluoropropene/HFPO mixture used. [c] Calculated on reacted acid fluoride **29**. [d] 3,3,4,4-Tetrafluoro-1,2-oxathietane *S,S*-dioxide is used, which isomerizes under the reaction conditions to form $FSO_2–CF_2–COF$.

that can be achieved depends, inter alia, on the radical R of the acid fluoride **29** and, thus, on the stability of the fluoroalkoxide **28**[102]. It has been possible, however, using special catalyst systems that favor the formation of **28** and suppress the reaction of HFPO leading to **7** or **25**, to obtain satisfactory yields of **30** even with fairly unreactive acid fluorides.

Table 4 contains a list of acid fluorides and catalyst systems used and the yields achieved.

The chain lengths of the HFPO addition products **30** are mainly dependent on the molar ratio of the acid fluoride **29** to HFPO used. Usually, the aim is to produce addition products **30** with n = 1-3.

When dicarboxylic acid difluorides **31** are used, the product distribution is further influenced by the possibility of addition of HFPO on one or both functional groups[128]. It has of course been possible to prepare the monoaddition products **32** (m + n = 1) in high yield (R_f is a completely



fluorinated group). Table 5 lists the results of some HFPO additions to **31** (for longer-chain compounds see, for example, [129]).

Perfluorodicarboxylic acid difluorides **31** are also frequently used for the synthesis of high-molecular perfluoropolyethers[51,76,80,132,133]. This "bifunctional oligomerization" of HFPO is discussed in detail in [76].

Table 5. Reactions of perfluorodicarboxylic acid difluorides **31** or perfluorolactones **33** with HFPO to give addition products **32**.

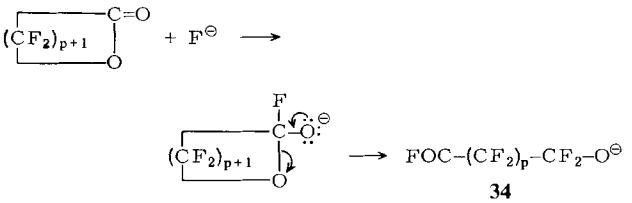
31 R_f	Molar ratio **31** : HFPO	Cat. [a]	m + n in **32** (Yield)	Ref.
–	1 : 2.37	A	1 + 1 (12.3%)	[103]
–		B	1 + 1 (40.3%)	[127]
CF_2	1 : 1.15	C	0 + 1 (85.9%)	[130]
$(CF_2)_2$	1 : 1	C	0 + 1 (80%)	[131]
$(CF_2)_3$	1 : 2.42	C	1 + 1 (80%)	[103]
$(CF_2)_3$	1 : 1.15	C	0 + 1 (75%)	[131]
$(CF_2)_4$	1 : 1.11	C	0 + 1 (79.9%)	[130]
$(CF_2)_4$		C	m + n = 2-6	[128]
$CF(CF_3)$	1 : 1.44	B	0 + 1 (71.4%) 1 + 1 (8.7%)	[132]
33 R_f	Molar ratio **33** : HFPO	Cat. [a]	m + n in **32** (Yield)	Ref.
CF_2	1 : 1	D	0 + 1 (81%)	[134]
$(CF_2)_2$	1 : 1.11	D	0 + 1 (87.8%)	[134]
$(CF_2)_2$	1 : 2.36	D	1 + 1 (82%)	[134]
$(CF_2)_3$	1 : 1.09	D	0 + 1 (85%)	[134]

[a] A = activated carbon, B = CsF/tetraglyme, C = CsF/diglyme, D = CsF/glyme.

Other starting materials for this type of reaction of HFPO are perfluorinated lactones **33**[134].

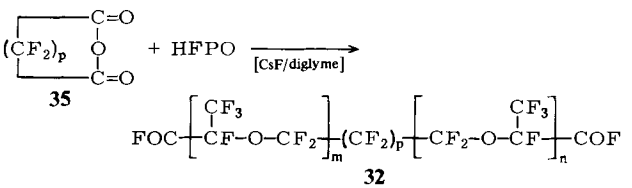
The same products **32** are formed that are also isolated when the unbranched perfluorodicarboxylic acid difluorides **31** (isomeric with **33**) are used as starting compounds (Table 5).

The reaction is presumably initiated by the addition of a fluoride ion to the carbonyl group of the lactone **33** with ring-opening. The alkoxide **34** obtained then reacts with HFPO to form **32** ($R_f = (CF_2)_p$).

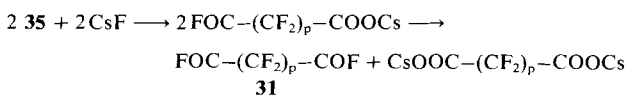


It is worth noting that no ring-opening takes place in the reaction of the lactone 3,5,5,6-tetrafluoro-3,6-bis(trifluoromethyl)-1,4-dioxan-2-one **102** with HFPO in the presence of fluoride ions (see Section 5).

The reaction of perfluorinated anhydrides **35** with HFPO similarly yields the addition products **32** ($R_f = (CF_2)_p$), though at the same time a substantial quantity of HFPO oligomers **25** is produced[135].

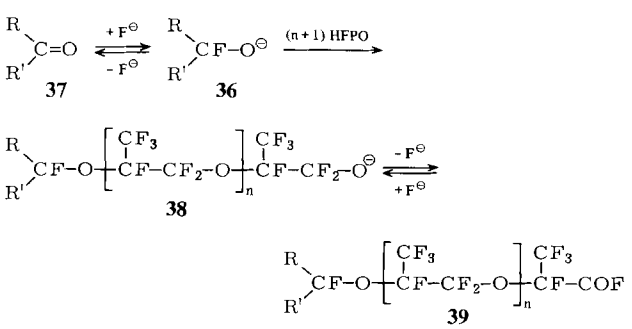


The reaction probably proceeds via the acid difluoride **31** ($R_f = (CF_2)_p$), which is formed by dismutation after ring-opening of **35**.



4.3.2. *Secondary Fluorinated Alkoxides*

Secondary fluorinated alkoxides **36**, which are obtained by the addition of a fluoride ion to a fluorinated ketone **37**[102], also attack HFPO at C-3 nucleophilically. The pri-



mary alkoxides **38** (n = 0) are obtained, which either yield the acid fluorides **39** (n = 0) after elimination of a fluoride ion or give the acid fluorides **39** (n ≥ 1) after reaction with further HFPO via the alkoxides **38** (n ≥ 1).

Fluorinated ketones **37** generally give better yields of addition products than do acid fluorides **29**. Furthermore, fewer byproducts (HFPO oligomers **25**) occur. Here, too, it is true that the formation of HFPO oligomers **25** can be largely suppressed by employing a suitable catalyst system if less reactive ketones are used[136]. Some examples are shown in Table 6.

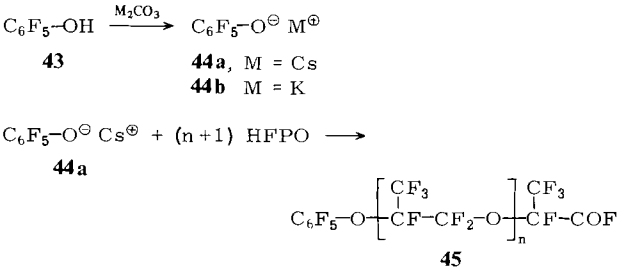


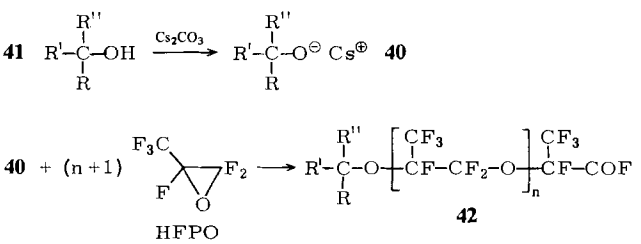
Table 6. Reactions of fluorinated ketones **37** with HFPO to give acid fluorides **39**.

37 R	37 R'	Molar ratio 37 : HFPO	Catalyst	n in **39** (Yield)	Ref.
CF_3	CF_3	1 : 1	CsF/diglyme	0 (50%)	[137]
		1 : 1.34 [a]	$(Me_2N)_3PF_2$/diglyme	0 (73.7%)	[91]
		1 : 1	$Me_3S^{\oplus}I^{\ominus}$/acetonitrile	0 (78.5%)	[106]
			KF/diglyme	0 (61%)	[98]
		1 : 0.89	KF/diglyme	0 (93%) [b]	[138]
CF_2H	CF_2H		CsF/diglyme	0	[137]
CF_3	C_2F_5	1 : 1.05	KF/tetraglyme	0 (81%)	[139]
CF_3	$Cl-CF_2-CF_2$	1 : 1.05	KF/tetraglyme	0 (72%)	[139]
CF_3	$CF_3(CF_2)_2$	1 : 5	CsF/diglyme	0–6	[137]
CF_3	$CF_3(CF_2)_3$	1 : 1.05	KF/tetraglyme	0 (80%)	[139]
$-(CF_2)_3-$		1 : 5	CsF/diglyme	0–6	[137]
$-(CF_2)_4-$		1 : 5	CsF/diglyme	0–6	[137]
$-O-CF(CF_3)-CF_2-O-CF(CF_3)-$		1 : 1.21 [a]	$(Me_2N)_3PF_2$/diglyme	0 (76.4%)	[91]
CF_3	CO_2CH_3	1 : 2.3	KF/adiponitrile/tetraglyme	0 (31%), 1 (10%)	[73]
CF_3	$CF_2-CO_2CH_3$	1 : 1.07	CsF/tetraglyme	0 (76%)	[112]
$CF_2CO_2CH_3$	$CF_2CO_2CH_3$	1 : 1.23	KF/adiponitrile/tetraglyme	0 (51%)	[136]

[a] Hexafluoropropene/HFPO mixture used. [b] Referred to HFPO used.

4.3.3. Tertiary Fluorinated Alcohols and Pentafluorophenolate

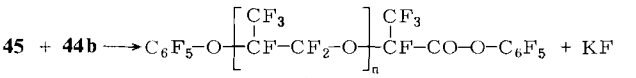
Only a few examples of the reaction of tertiary alkoxides **40** with HFPO have so far been reported[79,140]. The starting compounds **40** are prepared by reacting fluorinated tertiary alcohols **41** with cesium carbonate and, unlike the primary and secondary alkoxides **28** and **36**, are stable in the pure form.



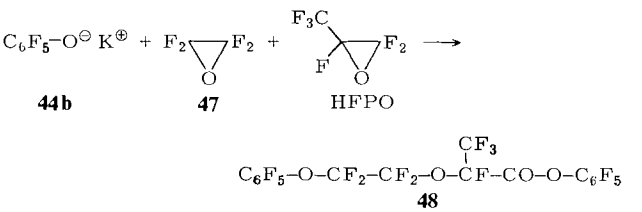
The reaction of the alkoxides **40** with HFPO normally yields higher oligomeric compounds **42**. When 1.14 mol cesium *tert*-perfluoroamylate is reacted with one mole HFPO, about 20% monoaddition product is isolated[140].

Pentafluorophenol **43** can also be converted with alkali carbonate into the phenolate **44**. The result of the reaction of **44** with HFPO is, however, greatly dependent on the cation. When the cesium ion is used (→ **44a**), the expected addition products **45** are formed[141,142]. **45**, n = 1, and **45**, n = 2, are formed together in 90% yield; the product ratio is 55 : 45.

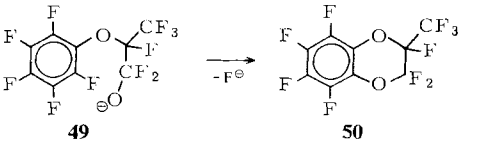
Skoblikova et al.[143] confirm these findings and also state that, when potassium pentafluorophenolate **44b** is used, the esters **46** are obtained instead of the acid fluorides **45**. They are produced by further reaction of the acid fluorides **45** with **44b**.



Experimental data are however available only for the reaction of **44b** with tetrafluoroethylene oxide **47** and HFPO, in which the ester **48** is one of the products isolated.



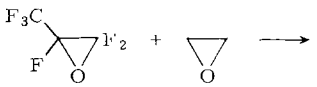
If the reaction of **44a** with HFPO is carried out in the presence of catalytic amounts of cesium carbonate, the alkoxide **49** cyclizes to benzodioxane **50** (yield up to 10%)[144].



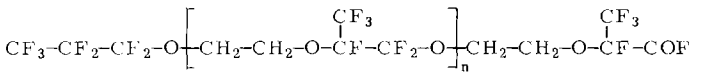
4.4. Reactions of HFPO with Ethers

4.4.1. Non-Fluorinated Ethers

HFPO can react with ethylene oxide **51** in the absence of catalysts to form products having the structure **52**[145].

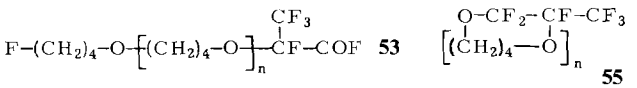


HFPO **51**

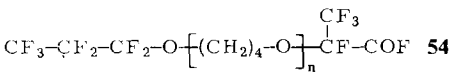


52 ($n \geqslant 0$)

Tetrahydrofuran (THF) also reacts with HFPO. At 0–40°C the products **53**–**55** are formed[146] (for the mechanism and kinetics of this reaction see[146, 147]).



53 **55**



54

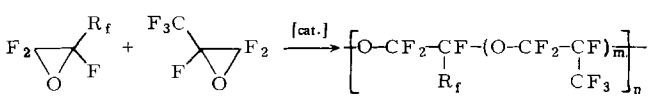
The reaction of HFPO with pure THF proceeds substantially more slowly than the oligomerization of HFPO in the presence of cesium fluoride. THF can therefore be used as a solvent in the preparation of HFPO oligomers **25**[69].

The reaction of HFPO with dimethoxyethane at −25 to +25°C also yields a mixture of substances, from which the following compounds have been characterized[146].

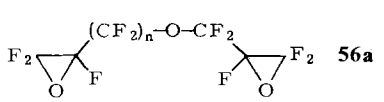
HFPO + $CH_3-O-CH_2-CH_2-O-CH_3$ ⟶
CH_3F + $CH_3-O-CH_2-CH_2-F$ + $CH_3-O-CF(CF_3)-COF$
+ $CH_3-O-CH_2-CH_2-O-CF(CF_3)-COF$
+ $CH_3-O-CH_2-CH_2-O-CF(CF_3)-CF_2-O-CH_3$
+ $CH_3-O-CH_2-CH_2-O-CF_2-CF(CF_3)-O-CH_3$
+ $CF_3-CF_2-CF_2-O-CH_3$

4.4.2. Fluorinated Ethers

HFPO can be copolymerized with other fluorinated epoxides **56** and **56a**. Polyethers having the general structure **57** are thereby produced. A fluorinated alkoxide is normally used as catalyst.



56 HFPO **57**

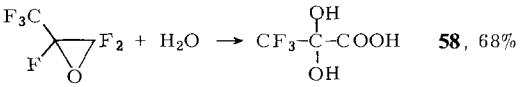


56a

The following epoxides have been used: **56**, $R_f=(CF_2)_n-CF=CF_2$, n = 0 to ≈10[148]; $R_f=(CF_2)_2X$, X = Cl, Br, C_3F_7[149]; $R_f=CF_2-O-X$, $X=(CF_2)_2SO_2F$[150], $(CF_2)_4COF$[150], $(CF_2)_2CN$[150, 151], $(CF_2)_3-O-C_6F_5$[150], $CF_2-CF(CF_3)-O-(CF_2)_2-CN$[150], C_6F_5[150]; **56a**, n = 3 or 6[151].

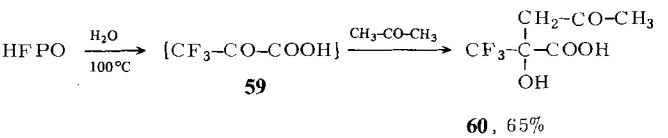
4.5. Reactions of HFPO with Water, Alcohols, and Thiols

HFPO reacts with water in dioxane as solvent (room temperature, glass ampule) to form the hydrate **58** of trifluoropyruvic acid[152].



HFPO **58**, 68%

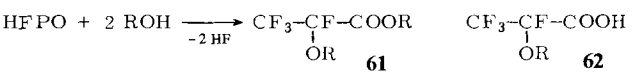
By raising the temperature and using SiO_2 the yield can be increased to 80% (reaction in steel vessel, solvent: ether)[152]. If hydrolysis is carried out in the presence of acetone, the trifluoropyruvic acid **59** produced as an intermediate reacts further to give the acid **60**[152].



59

60, 65%

When primary or secondary alcohols are used instead of water, solvolysis of HFPO is not as complete and the 2-alkoxytetrafluoropropionic acid esters **61** are obtained. The same reaction with the addition of alkali yields the 2-alkoxytetrafluoropropionic acids **62**.



61 **62**

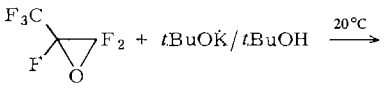
One special case is the reaction of HFPO with methanol/potassium hydroxide solution and hydrogen peroxide, which leads to trifluoroacetic acid[153]. Table 7 lists the results of the reaction of HFPO with alcohols.

Table 7. Reactions of alcohols with HFPO to give esters **61** or acids **62**.

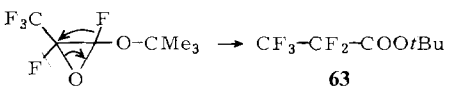
ROH/MOH	Yield [%] **61**	**62**	Ref.
MeOH/—	up to 96		[52, 152, 154, 155]
MeOH/KOH		16 [a]	[153]
EtOH/—	up to 70		[52, 53, 152, 156]
EtOH/NaOH		69	[154]
*i*PrOH/—	52		[52, 154]
s-BuOH/—	28		[154]
$ClCH_2-CH_2OH$/—	42		[52, 154]
$CH_2=CH-CH_2OH$/—	41		[52]
Ph−OH/—	13		[52, 154]
$H(CF_2)_2CH_2OH$/—	14		[52, 154]
$H(CF_2)_4CH_2OH$/NaOH		46	[157]
$H(CF_2)_6CH_2OH$/NaOH		67	[157]

[a] With 22% conversion.

HFPO is not affected in *tert*-butyl alcohol even in the presence of fluoride ions. On the other hand, a solution of potassium *tert*-butoxide in *tert*-butyl alcohol reacts with HFPO even at 20°C. The *tert*-butyl perfluoropropionate **63** is isolated in 91% yield[158]. The formation of the "abnormal" product would seem to be due to the steric hindrance of the alkoxide.



HFPO



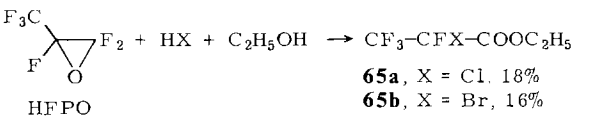
63

Ethanethiol reacts with HFPO to form the thio ester **64**[52, 154].

HFPO + 2 EtSH ⟶ CF_3–CF(SEt)–COSEt **64**, 40%

4.6. Reactions of HFPO with Hydrogen Halides and Sodium Iodide

The reaction of HFPO with solutions of HCl or HBr in ethanol was first described as long ago as 1966. The halide attacks the epoxide at C-3 to give the 2-chloro- and 2-bromotetrafluoropropionic acid ethyl esters **65a** and **65b**, respectively[52, 154].



HFPO

65a, X = Cl, 18%
65b, X = Br, 16%

A substantially higher yield is quoted in the literature[53] for 2-bromotetrafluoropropionic acid **66**.

HFPO + HBr(H_2O) ⟶ CF_3–CFBr–COOH
66, 74%

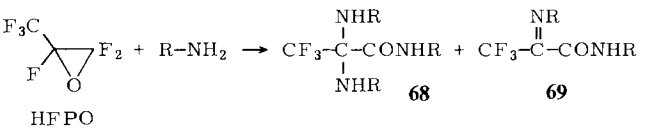
The reaction of HFPO with sodium iodide in acetone proceeds spontaneously and, after treatment with ammonia, yields the ammonium salt **67** of 2,3,3,3-tetrafluoropropionic acid[159].

HFPO $\xrightarrow[-F^{\ominus}]{+I^{\ominus}}$ CF_3–CFI–COF $\xrightarrow[-I_2]{+I^{\ominus}}$ $[CF_3–CF–COF]^{\ominus}$
$\xrightarrow{CH_3–CO–CH_3}$ CF_3–CHF–COF $\xrightarrow[2)\ NH_3]{1)\ H_2O}$ CF_3–CHF–$COONH_4$
67

See Section 6.2 for details of the reaction of HFPO with anhydrous hydrogen fluoride.

4.7. Reactions of HFPO with Ammonia, Primary Amines, and Dimethylaminotrimethylsilane

Unlike secondary and tertiary amines, which yield perfluoropropionic acid derivatives when reacted with HFPO, ammonia and most primary amines attack the HFPO at C-3. Depending on the group R, compounds having the structure **68** and/or **69** are obtained[52].



HFPO **68** **69**

R	**68**, yield [%]	**69**, yield [%]
H	41 (10.5 [152])	–
Et	–	50
Ph	70	–
o-Cl–C_6H_4	25	5
m-Cl–C_6H_4	64	–
p-Cl–C_6H_4	70	–
o-MeC_6H_4	–	52
p-MeC_6H_4	69	–

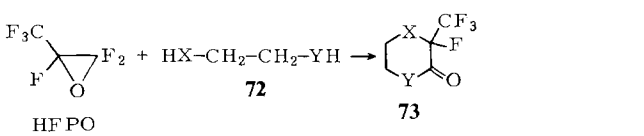
In these reactions small quantities of perfluoropropionic acid derivatives occur as by-products[64]. See Section 4.1 for details of reactions of primary amines in which the perfluoropropionic acid derivative is the main product.

Trimethyl(dimethylamino)silane **70** is so far the only highly substituted amine that reacts with HFPO without forming perfluoropropionic acid fluoride **7** or its derivatives. Instead the substituted propionic acid amide **71** is formed[66].

HFPO + 2 Me_3SiNMe_2 ⟶
70
CF_3–CF(NMe_2)–$CONMe_2$ + 2 Me_3SiF
71

4.8. Reactions of HFPO with Bifunctional Alcohols, Thiols, and Aromatic Amines

Some bifunctional nucleophiles react with HFPO to form heterocyclic compounds. A frequent side reaction is isomerization of HFPO to perfluoropropionic acid fluoride **7**, which reacts to form derivatives (e.g. **74**, **81**, **82**) (see Section 4.1). Thus, the 1,2-bifunctional ethanes **72** react with HFPO to yield heterocyclic compounds having the structure **73**[64].

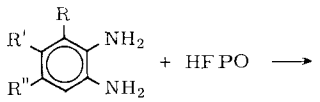


HFPO **72** **73**

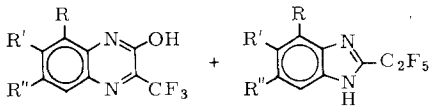
+ C_2F_5–CO–X–CH_2–CH_2–Y–H
74

X	Y	**73**, yield [%]	**74**, yield [%]
O	O	40	
O	S	19	11
S	O	21	
S	S	26	40

In an analogous way, when *o*-disubstituted arenes **75**, **76**, **77** are used, the benzo-annelated compounds **78**[160], **79**[60], and **80**[60], respectively, are produced.



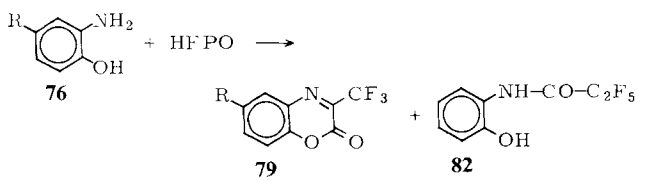
75



78 81

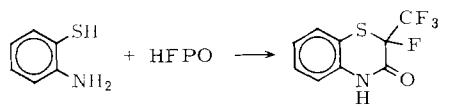
R	R′	R″	78, yield [%]	81, yield [%]
H	H	H	84 [60], 22	10
H	Me	H	43	
H	Cl	H	31 [a]	16.5
H	H	COOH	24.9	
–(CH=CH)$_2$–		H	53	

[a] By-product: **78**, R = R′ = H, R″ = Cl (1.5%).



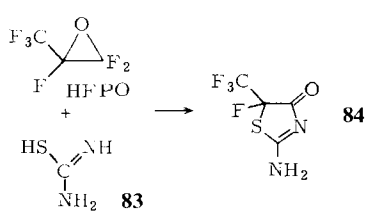
76 79 82

R	79, yield [%]	82, yield [%]
H	66 (in dioxane) 45 (in CH_3CN)	(≤7) 22
Me	76	
Cl	83	



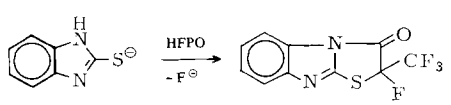
77 80 (26%)

Thiourea **83** and HFPO react quantitatively to give the 2-aminothiazolone **84**[53].

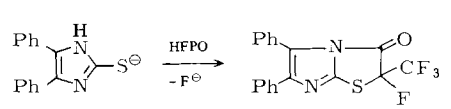


84

Analogously to the synthesis of **84**, the heterocyclic compounds **87** and **88** are accessible when 2-benzimidazole thiolate **85** or 4,5-diphenyl-2-imidazole thiolate **86** and HFPO are used as the reactants[61].

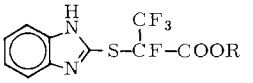


85 **87**, 55%

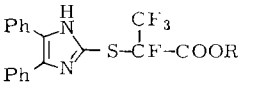


86 **88**, 60%

The reactions were carried out in aprotic solvents such as acetonitrile or dioxane. When an aliphatic alcohol is used as solvent, ring closure does not take place and the esters **89** and **90**, respectively, are obtained[61].



89, R = Me 81%
Et 89%
*i*Pr 77%
CH_2–CH_2–Cl 72%

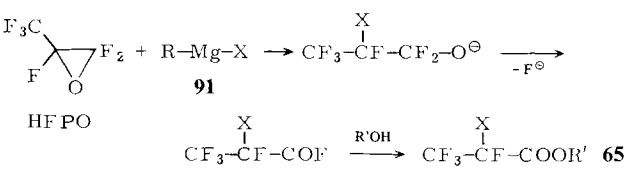


90, R = Me 82%
Et 85%
*i*Pr 77%

4.9. Reactions of HFPO with Organometallic Compounds

4.9.1. Grignard Reagents

Equimolar quantities of Grignard reagents **91** and HFPO give the 2-halogenotetrafluoropropionic acid esters **65** in yields of up to 65% if work-up is carried out in an aliphatic alcohol[159].

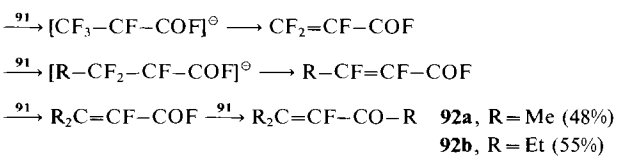


HFPO **91** **65**

This, however, applies only to Grignard reagents **91** with X = Cl or Br; no defined product could be obtained when methylmagnesium iodide was used.

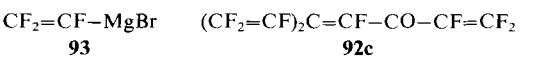
The reactions of **91** with HFPO in the molar ratio 1 : 1 do not yield compounds that indicate the incorporation of an alkyl group in the HFPO molecule. Perfluoropropionic acid derivatives are likewise not detectable.

Excess Grignard reagent **91** causes secondary reactions that give the unsaturated ketones **92**[159].



92a, R = Me (48%)
92b, R = Et (55%)

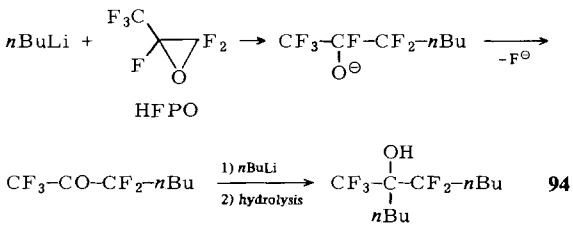
The reaction of trifluorovinylmagnesium bromide **93** with HFPO in a molar ratio of 4 : 1 yields only very high-boiling material, whose formation via the ketone **92c** (R : $CF=CF_2$) can be explained by further reaction with **93**[159].



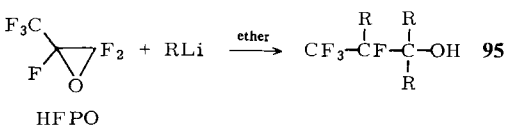
93 **92c**

4.9.2. Alkyllithium Compounds

The reaction of HFPO with butyllithium in hexane is another example of the attack by a nucleophile at C-2 of HFPO. The tertiary alcohol **94** is obtained[161].



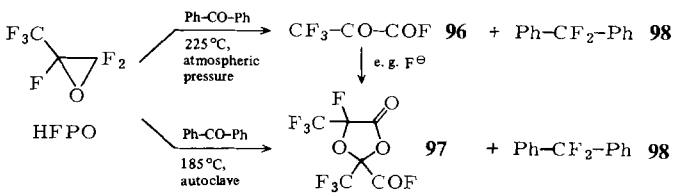
By way of contrast, in the presence of ether the nucleophile attacks primarily at C-3, and the tertiary alcohol **95**, R = *n*Bu, is produced in 55% yield. Other alkyllithium compounds have also been used for this reaction[161] (R = Me, Et, *n*Pr, *n*-C_5H_{11}; yields 92, 52, 45, 44%).



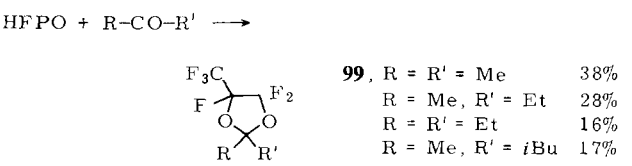
Attempts to react HFPO with pentafluorophenyllithium, trifluorovinyllithium or trifluoropropynyllithium failed to produce any defined products[161].

5. Perfluoropyruvic Acid Fluoride and Derivatives

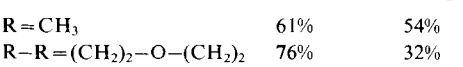
The reaction of HFPO with carbonyl compounds such as benzophenone (or benzaldehyde) at temperatures of about 200°C yields monomeric **96** or dimeric perfluoropyruvic acid fluoride **97**[162], depending on the reaction conditions; difluorodiphenylmethane **98** is formed as a by-product[163].



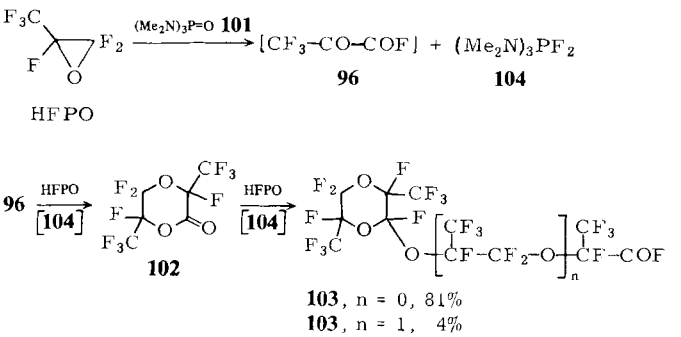
Unlike the reaction just described, the reaction of HFPO and aliphatic ketones at temperatures of 20–60°C gives moderate yields of 1,3-dioxolanes **99**[164].



Reaction of HFPO with dimethylformamide[165,166] or other *N*-formylated secondary amines[166] leads to formation of **97**, even below room temperature. Partially fluorinated tertiary amines **100** are thereby produced in equimolar quantity to the reacted HFPO.

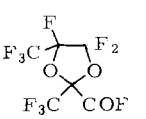


Perfluoropyruvic acid fluoride **96** occurs as an intermediate product in the reaction of HFPO with hexamethylphosphoric acid triamide **101**. It reacts with further HFPO to give the dioxanes **102** and **103**[167]. The difluorophosphorane **104** produced from **101** acts as a catalyst in the further reaction of **96** with HFPO (for the further use of **104**, see Tables 1, 4, and 6).



The reaction of HFPO with a mixture of dimethylformamide and **104** or **101**, similarly gives the products **102** and **103**, whereby the dimethylformamide is required solely as a reagent for the production of **96**, whereas the **104** produced from **101** or introduced direct is used as a catalyst for the formation of **102** and **103**[168].

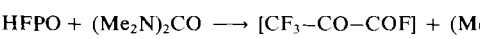
The reaction of **96** with HFPO to give dioxane **102** (73% yield) using cesium fluoride in diglyme as the catalyst has also been described[162]. Heating the reaction mixture to 140°C leads to formation of the dioxolane **105**.



105, 70%

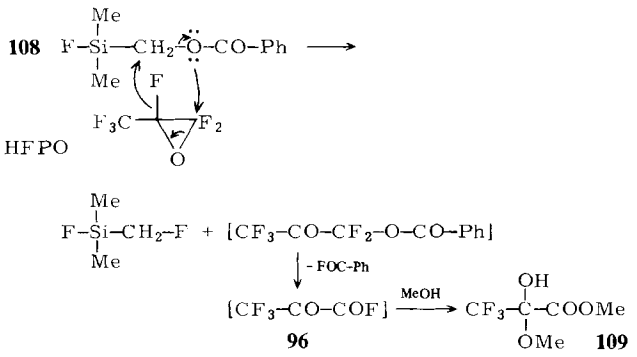
HFPO also reacts with tetramethylurea **106** to give **96** and its derivatives[93].

Evidently, the oligomerization of HFPO under the influence of the **107** produced proceeds substantially faster than the reaction with **106**, because mainly the simple oligomers **25** are isolated[93].

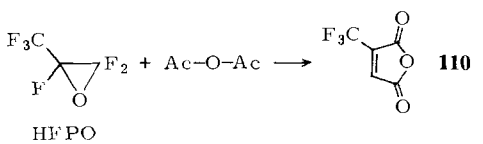


Perfluoropyruvic acid fluoride **96** is present as an intermediate product in two more reactions of HFPO.

The reaction of HFPO with the silane **108** is likewise formulated in terms of intermediary perfluoropyruvic acid **96**. Work-up with methanol furnishes the trifluoropyruvic acid derivative **109**[169].



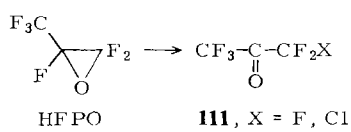
The unexpected formation of α-trifluoromethylmaleic anhydride **110** from HFPO and acetic anhydride also evidently proceeds via **96**. The proposed mechanism was verified by reaction of **96** (used as dimer **97**) with acetic anhydride[163].



6. Reactions of HFPO with Electrophiles

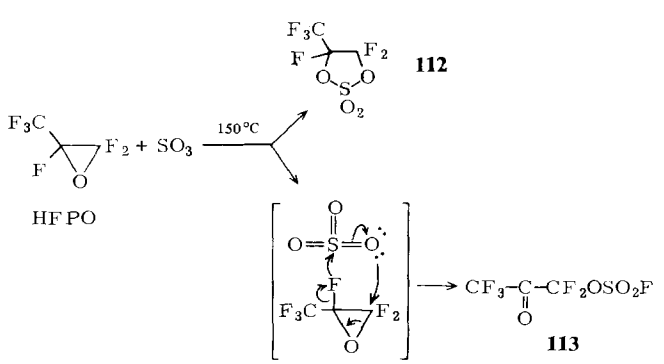
6.1. General

The numerous reactions of HFPO with nucleophiles underline its electrophilic properties. As is to be expected, reactions of HFPO with electrophiles are rarely observed, especially as they require even higher temperatures. The oxirane ring is changed into a keto function; in contrast to the reactions with nucleophiles, the oxygen atom remains bound to C-3 of HFPO.



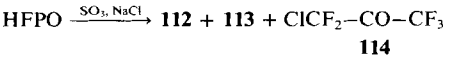
There are as yet no agreed ideas on the mechanism of formation of the keto derivatives **111** from HFPO and the various other reactants with their differing degrees of electrophilicity.

On reaction of SO_3 with HFPO at 150°C[170] the addition of SO_3 at the oxirane ring to give 1,2-perfluoropropylene sulfate **112** competes with the fluorophilic attack of SO_3 at the fluorine atom on C-3 of HFPO to form 2-oxoperfluoropropyl fluorosulfate **113**.



Since **112** cannot be isomerized to **113** either thermally or in the presence of KF, SO_3 or NEt_3, two independent synthesis routes are assumed[170]. **113** is similarly formed when HFPO is heated with FSO_3H to 200–220°C, and is the sole product formed even at room temperature when chromium(III) oxide is added[21].

If NaCl is added to the reaction mixture of HFPO and SO_3, formation of chloropentafluoroacetone **114** occurs in addition to **112** and **113**[170].

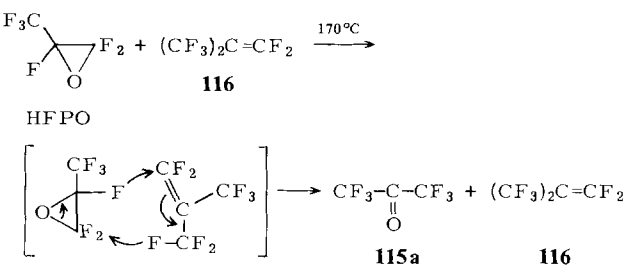


114 is also found as the main product in the thermal reaction of HFPO with $CaCl_2$[171] and with SO_2Cl_2[170], whereas predominantly hexafluoroacetone **115a** can be isolated alongside **114** when $SbCl_5$ is used[170]. This difference in behavior can be explained by the firm bonding of fluorine in calcium or sulfonyl fluorides.

6.2. Isomerization of HFPO to Hexafluoroacetone

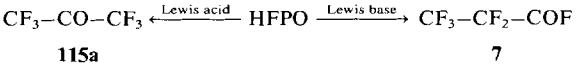
The rearrangement of HFPO in the presence of catalysts, which facilitate the migration of the F atom from C-3 to C-2 of HFPO, is an important route to the reactive hexafluoroacetone **115a**.

The highly electrophilic octafluoroisobutene **116** acts in this way. When it is heated with HFPO to 170°C, it brings about isomerization to **115a** in 77% yield and can be recovered as such[170].



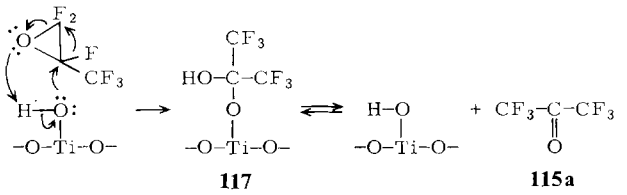
Isomerization of HFPO to **115a** in the presence of SbF_5 must be formulated similarly but can be made to yield **115a** almost exclusively with quantitative conversion of HFPO[172, 173].

Metal oxides, too, can be employed for rearrangement reactions of HFPO, especially in the vapor phase[174]. Depending on their characteristics as Lewis acids or Lewis bases, either **115a** or **7** or mixtures of both are then obtained.



Metal oxides, such as TiO_2, γ-Al_2O_3 or Cr_2O_3, which have OH groups at their large surface after calcination at 400–500°C max., selectively catalyze the rearrangement of HFPO to **115a**. IR spectroscopic investigations of TiO_2,

which was treated with HFPO[175] or with **115a**[176], showed that both isomers are not absorbed physically at the surface but react chemically with OH groups at the surface to give the same structural element **117**. When the temperature is raised, only **115a** is liberated from the surface[175].



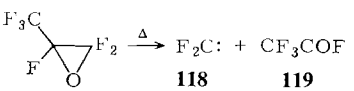
117 **115a**

The activity and selectivity of γ-Al_2O_3 and Cr_2O_3 are said to be improved if they are pretreated with HF or NH_4F[177-180], treated with HFPO[181], or assisted by promoters such as perfluoroketones or perfluoroalkyl fluoroformates[182]. Similarly, the use of mixed oxides, e.g. of SiO_2/Al_2O_3[177], Cr_2O_3/Al_2O_3 and Cr_2O_3/TiO_2[179,180], is described for HFPO conversions up to 100% and selectivities for **115a** up to 97% at 110–130°C.

Differing results have been obtained in the isomerization of HFPO to **115a** in the liquid phase. Whereas $AlCl_3$ in liquid SO_2 at room temperature rearranges 79% of the HFPO to **115a** and some **7**[174], conversion in hydrogen fluoride at 100°C under autogenous pressure proceeds at a conversion rate of 99% and a selectivity of 99%[183]. **115a** then appears as an adduct with HF, which can be used directly for addition and condensation reactions with phenols and methylarenes.

7. HFPO as a Source of Difluorocarbene

When heated to temperatures above 150°C, HFPO decomposes exclusively into difluorocarbene **118** and trifluoroacetyl fluoride **119** with a half-life of about 6 h at 165°C[184].

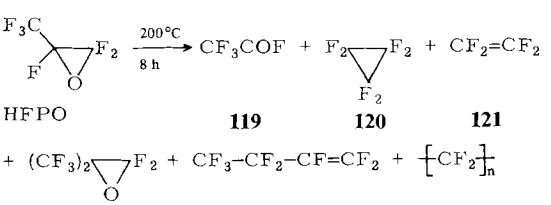


118 **119**

HFPO

In the absence of suitable reactants hexafluorocyclopropane **120** and **119** are the main products at 200°C. The byproducts occurring in the reaction of **118** with itself or with HFPO are tetrafluoroethylene **121**, octafluoroisobutene oxide **139a**, perfluoro-1-butene and polytetrafluoroethylene[185].

Of the starting materials that eliminate difluorocarbene **118** purely thermally, HFPO offers several advantages.



HFPO **119** **120** **121**

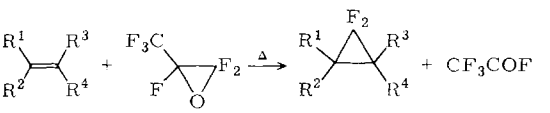
139a

Thus, it decomposes at lower temperatures (170–220°C) than **120** and **121** and yet is much more easily accessible than the fluoro(trifluoromethyl)phosphoranes $(CF_3)_{5-x}PF_x$ (x = 1–4), which eliminate **118** at even lower temperatures. HFPO can be ranked alongside sodium chlorodifluoroacetate in terms of use as a donor of **118**, being suitable chiefly for reactions with low-boiling substances.

7.1. Thermal Reactions of HFPO with Alkenes

7.1.1. Fluorocyclopropanes

HFPO does not react with olefinic double bonds below the elimination temperature of **118**. By way of contrast, mixtures of HFPO with alkenes **122** react above 170°C to give cyclopropanes **123**, in which **118** once again occurs as a ring component.

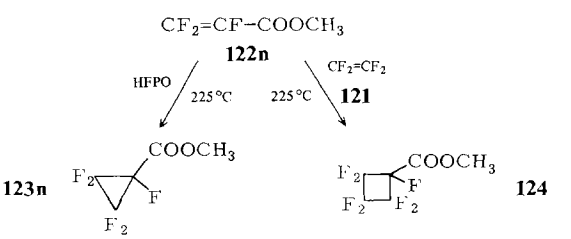


122 HFPO **123** **119**

Almost exclusively **119** occurs as byproduct, which generally does not react with **122** and can be easily removed from the reaction product because of its low boiling point. Table 8 lists some cyclopropanes **123** accessible by this route which are derived from non-halogenated as well as partially- to perhalogenated olefins.

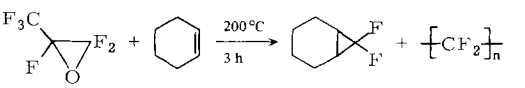
Sargeant succeeded in showing that **118** produced from HFPO adds stereospecifically, e.g., to *trans*-**122d** to give *trans*-**123d**[185]. The *cis*-isomer of **122d** behaves analogously. The pure isomers **123d** are converted into the equilibrium mixture (*cis*:*trans* = 33:67) only on prolonged heating to 200°C.

An interesting observation is that, at 225°C, HFPO reacts with **122n** to form **123n**[199], while **121** does not liberate any difluorocarbene **118** but undergoes cycloaddition with **122n** to give methyl heptafluorocyclobutanecarboxylate **124**.



123n **124**

118 adds to cyclohexene to give difluoronorcarane **125** in only moderate yield[200]; it also reacts with itself to give polytetrafluoroethylene.



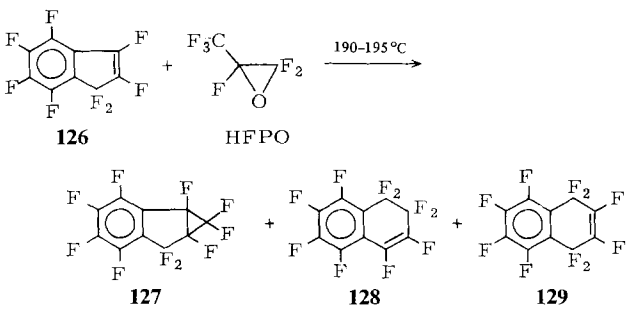
HFPO **125**, 35%

Table 8. Reactions of alkenes **122** with HFPO to give fluorocyclopropanes **123**.

	R^1	R^2	R^3	R^4	T [°C]	t [h]	**123** B.p. [°C]	Yield [%]	Ref.
a	Cl	H	H	H	200	8	—	50	[186]
b	Br	H	H	H	185	8	68-68.5	—	[187-189]
c	F	Cl	H	H	185	8	31	—	[188-190]
d	F	Cl	H	F	180	6	25-28	57	[185, 191]
e	F	Cl	F	Cl	185	6-8	37-40	85	[185, 191, 192]
f	F	F	H	F	185	6	−10	65	[191]
g	CH_3	F	H	H	185	6	34	—	[190, 193]
h	CH_3	CF_3	H	H	185	5.75	51	1	[193]
i	CF_2Cl	Cl	F	F	185	8	57-58	60-70	[194-196]
k	CF_2Br	Br	H	H	185	8	[a]	67	[197, 198]
l	CF_3	F	F	F	—	—	—	50	[185, 200]
m	CF_3O	F	F	F	210	8	−4 to −2	60	[185, 200]
n	$COOCH_3$	F	F	F	225	—	[b]	17	[199]
o	n-C_5H_{11}	H	H	H	200	3	129-130	56-88	[200]
p	$H(CF_2)_5$	F	F	F	200	—	180-182	53	[200]
q	n-C_6F_{13}	F	F	F	200	—	94	—	[200]
r	C_6F_5	Cl	F	F	215	—	—	—	[201]
s	C_6F_5	F	F	F	190	—	—	—	[201]

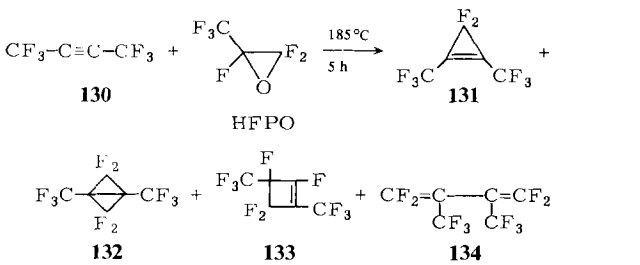
[a] B.p. 62-64°C/100 torr. [b] M.p. 41-43°C.

The cycloaddition product **127** obtained on reaction of **118** with perfluoroindene **126** partially rearranges at 190—195°C into the dihydronaphthalenes **128** and **129**, which are the main products at 230°C[202].



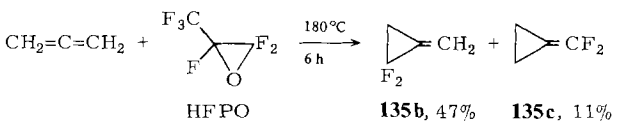
7.1.2. Fluorocyclopropene and Difluoromethylenecyclopropanes

If difluorocarbene **118** is eliminated from HFPO in the presence of alkynes or allenes, both 1:1 and 2:1 addition products are obtained. On being heated with HFPO to 185°C hexafluorobutyne **130** adds **118** to give 3,3-difluoro-1,2-bis(trifluoromethyl)cyclopropene **131**[203].

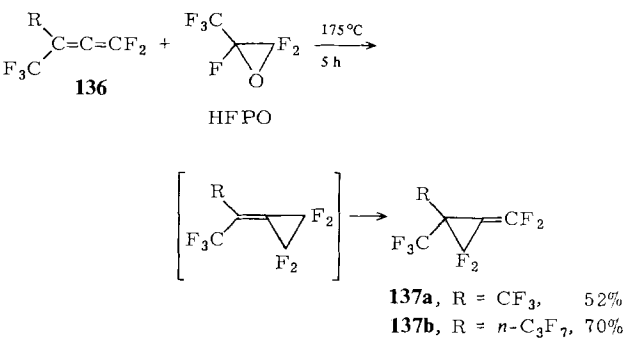


Moreover, an isomeric mixture of 2:1 adducts of **118** and **130** (perfluoro-1,3-dimethylbicyclo[1.1.0]butane **132**, perfluoro-1,3-dimethylcyclobutene **133**, and perfluoro-2,3-dimethylbutadiene **134**) is isolated.

An exocyclic double bond is preserved in the reaction of allenes with HFPO at 175—180°C. The reaction conditions are mild enough, e.g., for allene to be converted predominantly into 1,1-difluoro-2-methylenecyclopropane **135b** with only very little being converted into the isomer 1-(difluoromethylene)cyclopropane **135c**[204], which is formed from **135b** by thermal rearrangement.



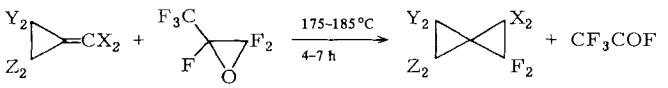
In the case of substituted perfluoroallenes **136**, on the other hand, the primary products are rearranged completely into the perfluoromethylenecyclopropanes **137** even at 175°C[205].



7.1.3. Fluorinated Spiropentanes

Also methylenecyclopropanes **135** add difluorocarbene **118** to the exocyclic double bond under the conditions of HFPO decomposition and are converted into fluorinated spiropentanes **138**. By this route it was possible to synthesize difluoro- (**138a**), tetrafluoro- (**138b**, **c**), hexafluoro- (**138d**) and perfluorospiropentanes (**138e**)[198]. The starting compounds **135b**, **c** are accessible as a separable mixture (see Section 7.1.2). **135d** and **135e** can be prepared from **123k**[179] or **123i**[194], which in turn are products derived

from alkenes and HFPO, by dehalogenation with zinc/dioxane[198].

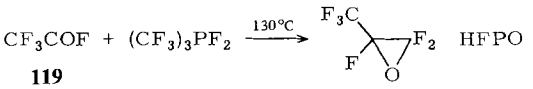


135 HFPO **138** **119**

	X	Y	Z	Yield [%]
a	H	H	H	34
b	H	H	F	–
c	F	H	H	–
d	F	F	H	63
e	F	F	F	36

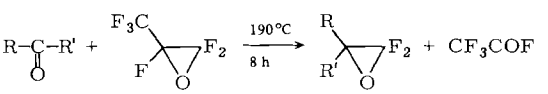
7.2. Reactions of HFPO with C=O, C=S, and C=N Double Bonds

The thermal decomposition of HFPO to difluorocarbene **118** and **119** is reversible; **119** reacts with **118**, which was generated at 130°C from $(CF_3)_3PF_2$, to give HFPO[184].



119

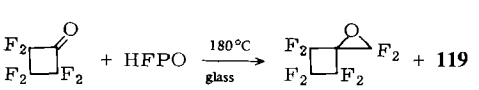
HFPO can also be employed for the synthesis of other perfluoroepoxides **139**, which remain stable at the temperatures for liberation of **118** from HFPO. Examples are the reactions of HFPO with perfluoroketones **115** at 190°C[200,206]. No data regarding yields are available, except in the case of **139a** (50%).



115 HFPO **139** **119**

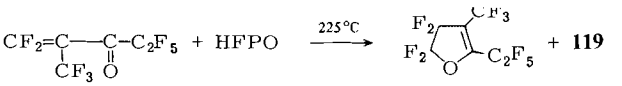
a, R = R' = CF_3; **b**, R = R' = C_2F_5; **c**, R = iC_3F_7, R' = CF_3; **d**, R = R' = CF_2Cl; **e**, R = CCl_3, R' = CF_3

Perfluorospiroepoxide **140**, which is highly stable to heat and radiation, can be obtained in yields of over 90% by reaction of HFPO with perfluorocyclobutanone at 180°C; however, at 220°C and in the presence of steel it is converted into a number of secondary products[207].



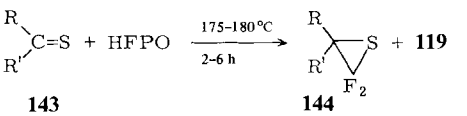
140

If difluorocarbene **118** is generated from HFPO in the presence of perfluoroethyl-(1-methylvinyl)ketone **141** at 225°C, perfluoro-2,3-dihydrofuran **142** is formed with the incorporation of keto function and conjugated C=C double bond[208].



141 **142**

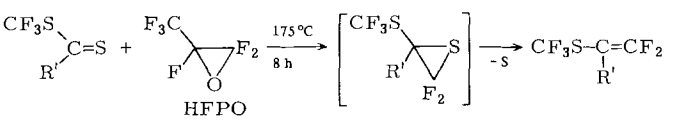
Co-pyrolysis of thiocarbonyl compounds **143** with HFPO at 175–180°C leads to formation of fluorinated thiiranes **144**, which are obtained in yields of up to 56% under strictly controlled reaction conditions[209–211].



143 **144**

	R	R'	Yield [%]
a	F	F	50
b	CF_3	F	42.5
c	Cl	F	20–30
d	CF_3	CF_3	56

For the preparation of **144a** this is the best laboratory method known so far. Less successful, on the other hand, was the attempt to produce CF_3–S-substituted thiiranes by reaction of thiocarbonyl compounds **143e–g** with HFPO; after splitting off of the sulfur, only the ethylenes **145e–g** could be identified[212].



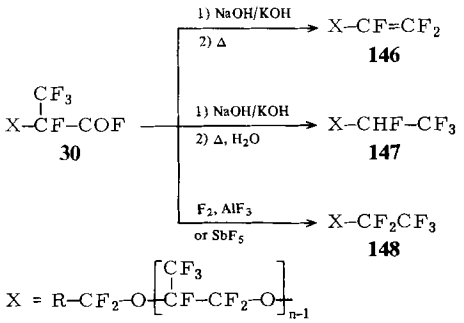
HFPO

143e, R' = CF_3S **145e**, 47.5%
143f, R' = Cl **145f**, 40.6%
143g, R' = F **145g** –

Pentafluoro-2-aza-1-propene, $CF_3–N=CF_2$, remains unchanged when it is heated with HFPO to 200°C[213]. CF_3COF **119** and $CF_2=CF_2$ were obtained as pyrolysis products of HFPO.

8. Uses

Some of the intermediate products of HFPO described above have now gained importance in industrial applications, particularly the perfluorinated 2-alkoxypropionic acid fluorides **30**, which have very different uses, depending on the type of modification of the skeletal unit $-CF(CF_3)COF$ derived from one molecule of HFPO. Industrially important derivatives of **30** are comonomers **146** with the trifluorovinyloxy group, which are accessible by dry pyrolysis of the alkali metal salts prepared from **30**. Thermal treatment in the presence of moisture leads, in contrast, to the products **147** with the tetrafluoroethoxy radical as a stable end group. The perfluoroethyl ethers **148** are formed on reaction of **30** with fluorinating agents[214].



8.1. Comonomers for the Modification of Polytetrafluoroethylene (PTFE)

Copolymers of tetrafluoroethylene **121** and vinyl ethers **146** extend the uses of fluoropolymers considerably, without reducing the unusual thermal stability and chemical inertness of PTFE.

Perfluoropropylvinyl ether **146**, $R=C_2F_5$, $n=1$, lowers the melt viscosity of the copolymer with **121** sufficiently to make injection molding and extrusion possible. Under the trademarks Teflon® PFA (du Pont) or Hostaflon® TFA (Hoechst AG) it is used for linings in pipes, valves, and pumps, and for wire and cable insulation[215,216]. Perfluoromethylvinyl ether **146**, $R=F$, $n=1$, copolymerizes readily with **121**, eliminates the crystallinity of PTFE when added in amounts of over 30 mol%, and gives a perfluorinated elastomer (Kalrez®, du Pont)[217]. This material is thermally stable up to 285 °C and has minimal gas permeability and no cold flow. It is suitable for the production of O rings, moldings, membranes, and hoses that are resistant to chemically aggressive media[218].

The copolymers of **121** and **146**, $R=FSO_2CF_2$, $n=2$ and $R=CH_3OOC-(CF_2)_2$, $n=1$-2, contain ion-exchange groups on a perfluorinated carbon skeleton. The main use for these products at present is in membrane technology for alkali chloride electrolysis (Nafion®, du Pont; Flemion®, Asahi Glass)[219,220].

8.2. Perfluorinated Polyethers

Oligomeric HFPO **25**, $n=8$-100, after treatment with fluorinating agents (elemental fluorine, AlF_3, SbF_5), furnishes chemically and thermally stable liquids of differing consistencies with unusual electrical and acoustic properties. The inert liquids of type **148** ($R=C_2F_5$) are used, inter alia, in the chemical industry, in nuclear engineering, in air liquefaction plants, etc.[221] (example: Krytox®, du Pont).

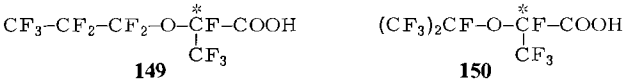
8.3. Oxygen-Dissolving Perfluorinated Inert Liquids

The physiological harmlessness and the comparatively high adsorption power of perfluorinated compounds of the type **147** for gases such as oxygen, nitrogen, and carbon dioxide have focused attention on their use as plasma volume expanders in medicine[222,223].

Such compounds are being tested for use in the perfusion of isolated organs and as oxygen carriers in extracorporeal fluid oxygenators (heart-lung machines)[224].

8.4. Auxiliary Reagents in Synthesis and Analytical Chemistry

Both the dimeric HFPO (**25**, $n=1$) and the product of the nucleophilically catalyzed reaction of hexafluoroacetone with HFPO (**39**, $n=0$, $R=R'=CF_3$) contain a chiral center. *Ishikawa* et al. have used the basic acids **149** and **150**, after separating them into the enantiomers, as chemi-



cally and optically stable chiral *N*-acylating agents for converting α-amino acids into their diastereomers, which can be separated by means of gas chromatography[138,225].

8.5. HFPO as Starting Product for Hexafluoroacetone

The isomerization of HFPO to hexafluoroacetone **115a** described in Section 6.2. opens up a new industrial route to this ketone which prevents the formation of the highly toxic chloropentafluoroacetone **114**. **115a** undergoes a series of novel reactions[227,228], besides the classical reactions of fluorinated ketones[226].

8.6. Outlook

Further derivatives of HFPO such as some partially fluorinated cyclopropanes **123**, which are being tested as inhalation anesthetics[187-190,192,193], are on the advent of being used commercially. Even products already in use are finding new applications. The versatility of HFPO is a challenge to the chemist to find new reactions and to devise new processes for converting HFPO into industrial products. The incentive will be all the greater, the more we succeed in incorporating all the special properties of HFPO into products with unusual stability characteristics.

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Recent Developments in the Field of β-Lactam Antibiotics

By Walter Dürckheimer*, Jürgen Blumbach, Rudolf Lattrell, and Karl Heinz Scheunemann

Dedicated to Professor Rolf Sammet on the occasion of his 65th birthday

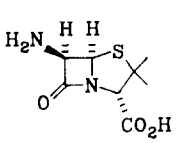
The era of β-lactam antibiotics, which represent the most important class of drugs against infectious diseases caused by bacteria, began more than fifty years ago with the discovery of penicillin G. Further improvements by isolation and structure elucidation of new natural compounds, and systematic chemical modification of these, is a striking example of to what extent chemistry can contribute to the progress of drug therapy. The complex relationship between structure and activity requires, even today, a largely empirical approach. The minimum structural unit for antibiotic activity had to be revised several times over decades. Both the activated β-lactam ring with an acidic group and the nature and spatial arrangement of the other substituents and rings decisively affect the potency, antibacterial spectrum, pharmacokinetics, and toxicity. Totally synthetic mono- and bicyclic compounds from the series of monobactams, penems, carbapenems, 1-oxacephems, and 1-carbacephems are increasingly joining the classic groups obtained by semisynthesis from 6-aminopenicillanic acid and 7-aminocephalosporanic acid.

1. Introduction

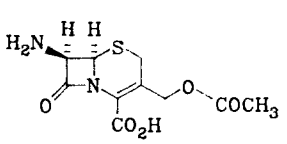
This review attempts to summarize the chemistry and biological activity of the β-lactam antibiotics that have gained significance in clinical practice in the last ten years or are now being clinically tested. Structures that could point the way for future developments are also presented. Drug combinations and prodrug forms are largely not dealt with, although, in therapy, a certain amount of progress can undoubtedly also be achieved with these. There are a number of detailed monographs and reviews on the extremely extensive field of β-lactam antibiotics, dealing with the chemistry, antibacterial activity, biosynthesis, microbiology, and mechanism of action[1–26].

The development in the field of antibiotics is characterized by the fact that, despite the discovery and structure elucidation of thousands of new antibiotics, only relatively few basic structures are to be found among the clinically important antibiotics. Penicillin G has passed on the dominant role it had from the very beginning to the group of structurally related β-lactams, which today constitute about 60% of the antibiotic market and are distinguished by high antibacterial activity, good tolerance, and therapeutic safety.

The further development of β-lactam antibiotics was considerably assisted by the easy technical accessibility of the penicillin and cephalosporin parent compounds, namely, 6-aminopenicillanic acid (6-APA) and 7-aminocephalosporanic acid (7-ACA). A large number of semisynthetic derivatives were isolated and tested. The proportion of successful compounds setting new standards in clinics was relatively low. The main reason for this lies in the complex mechanism of action. The relationships between structure and biological activity are difficult to quantify and do not permit rational design. A great deal of progress originates from chance observations or knowledge which nature hands on to us during the elucidation of the structures of new antibiotics. And so it happened that an acylation product of 7-ACA produced purely by accident was the impetus for the synthesis of the highly active group of aminothiazole cephalosporins. Intensive work on carbapenems and monocyclic β-lactams began in the mid-seventies with the isolation of thienamycins and monolactams from bacteria.



6-APA



7-ACA

The biologically active principle of all β-lactam antibiotics is the β-lactam ring, the reactivity and selectivity of which towards biological substrates can be decisively influenced by substituents or fused rings[21]. The antibacterial properties are based on the ability to selectively inhibit enzymes essential for the synthesis of the stabilizing framework of the bacterial cell wall, the peptidoglycan; this inhibition is accompanied by cleavage of the β-lactam ring.

In recent years, better understanding of the mechanism of action of β-lactam-binding enzymes—described as PBPs (penicillin-binding proteins)—has been achieved. These are transpeptidases which are generally bound to membranes[22]. Some species of *Streptomyces* secrete water-soluble D-alanyl-D-alanine peptidases during growth. Several authors have used such enzymes as models of membrane-bound systems and have investigated binding kinetics with β-lactam antibiotics and β-lactamase inhibitors. From these kinetic data, it can be deduced that, in the first step, β-lactams are reversibly bound to the target enzymes. The

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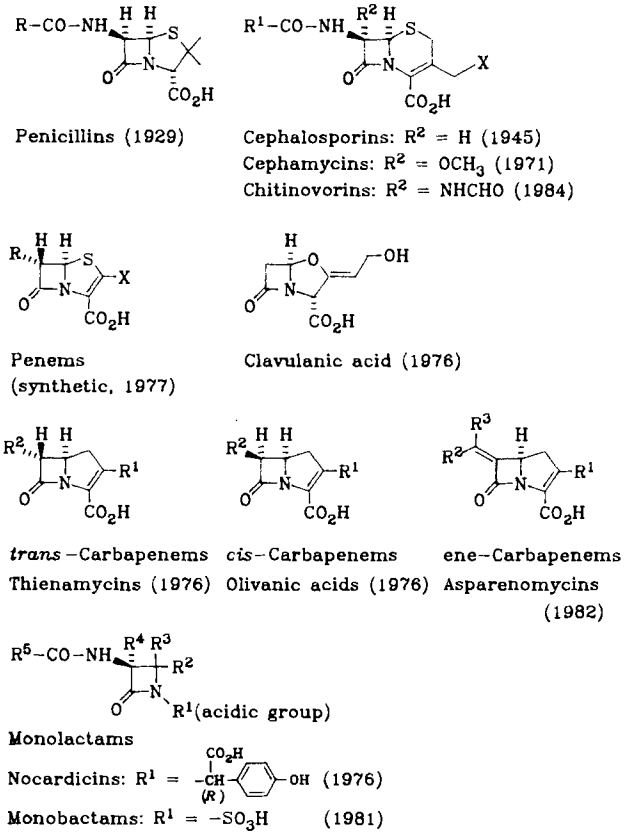


Fig. 1. Basic structures of important categories of β-lactam antibiotics (year of discovery of first compound of this type in brackets).

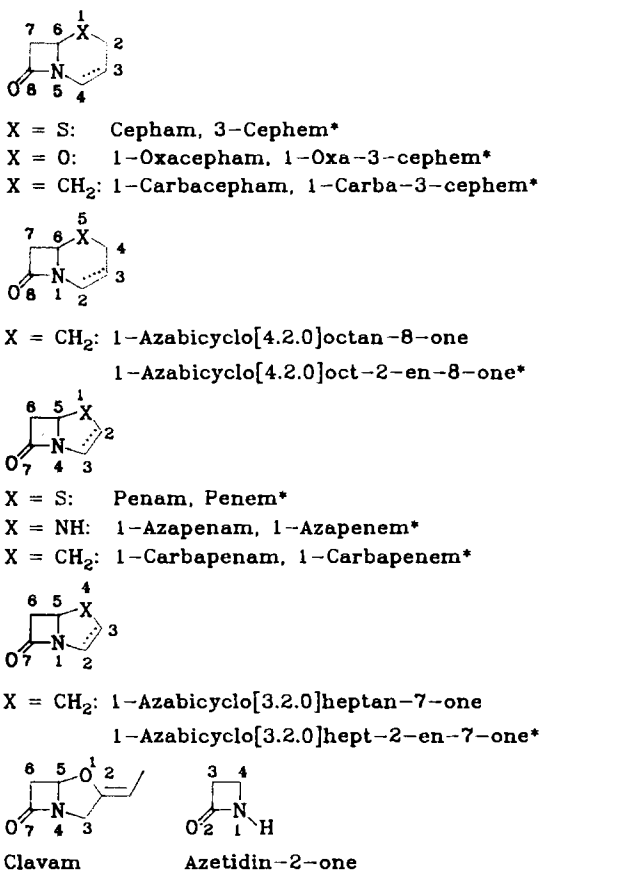


Fig. 2. Nomenclature and numbering of β-lactam skeletons. Names that are followed by a star apply to the compounds with the indicated double bond in the six- or five-membered ring.

following irreversible acylation step is dependent on the nature of the substituents on the β-lactam, which, by dint of additional binding sites on the enzyme, can have a considerable inductive effect. Recently, the three-dimensional structure of a DD-carboxypeptidase/transpeptidase from *Streptococcus R.* 61 was successfully elucidated to a resolution of 2.8 Å, and the specific binding site for β-lactam antibiotics was located[23].

In microorganisms, the interactions with the β-lactam antibiotics are complex and vary from species to species. In Gram-negative bacteria a multilayer cell-wall structure often prevents the active substances from penetrating into the cell. To complicate matters, specific enzymes (the β-lactamases) cleave the β-lactam antibiotics before the target enzymes are reached[17,24,25]. To be antibacterially active, β-lactams have to have the following basic properties:

- good permeation through the outer layers of the cell wall
- high stability against deactivating enzymes, in particular β-lactamases
- a high affinity for the target enzymes (PBPs) essential for bacterial cell-wall biosynthesis.

The combination of these properties, which can nowadays be individually evaluated by special experimental arrangements, determines the antibacterial effectiveness. The minimal inhibitory concentration (MIC) and the minimal bactericidal concentration (MBC) are criteria for assessing the potency. These parameters are determined in vitro.

The pharmacokinetics and toxicity of the antibiotics are of crucial importance for their effectiveness in man[26].

The clinicopharmacological parameters for assessing compounds and ascertaining the optimal regimen are the mode of administration (enteral or parenteral), the distribution up to the site of infection, serum and tissue levels, serum binding, the serum elimination half-life, biotransformation (metabolism), excretion, and the nature and frequency of adverse effects.

The basic structures of important β-lactam antibiotics are presented in Fig. 1. Fig. 2 shows the nomenclature and numbering. The abbreviated chemical names for the β-lactam framework, which are listed on the figure, are often used as an alternative to systematic nomenclature.

2. Penicillins and Cephalosporins

2.1. Structure and Activity

In the last decade, β-lactam research made considerable progress. The antibacterial activity was substantially improved and the activity spectrum appreciably extended in such a way that pathogens which were resistant to the older antibiotics are inhibited by the new compounds. Moreover, the pharmacokinetic properties were improved and the adverse reactions reduced. The development was mainly concentrated on semisynthetic penicillins and cephalosporins. Tens of thousands of semisynthetic derivatives were produced, mainly by reacylation of the amino

group in 6-APA and 7-ACA and, for the cephalosporins, additionally by nucleophilic substitution of the 3′-acetoxy group. Exceptional importance for antibacterial activity is attributed to the 6β- or 7β-acylamido side chain[*], the nature and spatial orientation of the substituents being contributory factors. Aromatically and heteroaromatically substituted acetic acid residues with polar substituents, e.g., hydroxy, carboxy, sulfo, and ureido, proved to be particularly advantageous. In cephalosporins, the substituents in the 3-position are extensively variable and affect antibacterial activity, metabolism, pharmacokinetics, and toxicity.

Various reviews have been published on the classification and biological activity of parenterally and orally administered penicillins and cephalosporins[1-3], which cover the field up to 1981. Since then, new developments in penicillins have been limited. For parenteral cephalosporins and for the nonclassic β-lactams, dynamic progress has taken place.

2.1.1. Penicillins

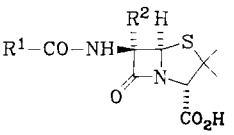
Structural variation of the first broad-spectrum antibiotic ampicillin **1**, which continues to be the most important standard orally administered compound, was a successful step forward in the penicillin field. *p*-Hydroxylation of the phenyl side chain to give amoxicillin **2** brought improvements with regard to absorption and a more rapid bactericidal effect (see Table 1). Ampicillin and amoxicillin are ineffective against β-lactamase-producing microorganisms. Combination with β-lactamase inhibitors[18], such as clavulanic acid **8** and sulbactam **9**, was consequently successful; although such inhibitors themselves show only slight antibiotic activity, they improve the effectiveness of these antibiotics by inhibiting β-lactam-cleaving enzymes.

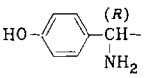
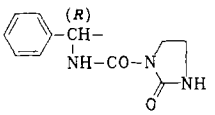
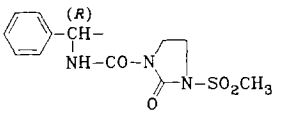
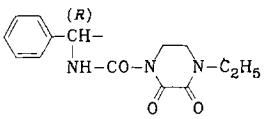
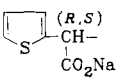
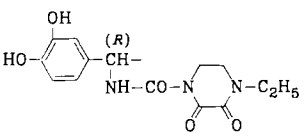
The acylation products of ampicillin and amoxicillin considerably extended the antibacterial spectrum to cover a great number of bacterial genera, provided that these are not pronounced β-lactamase-producing organisms. From Bayer research came the parenterally administered ureidopenicillins azlocillin **3** and mezlocillin **4**, which cover Gram-positive cocci, Enterobacteriaceae, *Bacteroides, Hemophilus,* and, especially, *Pseudomonas*. Piperacillin **5** (Toyama/Pfizer) is comparable in activity to azlocillin against *Pseudomonas*. Its antibacterial spectrum is extensive and includes that of mezlocillin which is mainly effective against Enterobacteriaceae and *Klebsiella*.

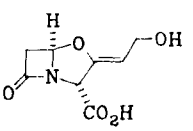
To solve the problem of penicillin resistance with Gram-negative organisms that form numerous β-lactamases, there are new approaches in which a methoxy group is inserted into the 6-position of the ring skeleton, characteristic of cephamycins (cf. Fig. 1). Temocillin **6** (6-methoxyticarcillin) is effective against β-lactamase-forming Enterobacteriaceae, but is ineffective against Gram-positive bacteria and *Pseudomonas*.

An extensive study of 6α-substituted penicillins was carried out at Beecham. The most potent compound in this series, BRL 36650 **7**[27], has a 6α-formylamino group. It is stable against plasmid-coded and chromosomally coded β-lactamases and, in its antibacterial spectrum, is comparable to the third-generation cephalosporins. 7-(Formylamino)cephalosporins were isolated recently as natural fermentation products of *Flavobacterium* species by Squibb[28a] and Shionogi and named chitinovorins by the latter group[28b,c].

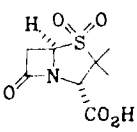
Table 1. Penicillins. The year of discovery is given below the generic name.



No.	R^1	R^2	Generic name and/or scientific code
1		H	Ampicillin (1962)
2		H	Amoxicillin (1971)
3		H	Azlocillin (1974)
4		H	Mezlocillin (1974)
5		H	Piperacillin (1977)
6		OCH_3	Temocillin (1982)
7		NHCHO	BRL 36650 (1984)



8, Clavulanic acid



9, Sulbactam (CP 45 899)

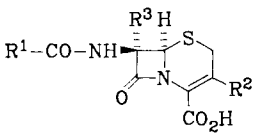
2.1.2. Cephalosporins

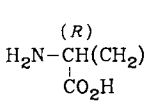
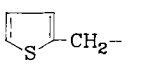
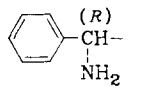
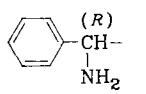
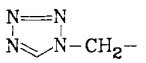
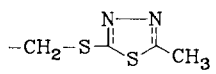
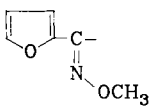
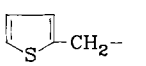
The development of cephalosporins began in 1945 with the isolation of cephalosporin C **10** from a *Cephalosporium acremonium* strain by *G. Brotzu* and with the structure elu-

[*] β and α indicate the spatial orientation of the substituents ("upwards" and "downwards", respectively) in penicillins and cephalosporins when the skeletons are drawn as they are here (N below, S upper right).

cidation by *Newton* and *Abraham* (1961). Cephalosporin C required substantial improvements in the antibacterial spectrum; one could make use of the vast experience of penicillin chemistry. An essential structural variant was discovered in the cephamycins (1971)—these are 7α-methoxycephalosporins with exceptional stability against β-lactamases. The most valuable property of the first semisynthetic cephalosporin, cephalothin **11**, was its high level of activity against penicillin-resistant staphylococci. Further development led to orally effective compounds (Table 2), e.g., cephalexin **12** or cefaclor **13**. However, the activity of these first-generation products against Gram-negative problem bacteria, such as *Proteus, Klebsiella, Shigella, Serratia, Bacteroides, Hemophilus,* and *Pseudomonas,* was insufficient. The main reasons were aggressive β-lactamases in these bacteria and inadequate penetration to the target enzymes. The second generation includes a number of parenterally effective cephalosporins which, on account of extensive stability toward β-lactamases, are also effective against Gram-negative bacteria. Cefazolin **14**, cefuroxime **15**, and cefoxitin **16**, for example, which nowadays play a major role in clinical practice, belong to this generation.

Table 2. First- and second-generation cephalosporins. The year of discovery is given below the generic name.



No.	R^1	R^2	R^3	Generic name
10		$-CH_2-O-COCH_3$	H	Cephalosporin C (1945)
11		$-CH_2-O-COCH_3$	H	Cephalothin (1962)
12		$-CH_3$	H	Cephalexin (1967)
13		$-Cl$	H	Cefaclor (1974)
14			H	Cefazolin (1970)
15		$-CH_2-O-CONH_2$	H	Cefuroxime (1975)
16		$-CH_2-O-CONH_2$	OCH_3	Cefoxitin (1972)

2.1.3. Aminothiazole cephalosporins: Cefotaxime

The most recent generation of cephalosporins, which gained admission to clinical practice a few years ago, will be considered in more detail here. The first example was cefotaxime **17**. This antibiotic was discovered in 1975 by *R. Heymès* et al.[29] in the course of a research program carried out jointly by Hoechst and Roussel-Uclaf. After numerous carboxylic acids had already been coupled with 7-ACA, it was very surprising that its acylation with the easily accessible 2-aminothiazol-4-ylacetic acid should afford a highly active key compound. This compound had to be further modified, since its β-lactamase stability was not entirely satisfactory. The introduction of a *syn* methoxyimino group onto C-2 of the 7-side chain was the decisive step in overcoming this obstacle. The *syn* configuration is essential.

It should be mentioned that Takeda (Japan) has independently synthesized the *anti*-methoxyimino isomer of cefotaxime and the corresponding amino compound obtained from this by reduction. Both compounds have only minimal antibiotic activity. With cefotaxime, a decisive improvement in the intensity of action and in the spectrum of parenterally administered cephalosporins was achieved. Whereas its activity against Gram-positive bacteria is comparable to that of the older cephalosporins (Table 2), an improvement by a factor of 10—100 is achieved with many Gram-negative bacteria. *Serratia,* indole-positive *Proteus,* and many multiply resistant strains of *E. coli, Proteus, Klebsiella,* and Enterobacteriaceae are covered. Cefotaxime was the first cephalosporin with clinically relevant activity against bacteria of the genus *Pseudomonas*[30].

2.1.4. Successors to cefotaxime

The astoundingly good antibiotic properties of cefotaxime triggered an avalanche of research on further modification of this molecule. All chemically modifiable positions in the cefotaxime molecule were manifoldly varied (Fig. 3). The 2-aminothiazol-4-ylacetyl side chain was also successfully combined with other β-lactam parent compounds, for example, with the 1-carba and 1-oxacephem skeleton[12,32] and with monolactam sulfonic acids (cf. Section 6).

Of the thousands of derivatives, a number of successor compounds have been chosen, some of which are already on the market or in clinical trial. Tables 3 and 4 contain the most important current aminothiazole cephalosporins.

Modifications in the 3-position and in the oxime: The compounds **18**—**25** in Table 3 differ from cefotaxime **17** in the 3-position; in **25** the oxime group is also modified.

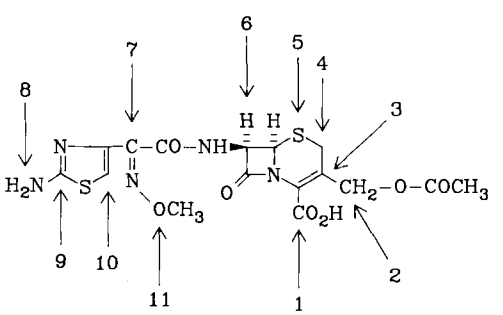
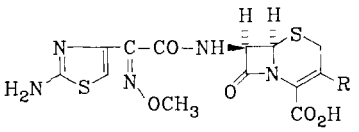
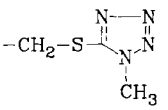
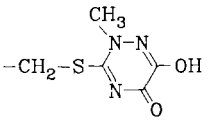
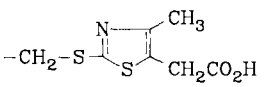
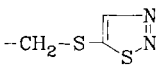
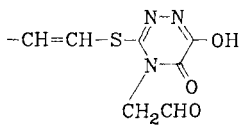
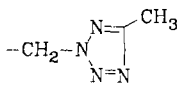
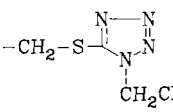


Fig. 3. Structural variation of cefotaxime **17**. The numbered arrows indicate the positions of modification.

Table 3. Aminothiazole cephalosporins.



No.	R	Generic name and/or scientific code	Ref.
17	$-CH_2-O-COCH_3$	Cefotaxime (HR 756)	[29, 30, 31, 41, 76, 78, 79, 80, 81]
18		Cefmenoxime (SCE-1365, A 50912)	[33]
19	$-H$	Ceftizoxime (FK 749, FR 13749)	[34, 42, 77, 96]
20		Ceftriaxone (RO 139904)	[35]
21		Cefodizime (HR 221)	[36]
22		L 105 (CL 251931)	[37]
23		Ceftiolen (RP 42980)	[38]
24		T 2525	[39]
25[a]		Cefotiam (SCE 963)	[40]

[a] Contains $-CH_2-$ instead of $-C(=N-OCH_3)-$.

The 1-methyltetrazol-5-ylthiomethyl group of cefmenoxime **18** is also found in other cephalosporins—for instance, in cefoperazone **35**, cefotetan **40**, or latamoxef (Scheme 3)—since it has a particularly favorable effect on the antibacterial activity. Recent studies have shown that 1-methyltetrazole-5-thiol, which appears in small amounts as a metabolite of these cephalosporins in man, can trigger alcohol intolerance (Antabuse effect) and blood coagulation disorders. The latter can largely be avoided by administering vitamin K.

The 3′-substituents bound via sulfur do not substantially alter the antibacterial spectrum compared to that of cefotaxime, but affect the pharmacokinetics, β-lactamase stability, and metabolism. In man, about 20% of cefotaxime is cleaved enzymatically to desacetylcefotaxime **17**, $R = CH_2OH$[41]. Ceftriaxone **20**[35] and cefodizime **21**[36], which have an additional acidic function, are characterized by high protein binding and a long serum elimination time (8 and 3 h, respectively).

The polar aminothiazole cephalosporins are summarized in Table 4. The favorable influence of a 3′-pyridinium group in cephalosporins on the antibacterial activity is already known from the older compounds cephaloridine **32**[49] and cefsulodin **33**[50]. The latter compound is very polar as a result of the additional sulfo group, penetrates easily through the cell wall of *Pseudomonas*, and has extremely good inhibitory values particularly against this bacterial genus, but is almost inactive against Gram-positive organisms. In aminothiazole cephalosporins, the introduction of a pyridinium residue led initially to the development of ceftazidime **26**[43], which also has very good inhibitory values against *Pseudomonas* and many other Gram-negative bacteria. Compared with cefotaxime, a distinct decrease in activity against staphylococci and other Gram-positive organisms is evident.

The combination of a neutral methoxyimino group with a 3′-cyclopentenopyridinium residue resulted in cefpirome **27**, which has a very extensive antimicrobial spectrum and inhibits the growth of isolates of *Pseudomonas*, Enterobacteriaceae, *Staphylococcus*, and enterococci at very low concentrations. Cefpirome is extremely stable against hydrolysis by plasmid-coded and chromosomally coded β-lactamases[44]. The successor compounds **28**[45], **29**[46], **30**[47], and **31**[48] have similar antibacterial spectra. The introduction of a pyridinium function into the 7-side chain, e.g., **34**[51], however, does not increase the antibacterial activity observed in the 3′-pyridinium compounds.

The effect of substitution in the oxime residue was extensively examined in the series cefotaxime **17**[29,31], ceftizoxime **19**[42], and cefpirome **27**[44c,d]. Compounds with lower alkyl groups are favorable. The introduction of acidic groups increases the activity against *Pseudomonas*. Cefotiam **25**, a compound without an oxime group, has diminished β-lactamase stability[40].

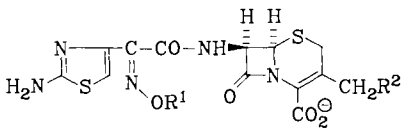
The effect of substitution in the pyridinium residue in the cefpirome series[44c,d,47b] was also examined in detail. Residues with annulated rings (cyclopentenopyridines, cyclohexenopyridines, quinolines, isoquinolines, thienopyridines, and furopyridines) exhibit high activity.

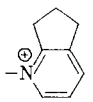
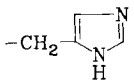
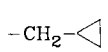
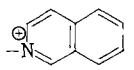
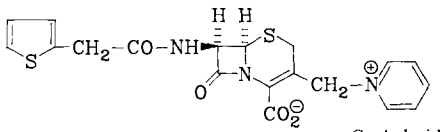
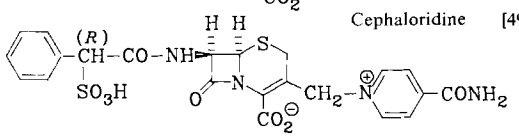
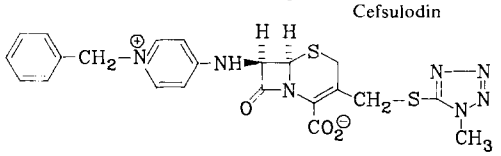
Oxidation of the cephem ring sulfur: Cefotaxime was oxidized to give the (*S*)- and (*R*)-sulfoxide and the sulfone of cefotaxime[52]. The (*S*)-sulfoxide (HR 109) is more active than the (*R*)-sulfoxide and is characterized by high β-lactamase stability and good penetrating ability in the case of Gram-negative bacteria; however, the activity against *Staphylococcus* and *Pseudomonas* is limited.

Modification of the 4-carboxy group: This polar group is essential for antibiotic activity. Only esters that are cleaved spontaneously or enzymatically in vivo are of interest as prodrug forms on account of their altered pharmacokinetics[53].

Modification in 7-position: The introduction of a 7α-methoxy group (cf. cephamycins, Fig. 1) often improves the β-lactamase stability and the activity against anaerobic bacteria. In the cefotaxime[31] and cefpirome series[54], the minimal inhibitory concentration (MIC) changes for the worse on introduction of this group.

Table 4. "Polar" aminothiazole cephalosporins.



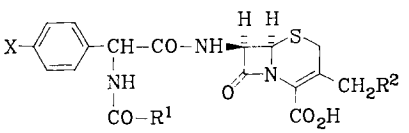
No.	R^1	R^2	Generic name and/or scientific code	Ref.
26	$-C(CH_3)_2CO_2H$		Ceftazidime (GR 20263)	[43]
27	$-CH_3$		Cefpirome (HR 810)	[44, 54, 92]
28			DN 9550	[45]
29			GR 32620	[46]
30	$-CH_3$			[47]
31	$-CH_3$		BMY 28142	[48]
32			Cephaloridine	[49]
33			Cefsulodin	[50]
34			L 640876	[51]

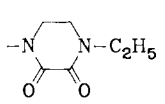
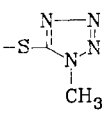
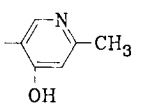
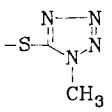
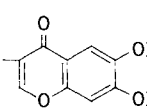
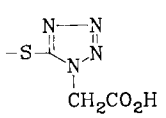
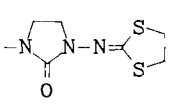
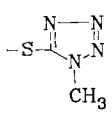
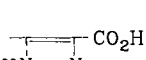
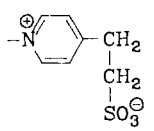
Modification of the aminothiazole ring: The amino group on the thiazole is essential. Derivatization or removal decreases the activity. Replacement of the hydrogen at C-5 of the thiazole ring with chlorine or bromine leads, in the cefotaxime[31] and cefpirome series[44d], to potent compounds which, however, bring no advantages over cefotaxime and cefpirome. By replacement of the 2-amino-1,3-thiazole residue with other amino heterocycles, e.g., 5-amino-1,2,4-thiadiazole, compounds with comparably good activity are obtained[55]. The antibacterial activity of 5-amino-1,3,4-thiadiazoles[56], 2-aminopyridines[57], 4-amino-1,3-pyrimidines[58], 5-amino-1,2,4-triazoles[59], and 2-amino-1,3-oxazoles[60,61] is distinctly lower.

2.1.5. *N*-Acylated Phenylglycine Cephalosporins

Cefoperazone **35** (Table 5) is a parenterally administered cephalosporin derivative showing structural relationship to piperacillin **5**, a ureido penicillin. **35** is a broad-spectrum cephalosporin with high activity against *Pseudomonas*. Its stability against TEM β-lactamases produced by *E. coli* is lower than that of the third-generation cephalosporins[62]. With cefpiramide **36**, E-702 **37**, KIT-180 **38**, and cefpimizole **39**, the excellent activity against *Pseudomonas*, caused by high affinity for PBP-3, is impressive. A pronounced inoculum effect, i.e., a deterioration in the MIC when there is a very high bacterial count in the culture medium, is observed with these compounds.

Table 5. *N*-Acylated phenylglycine cephalosporins.



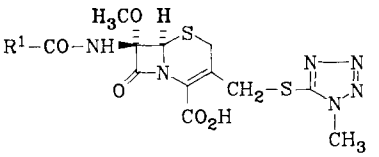
No.	X	R^1	R^2	Generic name and/or scientific code	Ref.
35	HO			Cefoperazone (T-1551)	[62]
36	HO			Cefpiramide (SM-1652)	[63]
37	HO			E-702	[64]
38	HO			KIT-180 (KI-6269)	[65]
39	H			Cefpimizole (AC-1370)	[66]

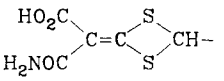
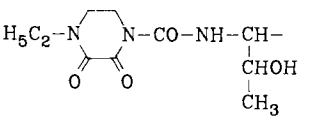
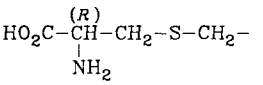
2.1.6. *Cephamycins*

The discovery of cephamycins opened up new possibilities of structural variation in the cephalosporin series[67]. These are 7α-methoxycephalosporins which are produced by *Streptomyces*. Similarly to cephalosporins, they can be varied semisynthetically. The 7α-methoxy group can be introduced stereoselectively into cephalosporins by several methods[67a] and imparts to these molecules excellent sta-

bility against β-lactamases. Cefoxitin **16** (Table 2) was the first cephamycin to achieve success in clinical practice, especially in the case of mixed infections with β-lactamase-forming anaerobes (e.g., *Bacteroides fragilis*). Table 6 shows more recent semisynthetic cephamycins which have a 3-[(1-methyltetrazolyl)thiomethyl] substituent. Cefotetan **40**, which has a tautomerizing 7β-acyl side chain, is less active against Gram-positive bacteria, but is more active against Gram-negative problem bacteria (e.g., Enterobacteriaceae, *Serratia, Proteus*) than cefoxitin and has a long half-life (3.3 hours in man). Cefbuperazone **41** is excreted to about 10% via the bile and, thus, is suitable for treating infections of the bile duct. Its activity against problem bacteria is comparable to that of **40**, while its effectiveness against anaerobes (e.g., *Bacteroides*), like that of all 7α-methoxycephalosporins, is very good. Compared with cefoxitin, cefminox **42** has advantages similar to those of **40** and **41**.

Table 6. Cephamycin derivatives.



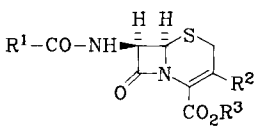
No.	R^1	Generic name and/or scientific code	Ref.
40		Cefotetan (YM 9330, ICI 15684)	[68]
41		Cefbuperazone (T 1982)	[69]
42		Cefminox (MT 141)	[70]

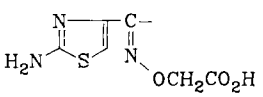
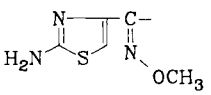
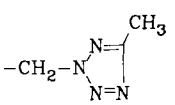
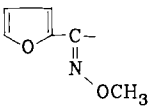
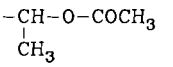
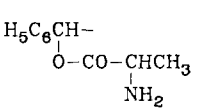
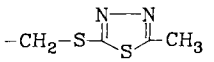
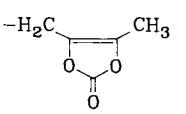
2.1.7. *Enterally Absorbed Cephalosporins*

The orally active cephalosporins in clinical practice, e.g., cephalexin **12** and cefaclor **13**, belong to the first generation with low β-lactamase stability. The aminothiazole cephalosporin FK 027 **43**, which contains a 3-vinyl group and has been known since 1981, is a new structural type. The compound is only moderately active against Gram-positive bacteria but, against Gram-negative organisms, comes close to the third-generation cephalosporins[71] (Table 7).

The method for improving enteral absorption, namely, esterification of the 4-carboxy group—e.g., by means of the pivaloyloxymethyl group in pivampicillin and the phthalidyl group in talampicillin (prodrug concept[53])—which was successful in penicillin chemistry, brought little success in the case of cephalosporins. Cefuroxime-Axetil

Table 7. Enterally absorbed cephalosporins.



No.	R^1	R^2	R^3	Generic name and/or scientific code	Ref.
43		$-CH=CH_2$	H	FK 027	[71]
44			$-CH_2-O-COtBu$	T 2588	[72]
45		$-CH_2-O-CONH_2$		Cefuroxime-Axetil	[73]
46				KY 109	[74]

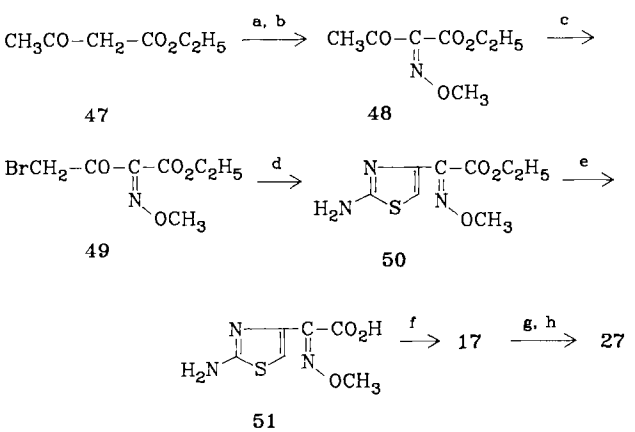
45 is in clinical trial. Enteral absorption is about 35%. Adverse gastrointestinal side effects have been reported in elderly patients[73b]. Human studies of the esters T-2588 **44** (pivaloyloxymethyl ester of **24**)[72] and KY 109 **46**[74] have begun.

2.2. Syntheses

On account of the high sensitivity of the β-lactam bond to acids and bases, all synthetic procedures in the β-lactam antibiotic series require agents that are selectively activating, protecting groups that can be split off gently, and reaction temperatures that are as low as possible. The following steps typify the semisynthesis of a cephalosporin antibiotic:

1. Chemical cleavage of cephalosporin C to 7-ACA[75]
2. Displacement of the 3′-acetoxy residue in 7-ACA with S- or N-nucleophiles
3. Synthesis of the 7-side-chain acid and, where necessary, protection of functional groups
4. Coupling of the side-chain acids to the 7-aminocephem skeleton and, if need be, removal of protecting groups
5. Preparation of stable, physiologically well-tolerated salts

The nucleophilic exchange of the 3′-acetoxy residue (step 2) can also be performed on cephems already bearing the appropriate 7-acyl side chain (step 4). Some cephem structures are not easily accessible from 7-ACA. In such cases, a longer synthetic route is necessary. For example, the 3-unsubstituted 7-amino-3-cephem skeleton is built up starting from penicillin via 3-methylenecephams (cf. Section 2.2.4). Scheme 1 shows the preparation of cefotaxime **17** and cefpirome **27** as an illustration of acylation and nucleophilic displacement.



Scheme 1. Synthesis of cefotaxime **17** and cefpirome **27**. a) $NaNO_2/H^{\oplus}$; b) $(CH_3)_2SO_4$/base; c) Br_2; d) H_2NCSNH_2; e) NaOH; f) coupling of the side-chain acid after activation (see Table 8); g) 2,3-cyclopentenopyridine/H_2O/pH=6–7; 60–70 °C or h) 2,3-cyclopentenopyridine/$(CH_3)_3SiI/CH_2Cl_2$, hydrolysis, precipitation as dihydroiodide salt.

2.2.1. *Acylation of the 7-Amino Group*

Table 8 contains a selection of activation reactions suitable for 2-(2-aminothiazol-4-yl)-2-(methoxyimino)acetic acids and many other acids. Methods that do not require protection of the 2-amino group in the thiazole ring, for example, condensation with thioesters or HOBT esters, are advantageous. Halogenated pyridinium salts[82] and tetramethylchloroformamidinium chloride[83] are also used for activation. With very polar components, the coupling is carried out advantageously in aprotic polar solvents, such as DMF, possibly with the addition of water[43b].

Table 8. Methods for activating 2-(2-aminothiazolyl)-2-(methoxyimino)acetic acids (cf. **51**) and protecting groups for the 2-amino group [a].

Protecting group	Activation method	Product	Ref.
Chloroacetyl	Acid chloride: PCl_5	**17** and 3′-derivatives	[76]
Trityl	Acid chloride: PCl_5	**26**	[43b]
Trityl	Anhydride: DCCD	**17**	[29]
Trityl	Mixed anhydride: $ClCO_2CH_2CH(CH_3)_2$	**17** (*anti*-form)	[29]
Formyl	Vilsmeier: $POCl_3$/DMF/BSA [b]	**19**	[77]
—	Vilsmeier: $COCl_2$/DMAA	**17**	[78]
Trityl	Mixed anhydride: tosylchloride	**17**	[79]
—	Active ester: HOBT	**17**	[80]
—	Thioesters: benzothiazole-2-thiol, other thiols	**17**	[81]

[a] Abbreviations: DCCD: dicyclohexylcarbodiimide; DMAA: *N,N*-dimethylacetamide; DMF: *N,N*-dimethylformamide; BSA: *N,O*-bis(trimethylsilyl)acetamide; HOBT: 1-hydroxy-1*H*-benzotriazole. [b] Active reagent: $(CH_3)_2\overset{\oplus}{N}=CHCl\ Cl^{\ominus}$.

To protect the carboxy function in 7-ACA derivatives, the *tert*-butyl, diphenylmethyl, and p-nitrophenyl esters are often used. Silylation of the carboxy and amino groups with chlorotrimethylsilane, bis(trimethylsilyl)acetamide, or specific silylating agents, e.g., *N*-methyl-*N*-(trimethylsilyl)trifluoroacetamide, increases the solubility in solvents of low polarity and frequently raises the reaction velocity and the yield.

2.2.2. *Substitution in the 3′-Position*

In cephalosporin derivatives, displacement of the 3′-acetoxy group by S- and N-nucleophiles is mostly carried out in aqueous solution (pH about 6) between 40 and 90 °C[84]. Similarly, the 3′-acetylacetoxy[76] and 3′-carbamoyloxy groups can be displaced[85]. In reactions with weak nucleophiles, simultaneous hydrolysis of the β-lactam ring reduces the yield[86]. Pyridine bases substitute better in the presence of a high molar excess of potassium iodide or potassium thiocyanate[49] (synthesis of **32**). The catalytic mechanism of these salts has not yet been clarified. A 3′-substitution in anhydrous solvents, e.g., acetonitrile, is achieved with the addition of acids or Lewis acids[84,86a,87]. A resonance-stabilized carbonium ion is proposed as polar intermediate[86a].

Halogen atoms in the 3′-position are excellent leaving groups. Synthesis via 3-methylenecephams requires considerable effort[88]. Direct halogenation of the 3-methyl group in 3-cephems leads to 2-cephems, unless the more devious route via the sulfoxides is chosen[89]. Conversion

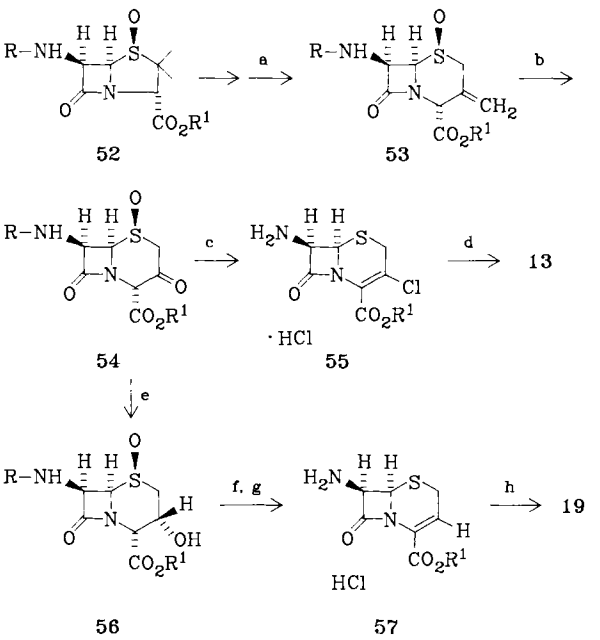
of the 3-hydroxymethyl group, resulting from enzymatic hydrolysis of the acetoxymethyl group, to a methyl halide group ($CH_2OH \rightarrow CH_2Cl \rightarrow CH_2I$) is also unsatisfactory (cf., for example, the synthesis of **31**)[48]. The preparation of 3-iodomethylcephems from appropriate 3′-acetates with iodotrimethylsilane brought decisive progress. By the use of the ester cleavage procedure developed originally by *Olah*[90] et al., 3-iodomethylcephems are formed which react, either in situ or after isolation, with diverse S- and N-nucleophiles[91]. Examples are the synthesis of the 3′-isoquinolinium derivative **30** from a silylated cefotaxime precursor[47a] and the synthesis of cefpirome **27**, in which an excess of pyridine base is important (Scheme 1, reaction h)[92]. The introduction of a 3′-carbamoyloxy group into cephalosporins has proved to be favorable for their effectiveness, since this group is not cleaved by esterases in the organism. Reaction of 3-hydroxymethylcephems with reactive isocyanates turned out to be a suitable synthetic route[43b,93].

2.2.3. *Synthesis of 3-Vinylcephalosporins*

3-Vinylcephems are obtained by several methods. Functionalization of the 3-methyl or 3-hydroxymethyl group by oxidation to an aldehyde and Wittig-Horner olefination[94] or condensation with *tert*-butoxybis(dimethylamino)methane is the method most frequently used (synthesis of ceftiolen **23**: $CH_3 \rightarrow CH{=}CHN(CH_3)_2 \rightarrow \rightarrow$ **23**)[38]. A 3-chloromethylcephem derivative is the starting material for **43**[71].

2.2.4. *Synthesis of 3-Chlorocephems and of 3-Unsubstituted Cephems*

3-Methylenecepham sulfoxides of the type **53** are easily obtained by the Kukolja rearrangement of penicillin sulfoxides **52**[95a]. The compounds **53** are key intermediates in the preparation of the clinically important 3-chlorocephalosporins and 3-unsubstituted cephalosporins of the cefaclor **13**[95] and ceftizoxime **19** type[96]. Scheme 2 shows a preferred reaction sequence. The 3-oxocepham **54**, obtained by ozonolysis of 3-methylenecepham-S-oxide **53**, reacts with $(PhO)_3PCl_2$ to give 3-chlorocephem **55**. Reduction of the 3-oxo group and dehydration yields the cephem skeleton without 3-substituents.



52 53 54 55 56 57

Scheme 2. Syntheses with 3-methylenecephams: 3-chlorocephalosporins such as cefaclor **13** and 3-unsubstituted cephalosporins such as ceftizoxime **19**. R=$PhCH_2CO$, R¹=protecting group. a) See [95a]; b) O_3; c) $(PhO)_3PCl_2$; d) 2-amino-2-phenylacetylchloride, deprotection; e) $NaBH_4$; f) PBr_3/DMF; g) PCl_5; h) 2-(2-aminothiazol-4-yl)-2-(methoxyimino)acetylchloride, deprotection.

3. 1-Oxacephalosporins

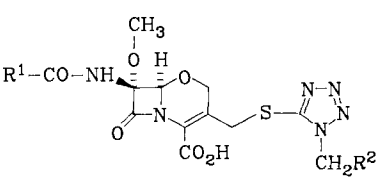
3.1. Structure and Activity

After semisynthetic cephalosporins had been obtained by replacement of peripheral residues and successfully launched in therapy, several teams began to vary the cephalosporin skeleton itself. Of the numerous variations, the 1-oxacephalosporins have the most interesting antibiotic properties. Racemic 1-oxacephalothin[97] was the first active compound of this series and was followed by D,L-1-oxacephamandole[98], which was twice as active as cephamandole. A four- to eightfold increase in activity was observed with the optically active 1-oxacephalothin, which was synthesized starting from penicillin[99]. Encouraged by these findings, Japanese firms, in particular, investigated the effect of various side chains on the biological activity of 1-oxa-3-cephem-4-carboxylic acid[100].

Replacement of sulfur by oxygen in the cephalosporin skeleton increases the skeleton's tension and intensifies the pyramidal character of the β-lactam nitrogen and, consequently, the reactivity of the lactam bond. The hydrophilicity of the entire molecule is increased, serum binding is reduced, and penetration of the cell wall of Gram-negative bacteria facilitated. The diminished β-lactamase stability of 1-oxacephems can be overcome by introduction of a 7α-methoxy group and an oxime or carboxy function in the C-2 of the 7-acetamido side chain[100,101].

The first broad-spectrum 1-oxacephalosporin, which belongs to the third generation of cephalosporins, is latamoxef, produced by Shionogi.

Structure-activity studies[100,101] revealed that the 2-carboxy group of the 7-side chain broadens the activity spectrum and, together with the 7α-methoxy group, leads to excellent β-lactamase stability, which also extends to the group of anaerobes *(Bacteroides fragilis)*. The *p*-hydroxy group increases the blood levels and prolongs the serum



Latamoxef (6059-S):

R^1 = HO–(*R,S*)–CH(–CO_2H)–,

R^2 = H

6315-S: $R^1 = F_2CH{-}S{-}CH_2{-}$, $R^2 = CH_2OH$

elimination half-life. The 3′-(methyltetrazolylthio) substituent increases the antibiotic effectiveness toward Gram-negative bacteria and impedes metabolism. (For a detailed review on microbiology, pharmacology, and adverse reactions see [16].) A new 1-oxacephalosporin is the compound 6315-S, which no longer shows activity against *Pseudomonas* but, instead, exhibits improved activity against *Staphylococcus*[102].

3.2. Synthesis

The configuration of active 1-oxacephalosporins is identical to that of natural cephalosporins. Stereoselective syntheses were elaborated by several teams[103, 104]. The principle of such a synthesis is shown in Fig. 4. The most frequent chiral starting material is 6-APA which, initially, is degraded to a monolactam. After oxidation to an *S*-oxide and C-6 epimerization, the thiazolidine ring is opened; a reactive leaving group X is inserted in the 4-position and, upon later closure to an oxazine ring, is replaced by an oxygen nucleophile. In order to obtain the desired (*R*)-configuration at C-6 (such as, e.g., in latamoxef), the adjacent chiral center at C-7, which directs the incoming substituent into the *trans* position, has to be epimerized.

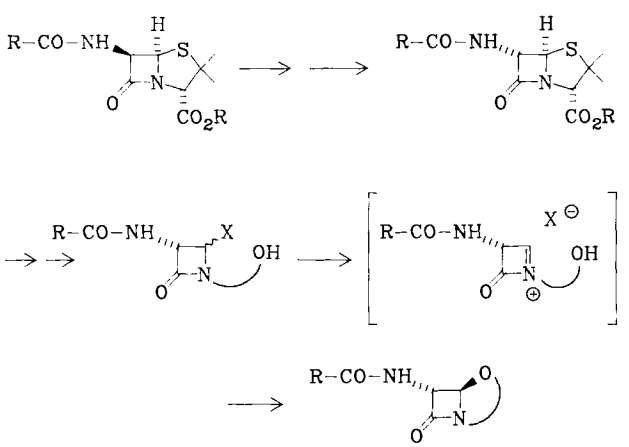
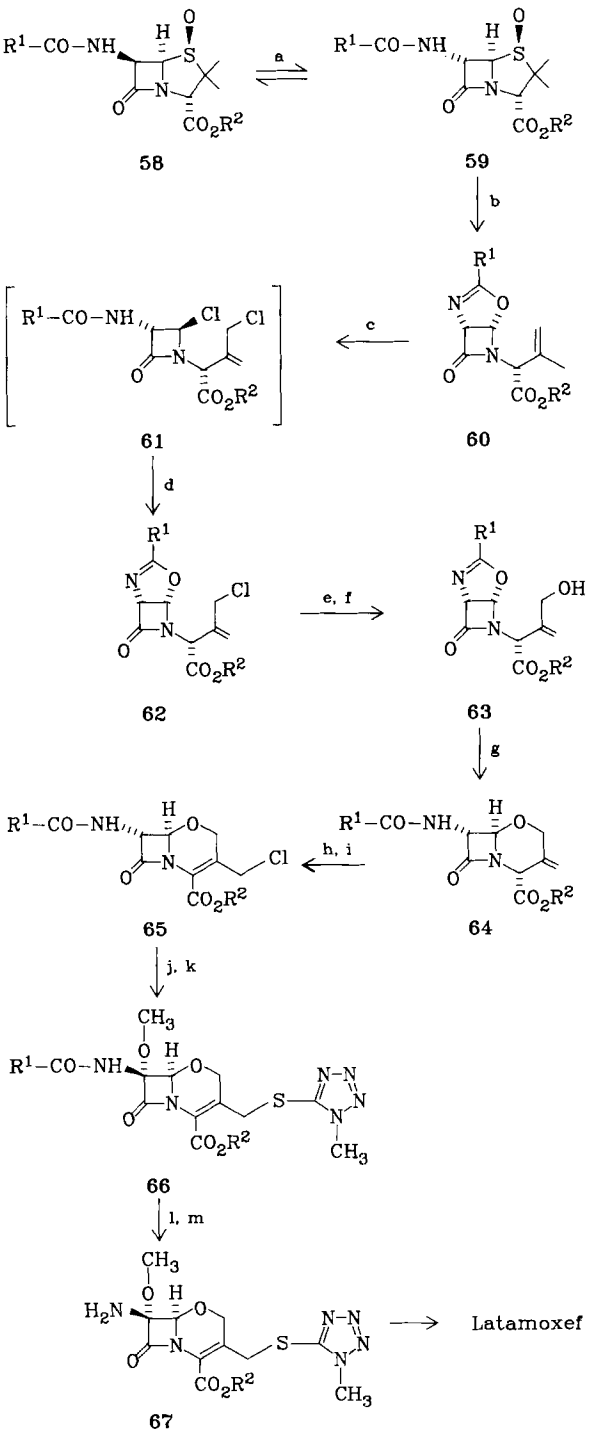


Fig. 4. Synthetic principle for 1-oxacephems.

Scheme 3 illustrates a rational synthesis of latamoxef[105], which utilizes all C atoms of 6-APA and is extremely variable with regard to side-chain substitution.

Starting from 6-APA, the sulfoxide **58**, which can easily be epimerized at C-6 with bases to give **59**, is obtained in high yield. Opening of the thiazolidine ring by heating with triphenylphosphane results in the bicyclic compounds **60**. This reaction can be applied to a wide range of *N*-acyl derivatives and esters (for the reaction mechanism see [106]). A similar ring opening of penicillin-S-oxides with normal configuration at C-6 has been described by *Cooper* et al.[107] and *Hatfield* et al.[108] (see Fig. 5).

Although direct allylic oxidation of **60** to **63** was intensively investigated, the indirect route via allylic chlorination with molecular chlorine or with SO_2Cl_2 to give **62**, which proceeds via an ene mechanism, proved to be superior for large-scale synthesis.



Scheme 3. Synthesis of latamoxef (6059-S). R^1=Ph, R^2=$CHPh_2$. a) base; b) 80 °C, PPh_3; c) Cl_2; d) $NaHCO_3$; e) NaI; f) dimethylsulfoxide (DMSO)/H_2O/Cu_2O; g) $BF_3 \cdot Et_2O$; h) Cl_2, hν; i) piperidine; j) ClO*t*Bu, $LiOCH_3$; k) sodium 1-methyltetrazole-5-thiolate; l) PCl_5, pyridine; m) CH_3OH.

Direct chlorine/hydroxy exchange is difficult due to the low reactivity of the allylic chloride **62**. It is better to substitute initially iodide for chloride and to introduce the allylic OH group with Cu_2O in DMSO-H_2O. It is assumed that DMSO forms an active alkylsulfonium intermediate with the allylic iodide. Cu_2O both activates the iodide and traps the resulting hydrogen iodide.

Allylic alcohol **63** is stereospecifically cyclized to (6*R*)-3-methylene-1-oxacepham **64** by proton or Lewis acid ca-

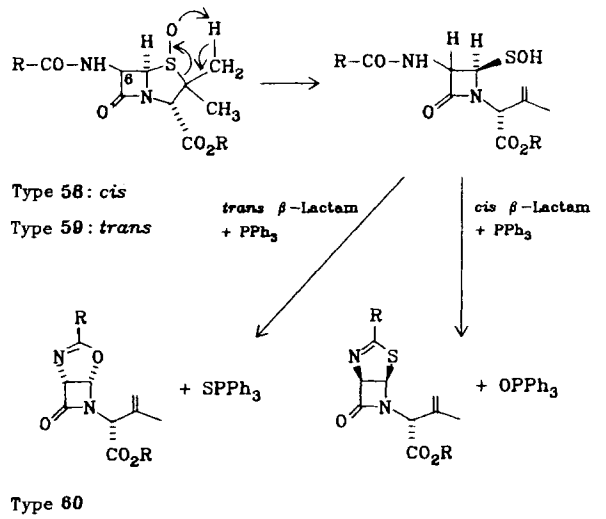


Fig. 5. Ring opening of penicillin-*S*-oxides with natural (*cis*) and unnatural (*trans*) configuration at C-6. With PPh_3, 2-thia- and (1*S*, 5*R*)-2-oxa-4,7-diazabicyclo[3.2.0]hept-3-en-6-one, respectively, are formed.

talysis. Intermediate **64** allows extensive variation at the 3-methylene group. Ozonolysis leads to the series of 3-substituted oxacephems[109]. Light-induced addition of chlorine to **64** and elimination of HCl to give **65** permits the construction of a chloromethyl side chain which can react with a large number of nucleophiles. By methoxylation of **65** at C-7, the acylamino group is again brought into the desired β-position; the product is subsequently converted, without isolation, into **66**.

Removal of the acyl group to give **67**, reacylation, and deprotection are effected by the usual methods. Unlike cephalosporins[110], the 7β-amino-7α-methoxyoxacephems **67** do not epimerize in acidic medium. Here, the configuration of the amino group is stabilized by a strong hydrogen bond to the ring oxygen[111].

The stereochemistry at C-6 and C-7 can also be controlled in a way different from that in Scheme 3 and Figure 5. If an oxygen nucleophile is passed on intramolecularly from the 3-amido side chain of the azetidinone by ring closure at C-4, only the *cis* arrangement of the two substituents is possible for steric reasons (Fig. 6). This strategy was applied by, among others, Fujisawa[112] (Scheme 4). The azetidinone **68**, accessible by cleavage of 6-aminopenicillanic acid benzyl ester, is acylated to **69** with protected glycolic acid. The methylthio group can be cleaved off with elemental chlorine to yield a 4α-chloroazetidinone which, without purification, cyclizes with silver salt catalysis to oxazoline **70**. In two successive steps—acylation at the dihydrooxazole nitrogen to give **71** and acid hydrolysis of the oxazolidine—the intermediate **73** is obtained. The reaction sequence can also be reversed (**70** → **72** → **73**).

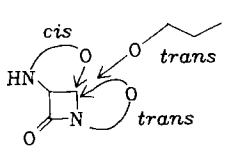
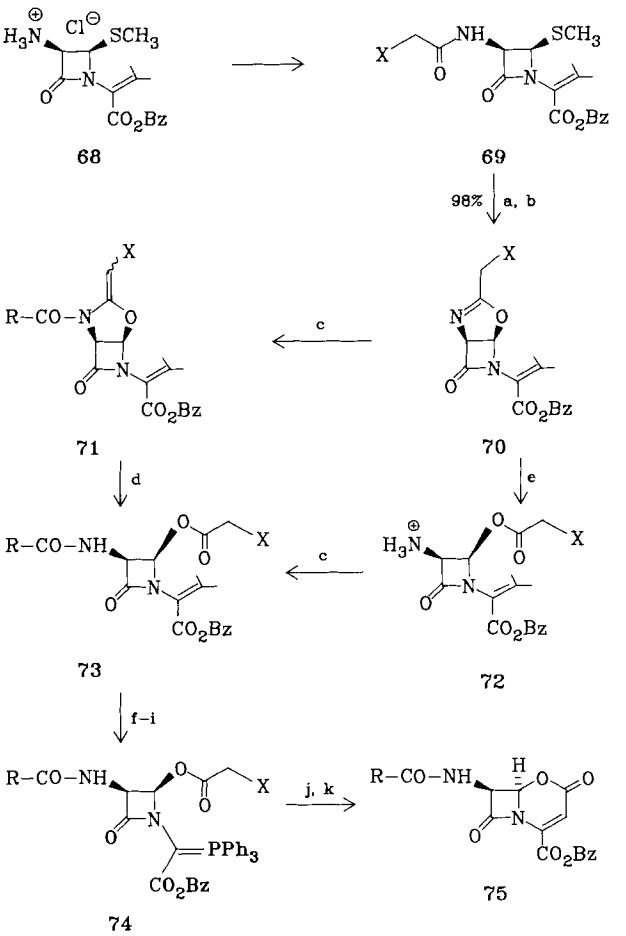


Fig. 6. Stereochemistry of the reactions of unsubstituted azetidiones.



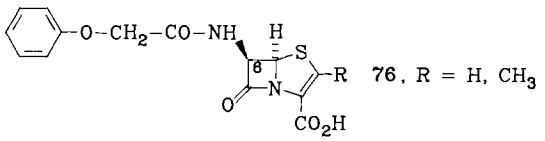
Scheme 4. Synthesis of the oxacephem skeleton. Bz=benzyl, X=$Cl_3C-CH_2-O-CO-O$, R=$Ph-O-CH_2$. a) Cl_2; b) $AgBF_4/Ag_2O$; c) $Ph-O-CH_2-COCl$; d) camphorsulfonic acid/H_2O; e) *p*-TosOH·H_2O; f) O_3; g) $Zn/EtCO_2H$; h) $SOCl_2$/pyridine; i) PPh_3; j) Zn/CH_3CO_2H; k) DMSO/Ac_2O.

The oxazine ring is built up by an intramolecular Wittig reaction which was elaborated for the first time by *Woodward* et al. for the total synthesis of cephalosporins[113] and, since then, has been used extensively in the total synthesis of other β-lactam skeletons. Ozonolysis of **73**, zinc/propionic acid reduction of the resulting oxalic acid monoamide, chlorination with thionyl chloride, and reaction with triphenylphosphane leads to the phosphorus ylid **74** in an overall yield of 42%. The trichloroethoxycarbonyloxy protecting group in **74** is cleaved off with zinc/glacial acetic acid, and the hydroxy ketone is oxidized by the *Moffat* method to the aldehyde which cyclizes spontaneously to give the oxacephem **75**.

4. Penems

In 1975, the synthesis of the new β-lactam skeleton **76**, which had hitherto not been found in nature, was announced by a team at the Woodward Research Institute in Basel and later published in detail[114, 115].

This type of compound, which is called a 'penem', can be regarded as a hybrid between penicillins and cephalosporins. It proved to be antibiotically active, but too unstable chemically and therefore unsuitable for practical use.

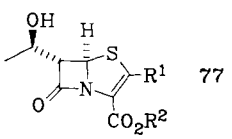


76, R = H, CH_3

Unexpectedly, it was soon discovered that the chemically more easily accessible and more stable 6-unsubstituted penems are also antibiotically active. In order to improve antibacterial activity and β-lactamase stability, various teams introduced new substituents into the 2- and 6-positions. In particular, the 6-(*R*)-hydroxyethyl group in the thienamycin-like 5,6-*trans* configuration has proved to be optimal so far. Consequently, penems of the type **77** were extensively varied at C-2 by many firms, including Merck Sharp & Dohme[117], Sankyo[118], and Hoechst[119], since this position also decisively affects the biological activity and bioavailability[*].

Meanwhile, 6-hydroxyethylpenems of the type **77** (Table 9) have been brought into clinical development by Schering/Plough and Farmitalia/Carlo Erba. The orally administered SCH 29482 **77a** had to be replaced by the parenterally administered SCH 34343 **77b**, since **77a** is degraded by endogenous enzymes, e.g., dehydropeptidase I, releasing small amounts of ethanethiol. FCE 22101 **77c** is parenterally active and is therefore being clinically tested as the orally administered prodrug ester FCE **77d** (22553).

Table 9. Penems **77** in clinical trial.



77

No.	R^1	R^2	Scientific code name	Ref.
77a	S–Et	Na	SCH 29482	[120]
77b	$S-CH_2CH_2-O-CONH_2$	Na	SCH 34343	[121]
77c	$CH_2-O-CONH_2$	Na	FCE 22101	[122]
77d	$CH_2-O-CONH_2$	$CH_2-O-COtBu$	FCE 22553	[122]

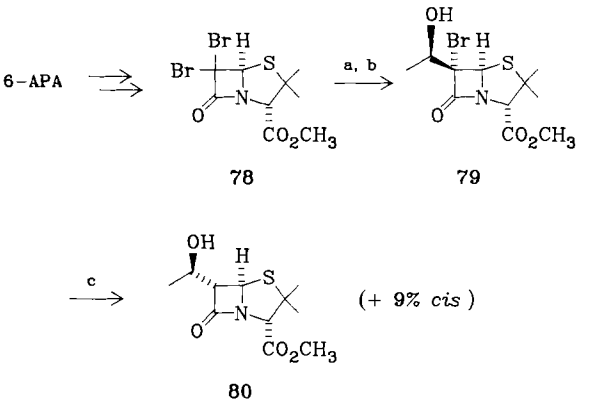
The 6-hydroxyethylpenems are broad-spectrum antibiotics with very good in-vitro activity against Gram-positive and Gram-negative bacteria. They also excellently inhibit anaerobes. However, they are not sufficiently active against *Pseudomonas*.

6-Hydroxyethylpenems are highly stable against plasmid-coded (e.g., TEM) and chromosomally coded (e.g., Kl) β-lactamases. These properties plus the possibility of finding enterally absorbable, highly active antibiotics by appropriate choice of the 2-substituent and/or the ester group make penems a class of very potent antibiotics.

A selection of interesting reactions elaborated in connection with the total synthesis of penems will be discussed in the following.

[*] For a summary of the chemistry and bacteriology of the penems see [116].

6-Aminopenicillanic acid (6-APA) is used in the majority of syntheses as an inexpensive chiral starting material into which the hydroxyethyl side chain can be introduced in a stereocontrolled way. As an example, the procedure of *Laenza* et al.[117] is described in detail (Scheme 5).

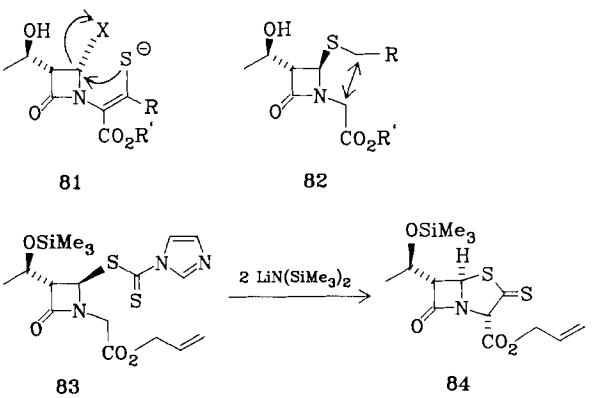


78 **79** **80**

Scheme 5. Synthesis of 6-hydroxyethylpenams. a) CH_3MgBr; b) CH_3CHO; c) Zn, pH 6–7.

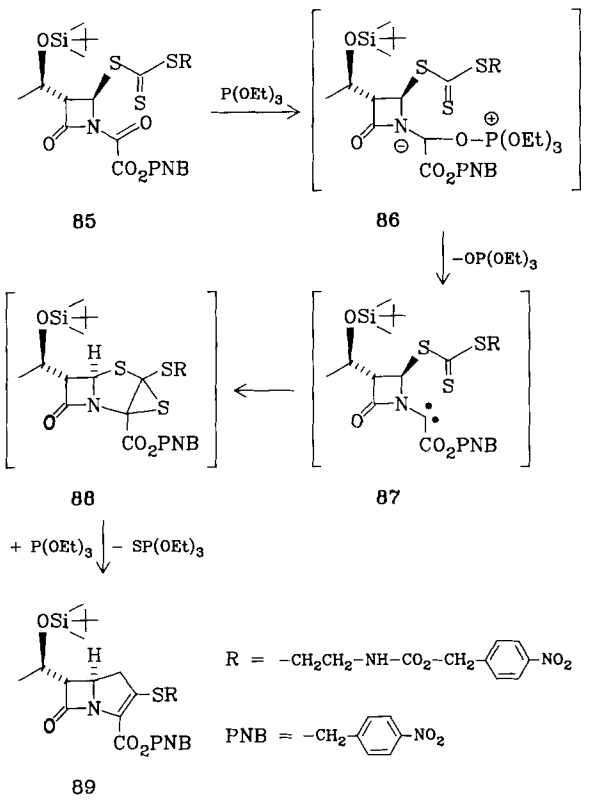
6,6-Dibromopenicillanic acid methyl ester **78**, easily obtained from 6-APA, reacts with methylmagnesium bromide to give an α-bromoenolate, which is reacted with excess acetaldehyde to give a mixture of stereoisomeric bromohydrins. The desired isomer **79** can be isolated in 66% yield. Mild reduction with zinc removes the bromine atom and simultaneously results in inversion at C-6. In the mixture, *trans*-hydroxyethylpenam **80** is formed along with ca. 9% of the *cis*-hydroxyethylpenam **80**. In general, it is further degraded to a hydroxyethylazetidinone onto which the thiazoline ring of the penem is annelated stepwise. Two strategies have been successful:

a) Ring closure by nucleophilic attack of the sulfur at C-4 of azetidinone **81**[118, 119, 123]. Defined configuration at C-4 is a prerequisite for stereocontrolled ring closure[119, 123].
b) Cyclization with formation of the double bond between C-2 and C-3 (see **82**). Besides the Wittig olefination already used by *Woodward* et al. in the first penem syntheses[117, 120a, 122, 124], two new procedures have been introduced recently: anion cyclization[117, 125] (**83** → **84**[125])



81 **82** **83** **84**

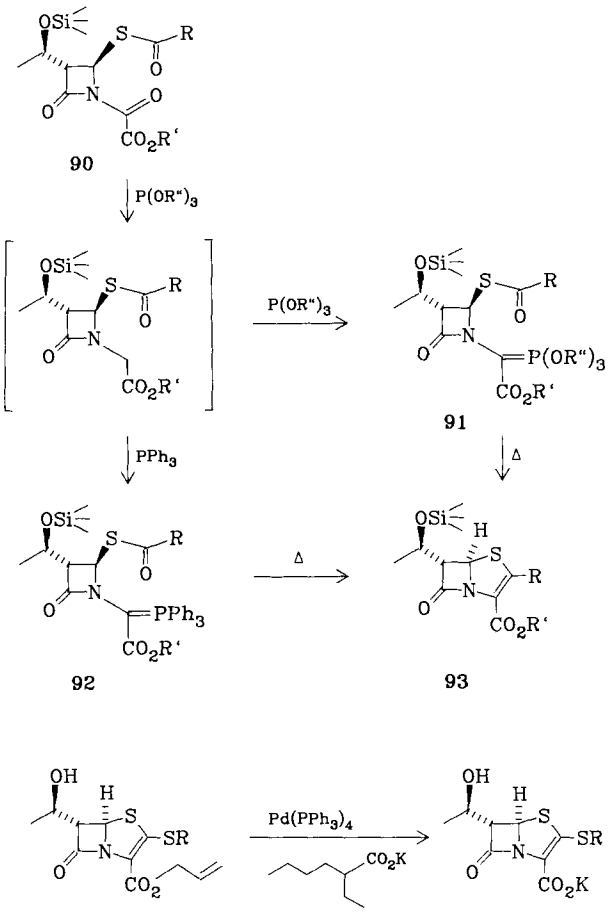
and, in particular, reductive cyclization of oxalic acid monoamides **85** with trialkylphosphites[126, 127]. The carbene **87**, which adds onto the C=S bond of the trithiocarbonate, is formed as intermediate. The thiiran **88** is desulfurized with a second equivalent of trialkylphosphite. Formation of a phosphorane is possible as a secondary reaction of the carbene with excess phosphite. Consequently, the desulfurization is carried out under high-dilution conditions and with gradual addition of the phosphite. If no sufficiently reactive C=X bond is available, this reaction becomes predominant[127].



85 86 87 88 89

The Farmitalia group[128, 129] found that the carbene formed intermediately can also trap other phosphorus(III) compounds. It is thus possible to prepare, e.g., the triphenylphosphoranes **92** in a single-step reaction, these being otherwise only accessible in several steps via the usual Woodward method. The phosphoranes **91** and **92** cyclize on heating to the penems **93**.

In looking for a stable carboxy protecting group, which can be cleaved off under the mild neutral conditions required by sensitive systems such as β-lactams, *Jeffrey* and *McCombie*[130] found that allylic esters, carbonates, and carbamates are cleaved smoothly and in high yields with catalytic amounts of $Pd(PPh_3)_4$. In the presence of alkali-metal salts of long-chain fatty acids, the alkali-metal salts of the deprotected carboxylic acids precipitate. The allyl protecting group has meanwhile also been successfully employed by other groups[125, 131].



90 91 92 93

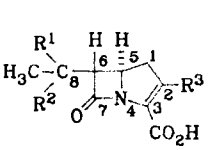
5. Carbapenems

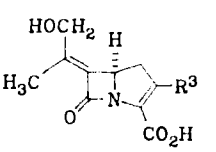
5.1. Structure and Activity

Since the discovery of thienamycin, an antibiotically highly active fermentation product of *Streptomyces cattleya*[132, 133], the number of thienamycin derivatives and of other closely related carbapenems of natural origin has risen to over thirty. These include epithienamycins, olivanic acids[134], carpetimycins[135], asparenomycins[136], pluracidomycins[137], and carbapenems of the PS group[138].

Table 10 gives a general outline of the structural differences between the groups. In general, the residue R^3 is cys-

Table 10. General outline of the carbapenems.





Asparenomycins

Type	R^1	R^2	H5/H6	C-6	C-8
Thienamycins	OH	H	*trans*	*S*	*R*
Olivanic acids	OH	H	*cis*	*R*	*S*
Pluracidomycins	$OSO_3^{\ominus}$	H	*cis*	*R*	*S*
Carpetimycins	OH	CH_3	*cis*	*R*	—
PS group	H	H or CH_3	*trans*	*R*	—

teamine or a derivative thereof. Hence, the amino group of this residue can be acylated, the sulfur can be present as sulfoxide, and the ethylene bridge can be dehydrogenated. In pluracidomycins, residues such as $-SO_3^-$, $-SOCH_2CO_2^-$, or $-SO-CH(OH)_2$ are bound to C-2. The hydroxy group of the C-6 side chain can be sulfonated. The isolation of the parent carbapenem has recently been reported[139]. Little is known about the biosynthesis of carbapenems. Glutamic acid seems to be a structural element. A summary of biosynthetic transformations within the carbapenem groups is given in [140].

The majority of carbapenems are highly active broad-spectrum antibiotics. Detailed investigation of the effect of the substitution pattern and stereochemistry in thienamycins and olivanic acids shows that high antibiotic activity is linked to the combination of *8S* and *cis* configuration or of *8R* and *trans* configuration at the β-lactam[141]. Stability against TEM β-lactamases is found both for the *trans* compounds and for sulfate esters of the (*8S*) *cis* compounds. TEM β-lactamases are only inhibited by (*8S*) compounds, whereby sulfonation at the 8-hydroxy group considerably further increases the inhibition. Table 11 gives a qualitative survey of these relationships.

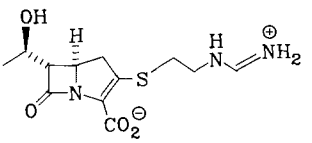
Table 11. Selected properties of carbapenems (for formulas see Table 10; $R^2 = H$).

Type	R^1	C-8	H5/H6	Antibiotic activity	Resistance against TEM β-lactamases	Inhibition of TEM β-lactamases
Thienamycins	OH	*R*	*trans*	+++	+	0
8-*epi*-Thienamycins	OH	*S*	*trans*	+	+	+
Olivanic acids	OH	*S*	*cis*	++	0	+
Pluracidomycins	$OSO_3^\ominus$	*S*	*cis*	++	+	++

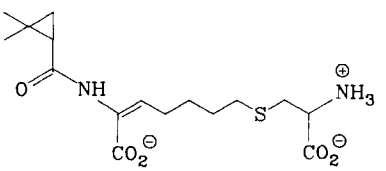
The carbapenems are highly reactive compounds on account of their strained ring system. They are sufficiently chemically stable only in a limited pH range around neutrality. This, plus the fact that it has so far not been possible to increase fermentation yields by strain optimization, has made their isolation in large quantities from culture filtrates difficult.

Consequently, the focus was soon placed, especially at Merck Sharp & Dohme, on a totally synthetic approach, particularly to thienamycin **106**. In the meantime, carbapenem total syntheses and formal total syntheses devoted to special stereochemical aspects have been introduced by a great number of teams (for a summary see [142, 143]). Thienamycin **106** is a highly active broad-spectrum antibiotic which is effective both against Gram-positive and Gram-negative bacteria and against *Pseudomonas* and *Bacteroides*, including β-lactamase-forming strains[144]. At high concentrations, it is unstable in aqueous solution: the amino group of the cysteaminyl portion cleaves the β-lactam ring intermolecularly.

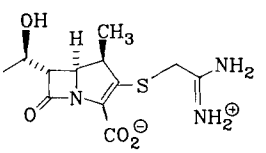
Formimidoylthienamycin (imipenem, MK-0787) **94** is a derivative combining improved chemical stability and extensive antibiotic activity[145–148]. This antibiotic, in which great hopes were placed in clinical practice, is inactivated in vivo, however, by dehydropeptidase I and has therefore unfavorable pharmacokinetics[149]. A combination of **94** and cilastatin **95**, a competitive inhibitor of this enzyme, which suppresses the metabolism of imipenem in the kidneys and prevents nephrotoxicity, is at present being clinically tested[150].



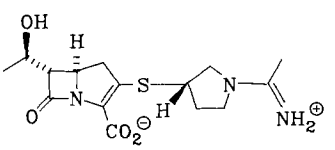
94, Imipenem



95, Cilastatin



96, L-646 591



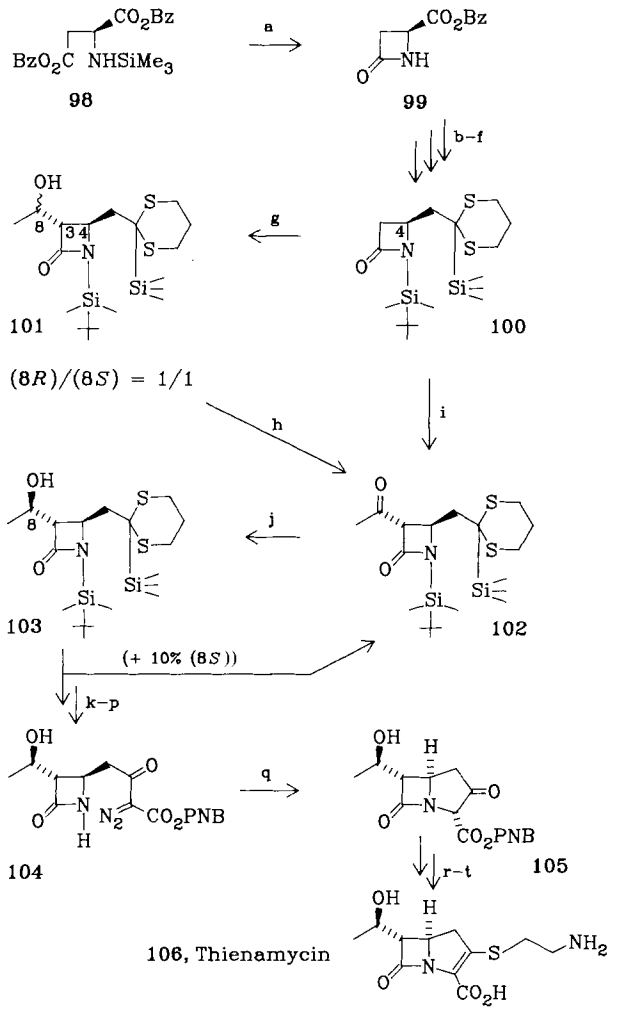
97

Compound L-646 591 **96** is a further development of imipenem **94**. The additional β-methyl group stabilizes the molecule toward dehydropeptidase. The side-chain amidino group, linked via carbon, affects the antibacterial activity in a similarly favorable way to that of the amidino group linked via nitrogen in **94**[151].

RS-533 **97**, developed by Sankyo in Japan, is also a highly active synthetic carbapenem[152].

5.2. Syntheses

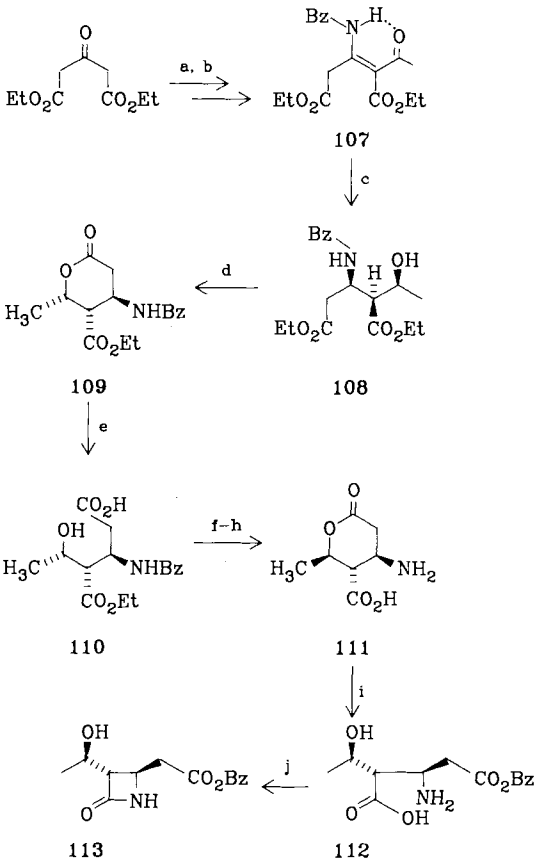
Scheme 6 shows a total synthesis of (+)-thienamycin **106**[153], which uses L-aspartic acid as chiral educt and builds up the carbapenem skeleton in a stereocontrolled way. The β-lactam ring closure with *tert*-butylmagnesium chloride at an early stage is one of the special features. By way of a five-step sequence, the C-4 side chain of the azetidinone is subsequently homologized by one C-atom to give the silyldithiane **100**, which is a carboxylic acid analogue. The total yield starting from L-aspartic acid amounts to 40%.



Scheme 6. Synthesis of (+)-thienamycin **106**. a) *t*BuMgCl, Et_2O; 2 N HCl, NH_4Cl; b) $NaBH_4$, MeOH; c) CH_3SO_2Cl, NEt_3; d) NaI, acetone; e) *t*$BuMe_2SiCl$, NEt_3, DMF; f) 2-trimethylsilyl-1,3-dithian-2-yllithium; g) $LiN(iPr)_2$, tetrahydrofuran (THF), CH_3CHO; h) $LiN(iPr)_2$, THF, 2 acetylimidazole (AcIm), THF; i) DMSO/trifluoroacetic anhydride, NEt_3; j) K-selectride, KI, Et_2O; k) $HgCl_2$, HgO, CH_3OH/H_2O; l) H_2O_2, MeOH; m) Im_2CO, THF; n) $(PNBO_2C-CH_2CO_2^{\ominus})_2Mg^{2\oplus}$; o) HCl/MeOH; p) HO_2C-*p*-$C_6H_4-SO_2N_3$, NEt_3, CH_3CN; q) 0.001 $Rh(OAc)_2$, toluene 80 °C; r) $ClPO(OPh)_2$, 4-dimethylaminopyridine (DMAP), iPr_2NEt, CH_3CN; s) $HS(CH_2)_2NHCO_2PNB$, iPr_2NEt; t) H_2, Pd/C (10%).

Diphenylphosphoryl chloride is superior to other activating reagents for the subsequent introduction of the cysteaminyl side chain. The (+)-thienamycin **106** thus prepared proved to be identical to the natural product.

Merck Sharp & Dohme have also published a technically feasible (±)-thienamycin synthesis[154, 155] which eliminates one of the apparent weak points in Scheme 6, namely, the expensive homologization of **99** (Scheme 7).



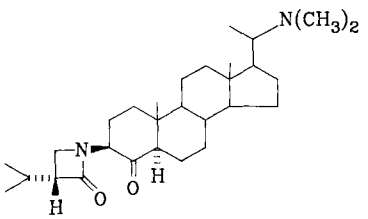
Scheme 7. The initial steps in a synthesis of (±)-thienamycin. a) $BzNH_2$, molecular sieves; b) ketene; c) $NaCNBH_3$, HOAc; d) HCl, CH_2Cl_2; e) 1.0 $NaHCO_3/H_2O$; f) 1.3 PPh_3, 1.3 diethylazodicarboxylate, THF; g) conc. HCl, reflux; h) $H_2/Pd(OH)_2/C$ (20%); i) $PhCH_2OH$, 70°C; j) NEt_3, DCCD, $PhCH_2OH$, 55°C.

The aldol condensation with acetaldehyde, by which the hydroxyethyl group in **100** is introduced, is stereoselective with regard to C-3 of the azetidinone: equal proportions of (8*R*)- and (8*S*)-isomers **101** are formed. The chirality of the side chain is removed by Moffat oxidation to 3-acetylazetidinone **102**, which can also be obtained in higher yield directly from **100** by acetylation. Subsequent reduction of the keto group with K-selectride is stereoselective. The unwanted (8*S*)-diastereomer forms only to 10% and can be recyclized. After cleavage of the dithiane **103**, the resulting carboxylic acid is elongated using a modified Masamune method and converted by diazo transfer into the carbene precursor **104**. **104** cyclizes quantitatively, under mild conditions in the presence of catalytic amounts of rhodium(II) acetate, to give 2-oxocarbapenam **105**. During the entire reaction sequence from **103** to **105**, the hydroxy group does not need to be protected.

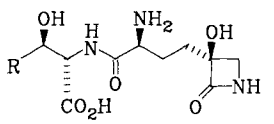
Starting from diethyl acetonedicarboxylate, the enamine **107**, in which a strong hydrogen bond forces the acetyl group into the *cis* position relative to the benzylamino group, is prepared. By stereoselective reduction with $NaCNBH_3$, the racemic diester **108**, which contains all atoms of the carbapenem skeleton except for two carbon atoms and in which all substituents except for the OH group have the desired relative configuration, is obtained. By way of the sequence **109** → **111**, the hydroxyethyl group can be epimerized via an intramolecular Mitsunobu reaction. The lactone **111** is opened to give the benzyl ester **112** by solvolysis in benzyl alcohol and converted into the azetidinone **113** with dicyclohexylcarbodiimide. Here, the reaction sequence joins up with the total synthesis of thienamycin in Scheme 6 (**113** corresponds to **103**).

6. Monocyclic β-Lactam Antibiotics

Monocyclic β-lactam antibiotics were first described in the mid-seventies. In fact, other monocyclic β-lactams of natural origin had already been found previously, such as pachystermine A **114**[156]—an alkaloid isolated from *Pachysandra terminalis* species—or tabtoxine **115a**[157] and its lower homologue [Ser²]tabtoxine **115b**[158]—a β-lactam

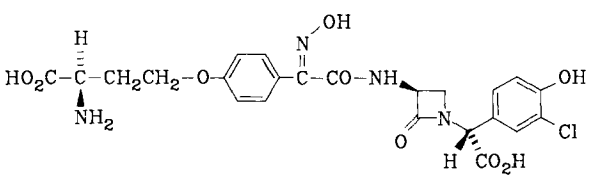


114, Pachystermine A



115a: R = CH_3, Tabtoxine
115b: R = H, [Ser²]Tabtoxine

produced on tobacco plants by the phytopathogenic bacterial species *Pseudomonas tabaci*, which causes chlorosis of the green leaves. The first stereospecific total synthesis of tabtoxine was described in 1983[159]. These β-lactams were at first treated as curiosities on the fringe of natural products chemistry, since no therapeutic significance was attributed to them. Only the development of highly sophisticated screening methods for new antibiotic structures[160], e.g., the use of extremely sensitive test strains of bacteria, made the discovery of a new class of monocyclic β-lactam antibiotics possible.

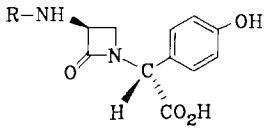


118, Chlorocardicin

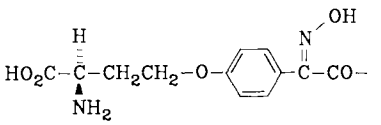
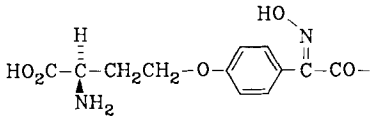
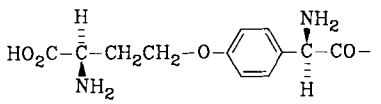
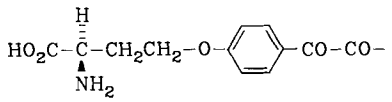
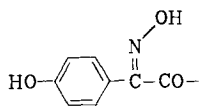
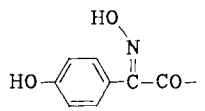
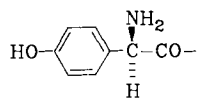
6.1. Nocardicins

Structural elucidation of nocardicin A **116a** and B **116b**[161, 162], the first two antibiotics isolated from the actinomycetes species *Nocardia uniformis subsp. tsuyamanensis* ATCC 21806, revealed their structural relationship to cephalosporins and penicillins: The configuration of the amide-carrying C-3 carbon of the β-lactam is identical, and an oxime function, which is only seldom observed in nature, is present. The nocardicins C-G **116c—g** could be isolated from *Nocardia uniformis*[163]. They are all derivatives of 3-aminonocardicinic acid (3-ANA) **117**, which is obtained by chemical[164] or enzymatic[165] deacylation of norcardicin (Table 12). Chlorocardicin **118** was recently isolated from the fermentation broth of a *Streptomyces* species[185]. Nocardicins have no therapeutic importance. Only nocardicin A shows moderate activity against some

Table 12. Nocardicins.



116, 117

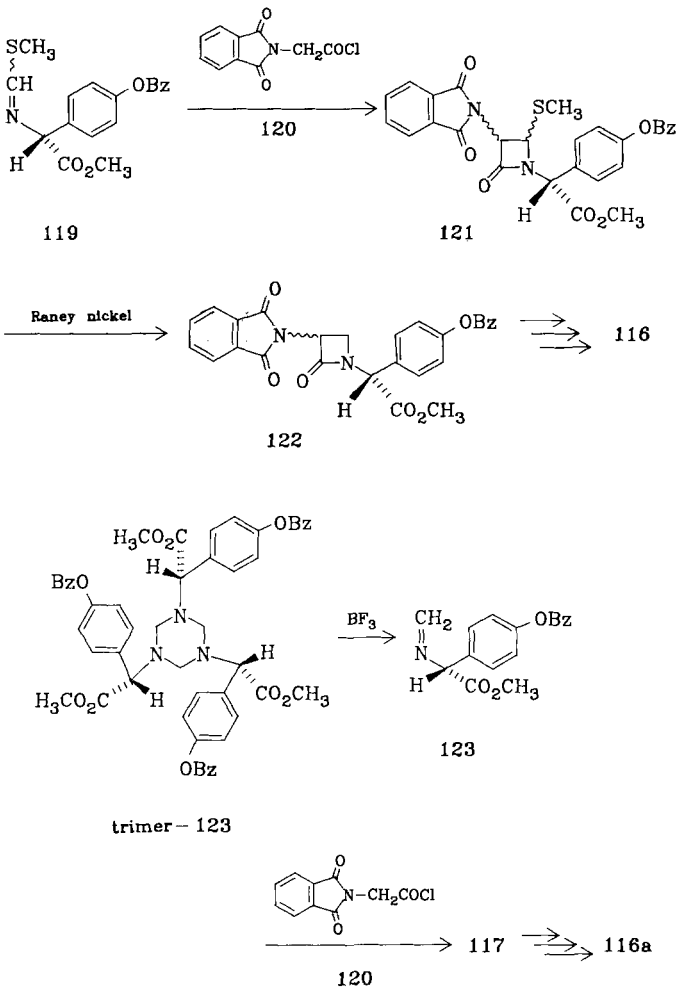
No.	Nocardicin	R
116a	A	
116b	B	
116c	C	
116d	D	
116e	E	
116f	F	
116g	G	
117	3-ANA	H–

Gram-negative species and against *Pseudomonas*. As with other β-lactam antibiotics, the antibiotic effect of nocardicin is based on the inhibition of murein-synthesizing enzymes.

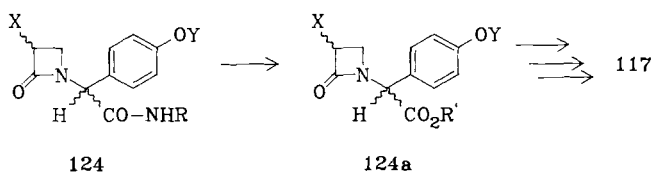
6.1.1. Total Syntheses of Nocardicin

Kamiya et al. built up the β-lactam ring from an acid chloride and a Schiff base by the classic method according to *Sheehan* and *Ryan*[166]. Since C-4 of the β-lactam remains unsubstituted, an easily removable group must be a constituent of the Schiff base. This problem was solved by the use of the methylthio compound **119**, synthesized from D-(4-hydroxyphenyl)glycine via several steps[167]. Desulfurization of the β-lactam **121** with Raney nickel leads to the 4-unsubstituted nocardicin precursor **122**. This intermediate is formed directly by release of the unstable formaldehyde imine **123** from its stable trimer (accessible from D-(4-hydroxyphenyl)glycine) using Lewis acid catalysis and reaction of **123** with acid chloride **120**[168]. *Curran* et al. pursued a similar strategy[169].

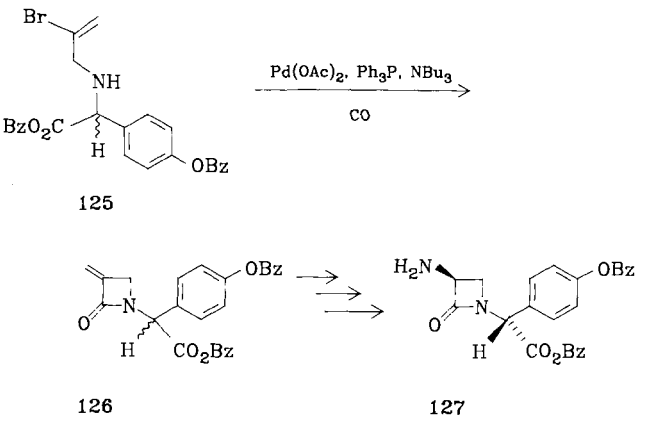
The azetidinone synthesis by a four-component condensation reaction according to *Ugi*[170] was elaborated independently by two teams. The problem of converting the



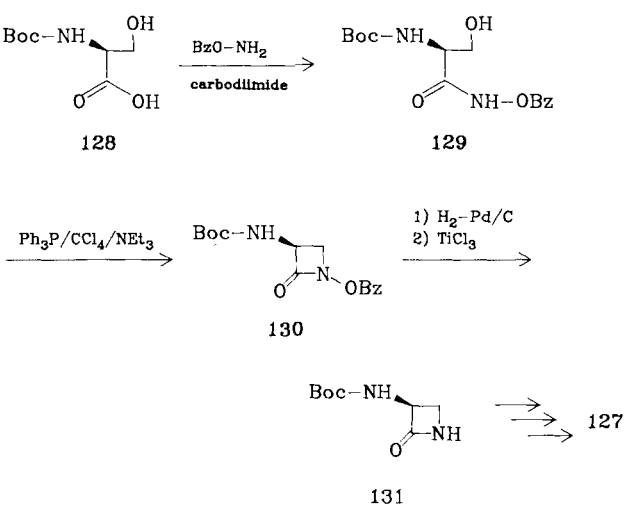
amides **124** resulting from this reaction into easily saponifiable esters **124a** was solved in different ways. Whereas *Isenring* and *Hofheinz*[171] converted the amide **124**, R = diphenylmethyl, thermally into the ester **124a**, R′ = diphenylmethyl, via the *N*-nitroso derivative, *Hatanaka* et al.[172] successfully achieved selective amide cleavage of **124**, R = *tert*-butyl, using imidoyl chloride with PCl_5 and subsequent methanolysis to give ester **124a**, R′ = CH_3.



Ban et al.[173] used the Pd-catalyzed carbonylation of α-bromoallylamine **125** to build up the β-lactam skeleton **126**, the 3-methylene group of which is converted into the 3-amino group of dibenzyl 3-ANA **127**. **125** is obtained from DL-(4-hydroxyphenyl)glycine. A further nonstereoselective 3-ANA synthesis was published by *Wassermann* et



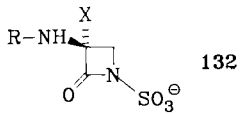
al. in 1979[174]. An important stereoselective cyclization to β-lactams was introduced by *Mattingly* and *Miller*[182,186]. *N*-Boc-L-serine **128** is converted with *O*-benzylhydroxylamine in the presence of a carbodiimide into the hydroxamic acid **129**. Due to the high acidity of the hydroxamic acid, cyclization to **130** with triphenylphosphane-CCl_4-triethylamine proceeds smoothly and in good yields, without racemization, elimination, and formation of by-products. Debenzylation by hydrogenolysis and reduction of the *N*-hydroxy-β-lactam with titanium trichloride affords **131** which, after amide alkylation and partial removal of the protecting groups, yields **127**, an intermediate of nocardicin synthesis.



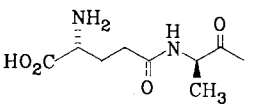
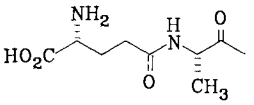
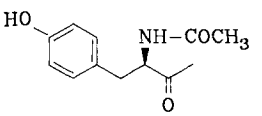
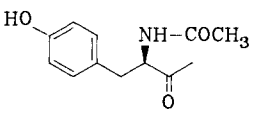
6.2. Monobactams

The most important group of monocyclic β-lactam antibiotics was discovered a few years ago. In 1981, teams from Takeda[175] and Squibb[176], independently of each other, described this new class of natural products. As characteristic feature, sulfazecins or monobactams—the latter name has meanwhile become widely accepted for the entire class—have a 4-unsubstituted β-lactam ring, a 3-acylamido group, and the function $>N-SO_3H$, which rarely occurs in nature. In some compounds, the acyl group consists of a di-, tri-, or oligopeptide; however, the

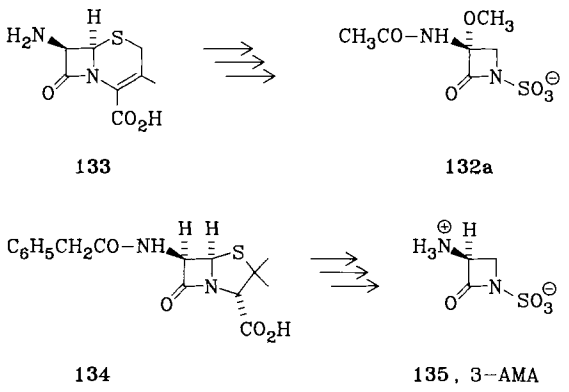
Table 13. Monobactams



132

No.	Generic name and/or scientific code	R	X
132a	SQ 26180	CH_3CO	OCH_3
132b	SQ 26445 Sulfazecin		OCH_3
132c	Isosulfazecin		OCH_3
132d	SQ 26700		H
132e	SQ 26875		OCH_3

monoacetylated compound has also been found. Natural monobactams mainly occur as 3-methoxy derivatives. The nonmethoxylated monobactams probably constitute an intermediate stage of biosynthesis. The first natural monobactams (Table 13) were detected by extensive screening programs with the aid of β-lactam-ultrasensitive bacterial test strains of *Bacillus lichenoformis*[175], *Pseudomonas aeruginosa PsC*^{ss}, and *Escherichia coli PG8*. In contrast to penicillins, cephalosporins, and nocardicins, monobactams are metabolic products of bacteria. **132b** was isolated from a number of different strains of *Gluconobacter sp., Pseudomonas sp., Agrobacterium radiobacter, Flexibacter sp.*, and *Chromobacterium violaceum*[177]. Due to its 3-methoxy group, it has high β-lactamase stability. Similar to nocardicins, natural monobactams only exhibit minimal antibiotic activity against Gram-negative bacteria and *Pseudomonas* and are hardly active against Gram-positive pathogens. The skeleton and the 3-acylamido side chain were varied in order to improve antibiotic activity. For this purpose, the parent compound, 3-aminomonobactamic acid (3-AMA) **135**, had to be synthesized. Its formation via deacylation of material obtained from fermentation broths was not practicable, since the fermentation product is a mixture of several monobactams which are difficult to separate and in which the methoxylated products, whose antibiotic activity is lower, predominate. Conversion of 7-aminodesacetoxycephalosporanic acid **133** into 3-acetyl-3-amino-3-methoxymonobactamic acid **132a**[178] and of penicillin G **134** into 3-aminomonobactamic acid **135**[179,180] proved the identity of the configuration of the 3-amino group of **135** with that of the 7-NH_2 of cephalosporins and

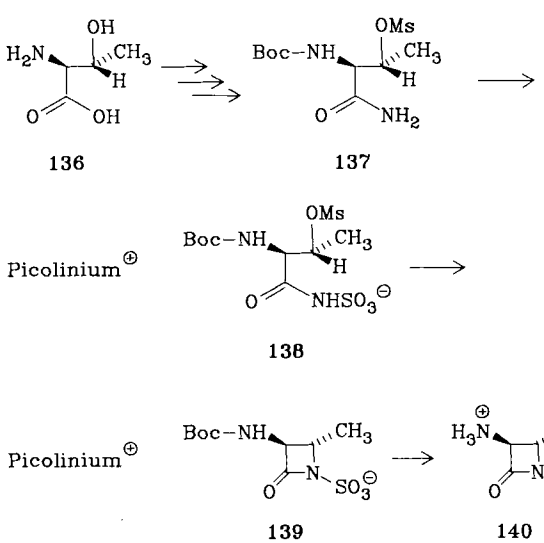


133 **132a**

134 **135**, 3-AMA

the 6-NH_2 of penicillins. 4-Substituted monobactams, however, are not accessible in this way. The only alternative is their total synthesis.

A stereospecific total synthesis of (*S*)-3-aminomonobactamic acids, which also permits preparation of 4-alkylated β-lactams, was published by Squibb[181]. An appropriate educt with two asymmetric centers is threonine **136**. It is essential to avoid racemization of either of these two centers in the following steps: after conversion of threonine into its amide and blocking of the α-amino group, the hydroxy group is converted by mesylation into a potential leaving group. Sulfonation of the amide nitrogen with the picoline-SO_3 complex acidifies the amide hydrogen atom sufficiently for intramolecular cyclization in the presence of potassium bicarbonate as base to take place. By removal of the protecting groups, (3*S*,4*S*)-*trans*-3-amino-4-methylmonobactamic acid **140** is obtained in ca. 50% yield (based on threonine); **140** is a suitable starting material for the synthesis of active monobactams.



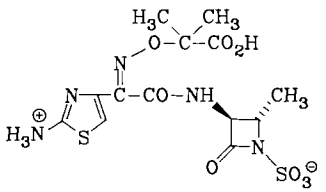
136 **137**

Picolinium$^{\oplus}$ **138**

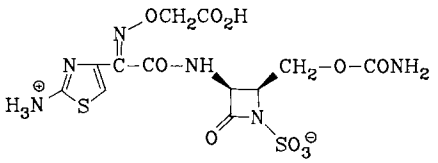
Picolinium$^{\oplus}$ **139** **140**

Structural variations of the 3-acylamido residue led to aztreonam (SQ 26776) **141**[183], a parenterally administered antibiotic with high activity against Gram-negative bacteria and *Pseudomonas*, comparable to that of third-generation cephalosporins, but only minimal activity against Gram-positive bacteria. **141** is highly stable against plas-

mid-coded and chromosomally coded β-lactamases, owing to the 3-acylamido side chain and to the 4-methyl group. Like most β-lactam antibiotics, aztreonam is distinguished by low toxicity and good tolerance.



141, Aztreonam

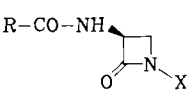


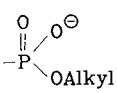
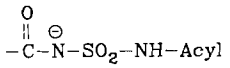
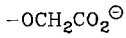
142, Carumonam

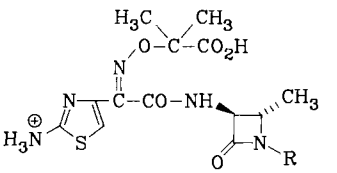
Meanwhile, another parenterally effective monobactam—carumonam (AMA 1080; Ro 17-2301) **142**, developed jointly by Takeda and Hoffmann-La Roche—has reached the clinical development stage. In its antimicrobial and pharmacological properties, it is comparable to aztreonam. Several syntheses, including a stereorational synthesis starting from L-ascorbic acid[184b], have so far been published[184a].

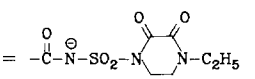
Monocyclic β-lactams with other electron-withdrawing acidic substituents at the β-lactam nitrogen were obtained by total synthesis and tested for antibiotic activity (Table 14). Depending on the 3-acylamido substituent, they exhibit moderate to good antibacterial activity[187]. SQ 82228 **143** and SQ 27327 **144**, for example, are comparable to aztreonam. Variation of the 4-substituent was extensively studied. Although higher homologues of methyl increase the stability of the monobactams against β-lactamases, their antibacterial activity diminishes[187, 191]. Of the functionalized 4-methylmonobactams, the 4-fluoromethyl compound **145** has received particular attention. **145**, independently synthesized by three teams[192–194], showed high antibacterial activity, comparable to that of aztreonam, against a number of Gram-negative species.

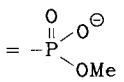
Table 14. Monocyclic β-lactams with negatively charged nitrogen substituents.

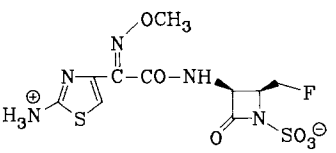


	X	Ref.
Monophosphams		[187]
Monocarbams		[187]
Monosulfactams		[188]
Oxamazins		[189]
N-(Tetrazol-5-yl)-azetidinones		[190]

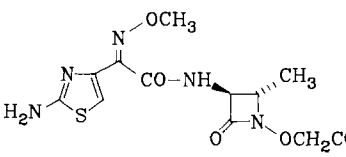


143, SQ 82 228, R = 

144, SQ 27 327, R = 



145



146a, SQ 82 531, R = $CH_2CO_2C(CH_3)_3$
146b, SQ 82 291, R = Na

A prodrug form of a monocyclic β-lactam has recently been reported[195]. After oral administration of SQ 82531 **146a** to animals, high blood levels of the parent compound **146b** were observed.

7. Conclusion and Outlook

This general survey has endeavored to describe the status of β-lactam antibiotics from the viewpoint of medicinal chemistry. The physicochemical and biological properties of this class of drugs have been scrutinized like no other, yet considerable research efforts are still being made to achieve further progress. The principle of drug optimization by modification has been outstandingly successful and is an example of the contribution that the synthetic chemistry of natural products can make to the treatment of infections. The new β-lactam antibiotics that have recently entered the market or are in clinical trial have exceptional antibacterial spectra and appreciably widen and improve therapeutic possibilities in severe and life-threatening infections. Progress of this kind is not always fully appreciated, since the treatment of infectious diseases is almost

taken for granted by the layman. Also, it is asking too much of many doctors to expect them to select the optimal drug for a specific infection.

The ideal antibiotic has undoubtedly not yet been found. The difficulties in advancing towards this goal lie in the considerable diversity of bacteria and in their defence strategy which has been optimized over billions of years. This strategy is an expression of the enormous variability of the living cell under selection pressure. The gradually increasing development of resistance in bacteria follows the principle of move and countermove, as in a game of chess. It is based on many different molecular mechanisms, of which the induction of β-lactamases, reduced ability to penetrate the bacterial cell wall, and lower affinity for the target enzymes of the bacteria under antibiotic treatment are of particular importance. The shift in the spectrum of pathogenic organisms is a further factor complicating the advance of antibiotic therapy. In particular, Gram-negative organisms and opportunists, for example, *Pseudomonas, Serratia,* and *Proteus* species, are nowadays triggering serious infections much more frequently than was formerly the case. The problem of chronic infections has not yet been solved.

New β-lactam antibiotics with improved properties demand much more sophisticated chemistry. In particular, the synthesis of new "nonclassic" compounds from the series of penems and carbapenems confronts the research chemist with the problem of transferring reactions that require specific conditions to large scale synthesis. For the future, it is important, by the combination of enzymatic and easy-to-perform stereoselective reactions, to elaborate short economical synthesis routes producing high yields[196]. The antibiotic market has become more price-sensitive and an upper price limit cannot be exceeded. Genetic engineering will help to develop better isolation procedures for natural antibiotics. By interfering with the microorganisms' DNA, it should be possible to develop species that give higher yields in fermentation or even enable the production of new antibiotics.

The quest for more potent antibiotics will have to remain a permanent task of chemotherapeutic research, if we want to maintain the high standard in the treatment of infectious diseases. The new drugs will have to be selected and evaluated with regard to efficacy, tolerance, and necessity according to very strict criteria before they can be used in clinical practice.

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Cationic Thionitrosyl and Nitrosyl Complexes**

By *Gabriele Hartmann* and *Rüdiger Mews**

Compared to the seemingly countless number of nitrosyl complexes that have been reported in the literature, the number of hitherto unequivocally characterized organometallic thionitrosyl complexes is pathetically small[1,2]. The main reason for this is the lack of a general method of synthesis[2]. Herein, it is shown that the thionitrosyl cation[4], like the nitrosyl cation[3], could also provide a general entry to such complexes when used as reaction partner in the form of the stable hexafluoroarsenate or hexafluoroantimonate.

The complex cation of the salt **1**[5] reacts with NS^+- and NO^+-salts with formation of the thionitrosyl- and nitrosyl-complex dications of the salts **2** and **3**, respectively.

$$\underset{\mathbf{1}}{[CpFe(CO)_2SO_2]^+AsF_6^-} + NS^+AsF_6^- \xrightarrow{-SO_2} \underset{\mathbf{2}}{[CpFe(CO)_2NS]^{2+}(AsF_6^-)_2} \quad (1)$$

$$\mathbf{1} + NO^+AsF_6^- \xrightarrow{-SO_2} \underset{\mathbf{3}}{[CpFe(CO)_2NO]^{2+}(AsF_6^-)_2} \quad (2)$$

$$\underset{\mathbf{4}}{[Re(CO)_5SO_2]^+AsF_6^-} + NS^+AsF_6^- \xrightarrow{-SO_2} \underset{\mathbf{5}}{[Re(CO)_5NS]^{2+}(AsF_6^-)_2} \quad (3)$$

$$\mathbf{4} + NO^+AsF_6^- \not\rightarrow [Re(CO)_5NO]^{2+}(AsF_6^-)_2 \quad (4)$$

In an analogous way, **4**[6] reacts with $NS^+AsF_6^-$ to give **5**, but does not react with $NO^+AsF_6^-$.

The reactions (1)—(3) proceed quantitatively. At first sight, the reaction of cations with cations to give dications seems absurd; but, if one reflects on the bonding in SO_2-complexes such as **1** or **4**[5–8], such a reaction is perfectly logical. The main contributer to formation of the metal-sulfur bond is the π-back bonding from the metal to the ligand. Since SO_2 is only a weak π-acceptor, stronger π-acids—such as, e.g., NS^+ or NO^+—should replace this ligand. **4** does not react with $NO^+AsF_6^-$ [Eq. (4)], thus indicating that the σ-donor ability of the ligands (that of NS^+ is greater than that of NO^+) is of importance for such reactions.

NO^+ can also replace CO in complexes[3,9,10].

$$\underset{\mathbf{6}}{[CpMn(CO)_3]} + NO^+AsF_6^- \xrightarrow[-CO]{SO_2} \underset{\mathbf{7}}{[CpMn(CO)_2NO]^+AsF_6^-} \quad (5)$$

$$\mathbf{6} + NS^+AsF_6^- \xrightarrow[-CO]{SO_2/-60^\circ C} \underset{\mathbf{8}}{[CpMn(CO)_2NS]^+AsF_6^-} \quad (6)$$

In liquid SO_2, the exchange proceeds according to Eq. (5) in high yields at room temperature, while **8** is formed almost quantitatively even at −60 °C. However, since **8** readily eliminates CO it was not possible to isolate the compound in analytically pure form[11]. Due to a lack of

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sufficient data, no unequivocal statements could hitherto be made about the ligand properties of NS^+ compared to those of NO^+[2]. It was concluded from a comparison of the IR spectra of $[CpCr(CO)_2NO]$[9, 12] and $[CpCr(CO)_2NS]$[13] (see Table 1) that the NS^+-ligand is the better π-acceptor. The same conclusion was drawn from the PE spectra and theoretical investigations[14]; yet it was also shown that NS^+ is the better σ-donor[14]. On changing the d^6-central atom M in the series of complexes $[CpM(CO)_2NX]^{n+}$ (X = O, S) from chromium(0) through manganese(I) to iron(II), the π-donor ability of the central atom dramatically decreases; ν(CO) and ν(NX) shift to higher wave numbers. The IR spectra of **2** and **3** show the highest ν(NS) and ν(NO) frequencies thus far found for organometallic compounds. In the nitrosyl complex cations of **3** and **7** the frequencies of the stretching vibrations lie distinctly higher than in the corresponding thionitrosyl complex cations **2** and **8**, respectively, an indication of the greater π-acidity of NO^+.

Table 1. Selected IR data of the complexes $[CpM(CO)_2NX]^{n+}(AsF_6^-)_n$ (Nujol or Kel-F mull) [cm^{-1}].

$[CpM(CO)_2NX]^{n+}$		X = O			X = S	
		ν(NO)	ν(CO)		ν(NS)	ν(CO)
Chromium(0) [9, 12]		1706	2020/1946		1165	2023/1963 [13]
Manganese(I)	**7**	1878 sh/ 1838 vs	2114/2075	**8**	1284	(2108/2070)
Iron(II)	**3**	1982	2198/2183	**2**	1388	2178/2165

A comparison of the IR data (Table 1) confirms the hypothesis that the acceptor ability of NS^+ compared to that of NO^+ depends on the charge density in the complex[15].

Experimental:

Exactly equimolar amounts (1–2 mmol) of the transition-metal complexes **1**, **4** or **6**, and of the NO^+ or NS^+ salts were weighed separately into a two-limbed flask in a dry box. After attachment of the flask to a vacuum apparatus, SO_2 (15 mL) was condensed onto both substances simulataneously at −196°C and the resulting solutions combined at −60°C. After warming to room temperature, the mixture was stirred for 12 h (in the case of **5**: 3 d) and the solvent removed. **2**, **3**, **5**, and **7** remained in almost quantitative yield as analytical pure residues[16]. **8** is synthesized at −60°C and the solvent is removed in vacuo at −40°C[17].

SO_2 seems to be especially suitable for reactions with nitrosyl and thionitrosyl salts, whereas the solvents CH_3CN[6] and CH_2Cl_2[13] mentioned in the literature can easily lead to exchange and decomposition reactions.

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1, 95217-85-9; **2**, 95217-87-1; **3**, 95217-89-3; **4**, 95217-91-7; **5**, 84303-53-7; **6**, 12079-65-1; **7**, 95217-92-8; **8**, 95217-94-0; $[Re(CO)_5NO]^{2+}(AsF_6^-)_2$, 95217-96-2; $NS^+AsF_6^-$, 31967-65-4; $NO^+AsF_6^-$, 18535-07-4; SO_2, 7446-09-5.

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[16] The elemental analyses of compounds **2**, **3**, **5**, and **7** are consistent with the calculated values. **2**: wine-red solid, sparingly soluble in SO_2, decomp. 172°C; IR (Nujol/Kel-F mull): 3130 m, 2178/2165 vs, 2118 sh, 2080 m, 2020 m, 1429 s, 1420 s, 1388 vs, 1362 sh, 1338 sh, 1252/1250 w, 1118 s, 1019 w, 1010 w, 880 s, 700 vs, 604 sh, 570 sh, 545 vs, 528 vs, 453 w, 438 w, 390 vs, 366 w, 320 w cm^{-1}. **3**: yellow-green solid, decomp. 137°C; IR (Nujol/Kel-F mull): 3128 s, 2198 vs, 2183 vs, 2140 sh, 2120 vw, 1982 vs, 1978 sh, 1963 sh, 1429 m, 1418 m, 1110 w, 884 m, 699 vs, 598 s, 568 s, 552 sh, 475 vw, 420 sh, 390 vs cm^{-1}. **5**: light-red solid, sparingly soluble in SO_2, decomp. 136°C; IR (Nujol mull): 2220 vs, 2200 w, 2178 sh, 2160 vs, 2068 m, 2038 sh, 1370 vs, 700 vs, 542 m, 522 m, 488 w, 392 vs, 318 vw cm^{-1}. **7**: light-green solid, decomp. 136°C; IR (Nujol/Kel-F mull): 2114 vs, 2075 vs, 1878 sh, 1838 vs, 1430 w, 1420 w, 1120 vw, 1022 vw, 869 m, 700 vs, 680 sh, 658 m, 628 s, 530 w, 395 vs cm^{-1}.
[17] **8**: light-brown solid; IR (Nujol/Kel-F mull): 3120 w, 2108 vs, 2070 vs, 1430 w, 1284 vs, 865 w, 700 vs, 672 w, 588 w, 568 w, 555 sh, 390 vs cm^{-1}. The elemental analysis of **8** always shows C < 7 and an N:S ratio of 1:1. On prolonged storage in solution at higher temperatures, **8** loses CO quantitatively with formation of a solid which is insoluble in SO_2.

Synthesis of $[Et_2N{-}C{\equiv}W(CO)_2(\mu\text{-}PPh_2)_2Mo(CO)_4]^{\ominus}$, the First Anionic Carbynemetal Complex; Addition of CO_2 to the W≡C Bond**

By *Ernst Otto Fischer**, *Alexander C. Filippou*, *Helmut G. Alt*, and *Ulf Thewalt*

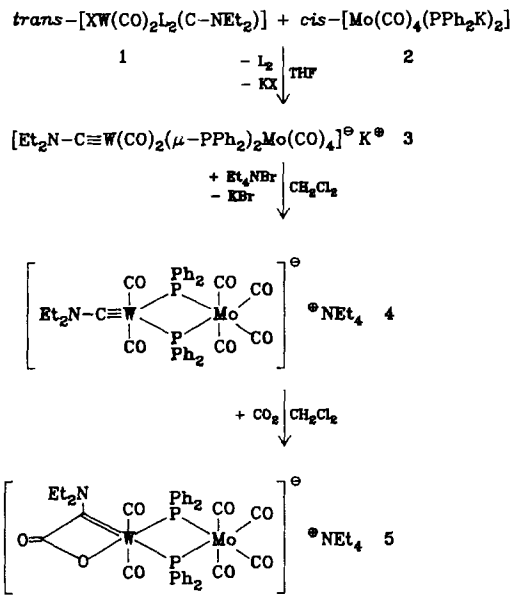
Dedicated to Professor Günther Wilke on the occasion of his 60th birthday

We were able to demonstrate that neutral and cationic carbyne(carbonyl)metal complexes are obtainable on allowing carbene complexes to react with boron trihalides at low temperature[1, 2]. In complete contrast, however, all attempts to isolate anionic carbyne complexes have hitherto failed. Thus, for example, on reaction of stable, substituted carbyne complexes of the type $[Br(CO)_2L_2WCR]$ (L_2 = phen, bpy; R = C_6H_5, CH_3) with KCN, replacement of CO by $CN^{\ominus}$ with formation of an anionic carbyne complex does not take place. Instead, as we have recently discovered, insertion of CO into the W≡C bond takes place with formation of an anionic ketene complex[3]. This finding automatically raises the question whether this insertion

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[**] Transition-metal carbyne complexes, Part 78. — Part 77: E. O. Fischer, J. Schneider, D. Neugebauer, *Angew. Chem. 96* (1984) 814; *Angew. Chem. Int. Ed. Engl. 23* (1984) 820.

reaction might be forestalled on appropriately varying the R moiety attached to the carbyne ligand (NEt_2 instead of C_6H_5 or CH_3).



Scheme 1. **1a**, X = Br, L_2 = bpy; **1b**, X = Br, L_2 = phen; **1c**, X = I, L_2 = bpy; **1d**, X = I, L_2 = phen.

In analogy to the synthesis of other substituted carbyne complexes[4] *trans*-$[XW(CO)_4(CNEt_2)]$ (X = Br, I)[5] was allowed to react with 2,2'-bipyridyl (bpy) or 1,10-phenanthroline (phen) in CH_2Cl_2 to give the carbyne complexes **1**. Reactions of complexes **1** with the Mo-compound **2** always lead to the same diamagnetic anionic complex **3**, which can be precipitated with Et_4NBr as counterion and, after careful purification, isolated as yellow, microcrystalline **4** in analytically pure form (total analysis). The complex **4** reacts with CO_2 in CH_2Cl_2 to give the red adduct **5**, which can be isolated from CH_2Cl_2 as dark red crystals $5 \cdot 1.5\,CH_2Cl_2$, the structure of which has been determined by X-ray diffraction analysis (Fig. 1)[6].

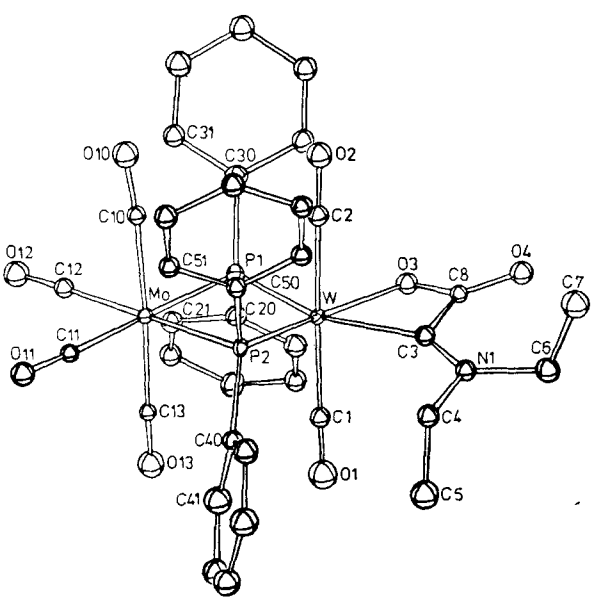


Fig. 1. Structure of the anion of **5** in the crystal [6].

A comparison of the IR, ^{1}H-NMR, ^{31}P-NMR, and ^{13}C-NMR spectra of compounds **4** and **5**, as well as the reactivity, lend support to the proposed structure of **4**. The IR spectra of **4** and **5** (Table 1) are very similar between 4000 and 300 cm^{-1}; it may be concluded, therefore, that the two compounds contain identical structural units. The spectrum of **5** contains an intense band at 1645 cm^{-1} due to the CO_2-unit of oxatungstacyclobutenone, a band which is missing in the spectrum of **4**.

Table 1. ^{1}H-, ^{13}C-, and ^{31}P-NMR data and selected IR data (carbonyl bands) of **4** and **5** in DMF.

	4	**5**
^{1}H-NMR [δ values] [a]	1.48 (t, 6H, CH_3; $^3J_{HH}$ = 6.7); 3.51 (q, 4H, CH_2; $^3J_{HH}$ = 6.7); 7.19, 7.27, 7.87, 7.96 (m, 20H, Ph)	1.29 (t, 6H, CH_3; $^3J_{HH}$ = 7.1); 3.41 (q, 4H, CH_2; $^3J_{HH}$ = 7.1); 7.27, 7.33, 7.67, 8.24 (m, 20H, Ph)
^{13}C-NMR [δ values] [b]	15.1 (CH_3), 49.6 (CH_2); 207.5 (Mo–CO_{cis} [c]; $^2J_{PC}$ = 4.4); 211.7 (Mo–$CO_{cis\text{-}trans}$ [d]; $^2J_{PC}$ = 4.4 and 5.5); 221.0 (W–CO [e]); 290.8 (N–C≡W, $^2J_{PC}$ = 13.2)	15.5 (CH_3), 48.6 (CH_2), 175.0 (W–O–C=O; $^3J_{PC}$ = 11.7 [f]); 205.9 (Mo–CO_{cis} [c]; $^2J_{PC}$ = 3.9 and 4.9); 208.9 (Mo–$CO_{cis/trans}$ [d]; $^2J_{PC}$ = 5.9 and 2.9); 218.1 (W–CO [e]); 242.9 (N–C≡W; $^2J_{PC}$ = 4.9 and 24.4)
^{31}P-NMR [δ values] [g]	+ 161.7 ($^1J_{WP}$ = 341.8)	+ 160.0 ($^1J_{WP}$ = 349.1, $^2J_{PP}$ = 4.9); + 160.8 ($^1J_{WP}$ = 222.2, $^2J_{PP}$ = 4.9)
IR [cm^{-1}]	2000 (s), 1908 (st), 1881 (m), 1834 (m)	2010 (s), 1918 (st), 1900 (m), 1877 (m), 1841 (m)

[a] 90 MHz in [D_7]-dimethylformamide (DMF), −20°C, δ values referred to DMF (δ = 2.74, 2.90, 8.04), coupling constants in Hz. [b] 90 MHz in [D_7]DMF, −20°C, δ values referred to DMF (δ = 30.1, 35.3, 162.7), coupling constants in Hz. [c] *cis* with respect to the two μ-PPh_2 bridges. [d] *cis* with respect to one μ-PPh_2 bridge, *trans* with respect to the other. [e] *J* not determinable. [f] The second coupling is not observed. [g] 90 MHz in [D_7]DMF, −20°C, δ values referred to 85% H_3PO_4 solution (ext.). Coupling constants in Hz.

The ^{1}H-NMR spectra of **4** and **5** (Table 1) show, along with the signals for the aromatic protons, the triplet and quartet expected for the diethylamino group on the carbyne carbon atom and on the carbene carbon atom, respectively. The ^{31}P-NMR spectrum of **4** shows only one signal for the two P-atoms, whereas the spectrum of **5** shows two signals; this is due to the different environment of these atoms (Table 1). In the ^{13}C-NMR spectrum of **4**, the signal of the carbyne C-atom (δ = 290.8) appears as a triplet, due to coupling with two homotopic P-atoms. The signal of the carbene C-atom of **5** (δ = 242.9), on the other hand, is split into a double doublet due to coupling with two diastereotopic P-atoms. The carbonyl ligands bound to the W-atom in **4** and **5** give rise, in each case, to only one signal, i.e., they are magnetically equivalent (Table 1).

The reaction of **4** with CO_2, leading to formation of **5**, not only affords further evidence in support of the proposed structure of **4**, it also opens up a route to new metallacycles. All these findings are indicative of **4** being the first anionic carbynemetal complex; anionic alkylidynemetal complexes, on the other hand, have been known for some time[8, 9].

Experimental:

All operations were carried out under argon using anhydrous and oxygen-free solvents.

1c: A solution of $[IW(CO)_4(CNEt_2)]$ (7.71 g, 15.2 mmol) in CH_2Cl_2 (100 mL) was treated at −40°C with 2.8 g (17.9 mmol) 2,2'-bipyridyl and the mixture

stirred at room temperature for 120 h. The color of the solution changed from orange to red and finally to violet, whereupon **1c** partially precipitated out. The mixture was then evaporated down and treated with Et_2O to complete precipitation of **1c**. Subsequent filtration and washing of the crude precipitate twice with Et_2O furnished 8.53 g (92%) of **1c** as permanganate-colored microcrystals.

4: The violet suspension of **1c** (1.17 g, 1.93 mmol) in THF (30 mL) was treated slowly at $-50\,^{\circ}C$ with a deep-orange solution of **2**. [Preparation of a solution of **2**: A solution of *cis*-$Mo(CO)_4(PPh_2H)_2$ [7] (1.97 g, 3.39 mmol) in THF (15 mL) is added to a suspension of KH (0.5 g, 12.5 mmol) in THF (15 mL) at room temperature; after 1 h, any excess KH is removed by filtration]. The reaction mixture was stirred for 2 h at room temperature; **1c** dissolved (brownish-yellow solution) and KI precipitated out. After filtration, the solvent was removed from the filtrate and the resulting brown residue was washed with 75 mL CH_2Cl_2 and dried in a high vacuum. The residue was then taken up in 20 mL CH_2Cl_2, treated with a solution of 2.03 g (9.66 mmol) Et_4NBr in 80 mL CH_2Cl_2, and filtered to remove insoluble KBr. After removal of solvent from the filtrate, dissolution of the residue in 100 mL THF, and removal of insoluble Et_4NX (X = Cl, Br, I) by further filtration, the final filtrate was evaporated down and treated with Et_2O to precipitate **4**; yield: 0.96 g (48%), yellow, finely crystalline powder.

5: A stream of dry CO_2 was passed into a solution of **4** (0.5 g, 0.48 mmol) in CH_2Cl_2 (50 mL) at $-10\,^{\circ}C$ until the brownish yellow solution turned dark red. After removal of the solvent, the residue was recrystallized from CH_2Cl_2; yield: 0.48 g (83%), red crystals which slowly lost their CH_2Cl_2 of crystallization at room temperature.

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[6] Monoclinic, space group $P2_1/c$; $a = 1655.3$, $b = 1423.8$, $c = 2216.0$ pm, $\beta = 109.18°$; $Z = 4$; 5581 independent diffraction data: Syntex $P\bar{1}$ single-crystal diffractometer, $Mo_{K\alpha}$-radiation ($\lambda = 71.069$ pm), graphite monochromator; $R_1 = 0.068$. Further details of the crystal structure analysis are available on request from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2, on quoting the depository number CSD 51202, the names of the authors, and full citation of the journal.
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$SiCl_2$: Photoelectron Spectroscopic Optimization of Various Syntheses**

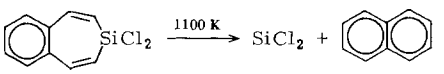
By *Hans Bock**, *Bahman Solouki*, and *Günther Maier*

Dedicated to Professor Rolf Sammet on the occasion of his 65th birthday

Dihalogensilanediyls (dihalogensilylenes) SiX_2[***], which, as coordinatively unsaturated species, can be inserted into many bonds between nonmetals[1], are available via several routes[1,2]: by high-temperature reaction of silicon halides with silicon[1,2a,b] and by thermolysis[1,2c] or photolysis[1] of appropriate organic precursors. We report here on the photoelectron (PE) spectrum of $SiCl_2$, obtained by reaction of hexachlorodisilane with silicon [reaction (a)], and on the optimization of reactions (b) and (c) by PE-spectroscopic on-line gas analysis[3].

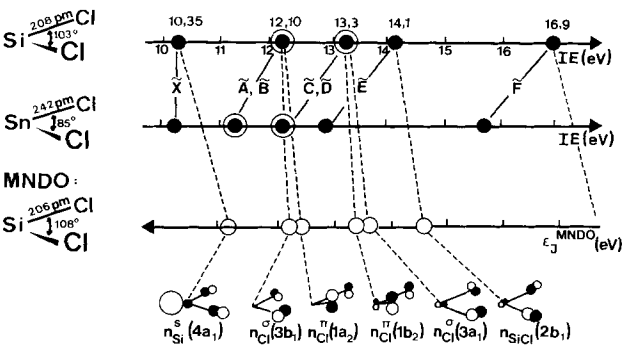
$$Cl_3Si{-}SiCl_3 \xrightarrow{1450\ K/Si_\infty} 3\ SiCl_2 \qquad (a)$$

$$Cl_3C{-}SiCl_3 \xrightarrow{>1250\ K/Si_\infty} SiCl_4 \xrightarrow{1450\ K/Si_\infty} SiCl_2 \qquad (b)$$



(c)

The PE spectrum of $SiCl_2$, which is necessary as a standard and was unknown up to now, is recorded during the selective reaction (a); between 9 and 17 eV, it exhibits an ionization pattern consisting of three single and two double bands (cf. Fig. 1).



Scheme 1.

An unequivocal assignment is achieved by comparison of the radical cation states $\tilde{X}$ to $\tilde{F}$ with those of the iso(valence)electronic $SnCl_2$[4] (Scheme 1), taking into consideration the opposing influences of decreased effective nuclear charge and reduced bond angle. The assignment is in agreement with the results of a geometrically optimized MNDO calculation, which satisfactorily reproduces the gas-phase structure of $SiCl_2$[2a] (Scheme 1). According to MNDO and ab initio SCF calculations[5], the Si center of $SiCl_2$ carries an appreciable positive charge, which accounts for the insertion reactions[1] in bonds between nonmetals.

The reaction of trichloro(trichloromethyl)silane with silicon powder [reaction (b)][3] is a further example for a PE-spectroscopically optimized high-temperature reaction (Fig. 1).

The following changes in the PE spectra[3], continuously recorded at short intervals, were observed with rising oven temperature: Above 1000 K, $Cl_3Si{-}CCl_3$ begins to decompose, and at 1250 K the known PE spectrum of pure $SiCl_4$ is observed (Fig. 1, middle). Transient chlorinated hydrocarbons can not be detected; possibly, either SiC is formed

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[**] Gas-phase reactions. Part 49. This work was supported by the Land Hessen, the Deutsche Forschungsgemeinschaft, and the Fonds der Chemischen Industrie.—Part 48: H. Bock, R. Dammel, *Angew. Chem. 97* (1985) 128; *Angew. Chem. Int. Ed. Engl. 24* (1985) 111.

[***] According to IUPAC rule D-6.12, silylenes are also called silanediyls.

on the Si surface or $(CCl_2)_\infty$ on cooler parts of the wall. At 1450 K, $SiCl_4$ reacts with Si—which can also be confirmed by direct reaction—almost completely to yield $SiCl_2$; according to the PE spectrum, only traces of unreacted $SiCl_4$ and of HCl are present, with the latter probably being formed by surface hydrolysis (Fig. 1, bottom).

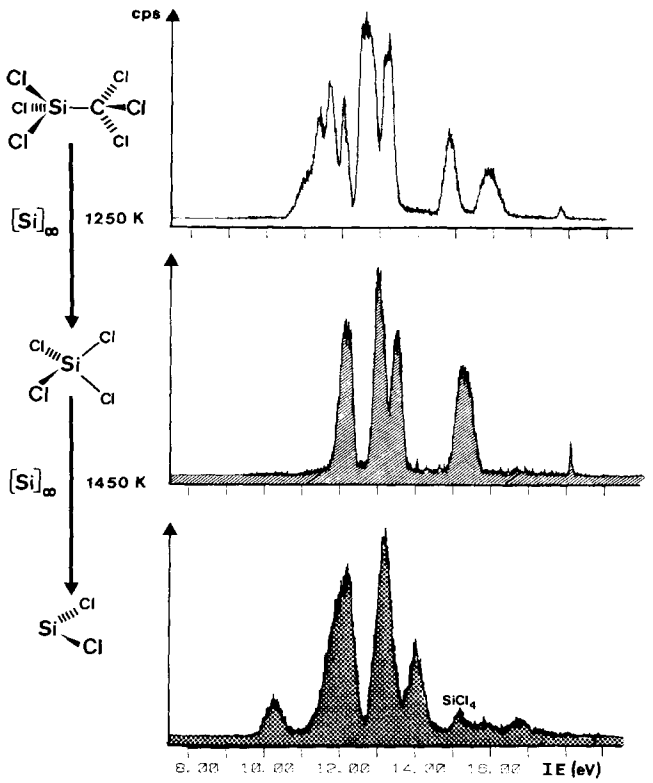


Fig. 1. He(I) PE spectra of $Cl_3Si-CCl_3$ (300 K, top) and of the products of its reaction with elemental silicon at 1250 and 1450 K (hatched: $SiCl_4$, dotted: $SiCl_2$, middle and bottom, respectively).

As a further route for the generation of $SiCl_2$, we investigated the thermolysis of 3,3-dichloro-3*H*-3-benzosilepin [reaction (c)], which eliminates naphthalene upon heating at 500°C; however, neither $SiCl_2$ nor secondary products have been reported[2c]. The PE-spectroscopically optimized thermal decomposition shows that at 1120 K the prominent bands of the benzosilepin have largely disappeared; the newly appearing bands in the low-energy region at 8.15, 8.90, and 10.0 eV (Fig. 2: ------▸) are assigned to naphthalene (Fig. 2; middle, hatched). If the PE spectrum of naphthalene is digitally subtracted from the PE spectrum of the product mixture, then the unequivocally identifiable band pattern of $SiCl_2$ emerges from the considerable background (compare Fig. 1 and Fig. 2 bottom).

These examples of synthetic routes to $SiCl_2$, which, with respect to the reaction temperatures [reactions (a) and (b)] as well as the required resolution [reaction (c)], are close to the present limits of measurement, demonstrate the advantages of digital recording of PE spectra in short time intervals as well as of their subtraction, termed "spectra stripping"[6]. It should also be possible to detect other silanediyls by PE spectroscopy, and to optimize their synthesis analogously.

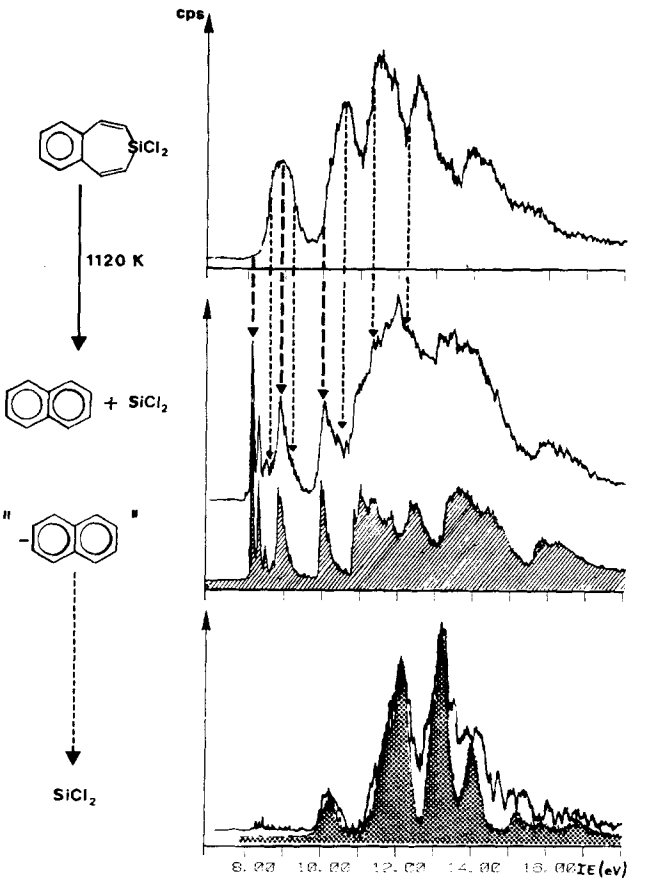


Fig. 2. He(I) PE spectra of 3,3-dichloro-3*H*-3-benzosilepin at 350 K (top) and of the product mixture after thermolysis at 1120 K (middle, new bands ------▸; disappearing bands – – →). Digital subtraction of the naphthalene PE spectrum (hatched) yields the ionization pattern of $SiCl_2$ (dotted, below).

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$SiCl_2$, 13569-32-9.

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[5] Dr. *P. Rosmus*, Universität Frankfurt, has meanwhile carried out an ab initio SCF calculation with a total of 74 groups of orbitals (Basis 11s/7p + 1d for Si and 11s/7p for Cl), giving a total energy of −1207.9059 a.u. and the following SCF eigenvalues: 10.37 eV (a_1), 12.56 eV (b_2), 12.95 eV (a_2), 13.85 eV (b_1), 14.20 eV (a_1), 14.96 eV (b_2) and 18.35 eV (a_1). The populations are Si: 13.55 e^-, Cl: 17.22 e^-; the dipole moment is calculated to be 1.8 D.

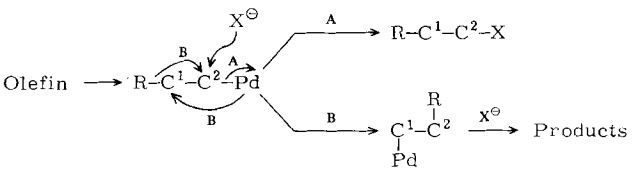
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Methyl Migration and Transannular 1,5-Hydride Shift on Oxidative Cleavage of C–Pd Bonds with $CuCl_2$**

By *Andreas Heumann** and *Jan-E. Bäckvall**

The oxidative cleavage of the carbon-palladium bond is an important reaction step in many Pd-catalyzed reactions[1]. The oxidizing agent—frequently $CuCl_2$ or $Pb(OAc)_4$[2]—weakens the C–Pd bond, so that the palladium residue becomes a good leaving group[3]. The organic end product is then formed, e.g., by a nucleophilic substitution (Scheme 1, Path A).

In the Wacker reaction—the oxidation of ethylene to acetaldehyde—cleavage at the C–Pd bond is accompanied by a hydride shift[4]. Several comparable rearrangement reactions (Scheme 1, Path B) have been observed in recent years: a Wagner-Meerwein rearrangement on the norbornane skeleton[5], ring expansion reactions[6], and a ring opening reaction[7]. In such cases, oxidative cleavage of the C–Pd bond is almost always the last step in catalytic multiple-step reactions of Pd^{II} salts with various olefins.



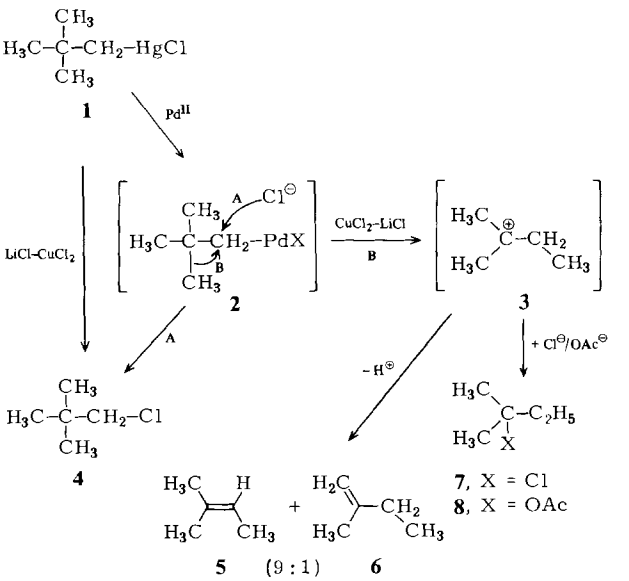
Scheme 1

The easy accessibility of palladium σ-complexes from stable organomercury compounds via a stereospecific metal-exchange reaction

$$\text{Alkyl–Hg–Cl} + PdX_2 \rightarrow \text{Alkyl–Pd–X} + HgXCl$$

makes possible the study of specific palladated compounds. Recently, *Bäckvall* and *Nordberg*[8] reported the selective synthesis and oxidative cleavage of β-phenylethylpalladium complexes and their rearrangement in the presence of $CuCl_2$–LiCl via phenonium ions.

We have now found that, upon oxidation of complexes having the composition $R–CH_2$-metal under similar conditions, a methyl migration as well as a hydride shift over five carbon atoms can take place. In such cases, the rearrangement reactions[9] are favored by a low concentration of chloride (little or no LiCl), whereas a direct substitution at the Pd-substituted carbon atom takes place preferentially at higher concentrations of LiCl. The neopentylmercury chloride **1** proved to be a suitable model for the study of the reactivity of C–Pd bonds[10]. **1**, which can be prepared via standard reactions (Grignard reaction, mercuration with $HgCl_2$), reacts only very slowly upon direct oxidation ($CuCl_2$–LiCl–HOAc), being directly substituted to give exclusively **4** (Scheme 2). The addition of catalytic amounts of $Pd(OAc)_2$ results in a completely different spectrum of products (Scheme 2), via the in situ formation of palladium σ-complex **2**. In addition to neopentylchloride **4** (direct substitution, Path A), the methylbutenes **5** and **6**, as well as the chloride and the acetate **7** and **8**, respectively, are found (Path B).



Scheme 2

The effect of LiCl on the $CuCl_2$ oxidation of **2** is apparent from Table 1. In the Pd-catalyzed reactions, the proportion of rearranged products predominates. This can be attributed to the intermediate formation of the cation **3**. The proportion of unrearranged neopentyl chloride **4** (reaction with S_N2 character) increases with increasing amount of LiCl. For the rearranged compounds **7** and **8**, the acetoxy compound **8** is present in slightly larger proportion for low concentrations of chloride. A similar trend was already observed in the catalytic oxidation of ethylene in acetic acid[11, 12].

Table 1. $Pd(OAc)_2$-catalyzed reaction of neopentylmercury chloride **1** in the presence of $CuCl_2$–LiCl–HOAc [a].

Concentration [mol/L]		Products [b, c]		
$CuCl_2$	LiCl	**4**	**7**	**8**
1	0.5	1	3	2
1	2.5	5	2	1

[a] 5 mL solvent: 90% HOAc; 0.5 mol/L **1**, 0.02 mol/L $Pd(OAc)_2$, 45–50°C, 42 h. [b] GC analysis (SE-30). The compounds **4**, **7**, and **8** were extracted from the reaction solution with pentane and partially separated by Kugelrohr distillation. The products were characterized by 200 MHz ^{1}H-NMR spectroscopy. [c] 2-Methyl-2-butene **5** and 2-methyl-1-butene **6** could be identified by ^{1}H-NMR spectroscopy (ratio 9:1). Their proportion of the product mixture could not, however, be determined.

If R in $R–CH_2$-metal is an alicyclic group, such as, e.g., cyclohexyl in **9**, a β-elimination and several rearrangement processes (alkyl migration, hydride shift) are possible in addition to the direct substitution. As is apparent from Scheme 3 and Table 2, a dependence of the product composition on the LiCl concentration is also observed for the reaction of **9** with $PdCl_2$–$CuCl_2$–LiCl. Surprisingly, practically no elimination products are formed; these should

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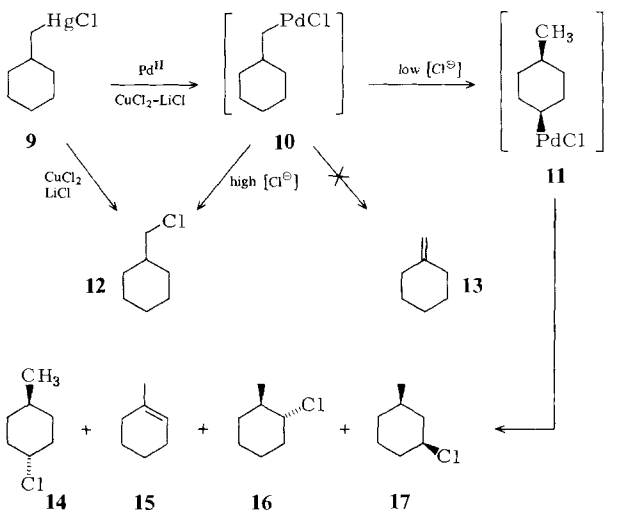
[**] This work was supported by the NFR (Sweden) and the CNRS (France) as part of an international exchange program.

indeed be favored owing to the neighboring presence of a tertiary hydrogen and a metal atom. Chlorocycloheptane, the product of an alkyl migration[6], could not be observed either.

Table 2. $PdCl_2$-catalyzed reaction of cyclohexylmethylmercury chloride **9** with $CuCl_2$–LiCl–HOAc [a].

LiCl concentration [mol/L]	Products [b] 12	15	16	17	14	Not identified
1.66	44	5	3	5	8	35
0.66	11	Traces	2	12	28	47
0.33	4	—	3	13	41	39
—	1	—	—	5	74	20

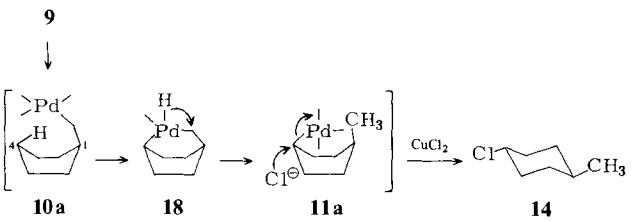
[a] 3 mL solvent: 90% HOAc; 0.33 mol/L **9**, 0.66 mol/L $CuCl_2$, 0.013 mol/L $PdCl_2$, 45–48 °C, 70 h. [b] GC analysis: glass capillary column (25 m) CW-20M, temperature program 80–120 °C with 4 °C/min, 1 bar H_2. We thank Dr. *G. Mallet*, Faculté de St.-Jérôme, Marseille, for help with the GC analyses. Yields of isolated products: 50–60%(based on $C_7H_{13}Cl$). The reaction products were identified by comparison of their ^{1}H-NMR spectra with those of authentic compounds (synthesized via chlorination of the respective alcohols with PPh_3/CCl_4) [13]. A large number of side products were not identified.



Scheme 3.

1-Chloro-4-methylcyclohexane **14** (74%), which is almost exclusively formed in the absence of LiCl, can be formed via two routes: It could arise via a series of elimination-addition reactions (of Pd–H) and subsequent chlorination, as suggested by *Henry*[14] for the case of palladation reactions on deuterated cyclohexene. However, the absence of elimination products as well as the high regio- and stereoselectivity of the reaction are hardly in accord with such a reaction mechanism. In contrast, a transannular 1,5-hydrogen migration, via a palladabicyclooctane, such as **18**, leads to **11a** (Scheme 4). The *trans* configuration in **14** is then the result of the normal[15] course of the catalyzed $CuCl_2$ oxidation of the C–Pd bond (configuration inversion, **11a** → **14**).

Although the 1,2-isomer **16** (*trans*) and the 1,3-isomer **17** (*cis*) are also formed, **14** is the main product of the rearrangement and thus the attack on the "*para*"-C^4–H group is the most favorable reaction. The C–H abstraction proceeds, accordingly, via a cyclic seven-membered transition state and differs from the long known radical C–H activation, the Hofmann-Löffler-Freytag reaction[16] (six-membered transition state).



Scheme 4.

The C–H activation in alkanes of transition-metal compounds has been intensively investigated for the last few years[17]. It seems of interest, therefore, to determine to what extent the reaction discussed here is extendable to *n*-alkanes. Preliminary experiments show that, in the oxidation of n-$C_8H_{17}HgCl$ with $PdCl_2$–$CuCl_2$–HOAc, mainly products of a 1,2-hydride shift are formed ($C_6H_{13}CHX-CH_3$, X = Cl, OAc). Whether the Pd–Cu-catalyzed functionalization of C–H bonds can be extended to more complex systems (e.g., steroids) remain to be investigated.

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1, 10284-47-6; **4**, 753-89-9; **5**, 513-35-9; **6**, 563-46-2; **7**, 594-36-5; **8**, 625-16-1; **9**, 33631-63-9; **12**, 1072-95-3; **14**, 13064-82-9; **15**, 591-49-1; **16**, 28046-83-5; **17**, 28046-86-8; LiCl, 7447-41-8; $CuCl_2$, 7447-39-4; $PdCl_2$, 7647-10-1; $Pd(OAc)_2$, 3375-31-3.

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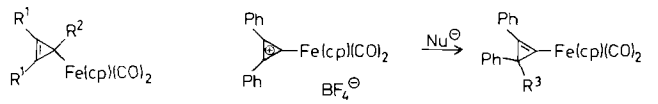
Dicarbonyl-η^5-cyclopentadienyl(1-cyclopropenyl)iron Complexes—A New Class of σ-Cyclopropenyl Complexes**

By *Rudolf Gompper* and *Ekkehard Bartmann**

Dedicated to Professor Günther Wilke on the occasion of his 60th birthday

Many types of coordination and reactions at transition-metal centers can be realized with the cyclopropenylium system[1]. Whereas π-complexes of cyclopropenyl ligands (with symmetrical as well as unsymmetrical coordination)[2] are today an extensive class of compounds, σ-cyclopropenyl complexes (which are often suspected as intermediates in the formation of π-complexes) have thus far not been generally accessible[3]. After the synthesis of σ-cyclopropenyl derivatives **1** of dicarbonylcyclopentadienyliron in which the metal is bonded to the methylene C atom of the cyclopropene[4], we now also report the preparation of complexes in which the metal is bonded to the double bond of the three-membered ring.

The complexes **3** are simply obtained by reaction of the salt **2**[4a,5] with nucleophiles ($Nu^{\ominus}$); they are yellow, crystalline substances which are stable under exclusion of light and air[6].



1 **a**: $R^1 = R^2 = Ph$
b: $R^1 = Ph$, $R^2 = H$
c: $R^1 = t\text{Bu}$, $R^2 = Me$
$cp = C_5H_5$

2

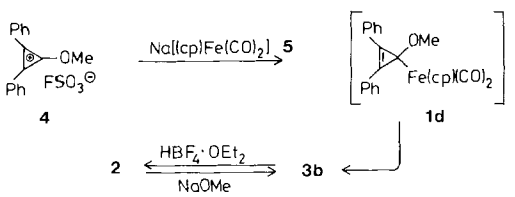
3 **a**: $R^3 = H$: 44%
b: $R^3 = OMe$: 54%
c: $R^3 = CN$: 70%

The direction of nucleophilic attack on **2** observed here is not uncommon. Other cyclopropenylium complexes, as well as donor-substituted cyclopropenylium salts in general[7] (the metal, too, is practically a donor), are attacked by nucleophiles not at the C atom that bears the donor but at one of the other two C atoms of the three-membered ring. In these cases, a ring opening, however, usually occurs as a following reaction.

The positions of the carbonyl bands in the IR spectrum and the singlets of the cyclopentadienyl protons in the ^{1}H-NMR spectrum confirm that compounds **3** and not isomeric complexes of the type **1** were actually obtained. They are not in agreement with the corresponding signals of the known compounds **1a**, **b**, and **c**[4], but do fall in the region in which dicarbonylcyclopentadienyl groups that are bonded to vinyl or phenyl groups or to other sp^2 centers absorb[8,9].

The intense IR bands between 1700 and 1800 cm^{-1} confirm the presence of cyclopropene derivatives and not products with opened rings.

The formation of **3b** is reversible; **2** can be recovered by addition of etheral tetrafluoroboric acid. **3b** is also an intermediate in the earlier described synthesis of **2** from methoxydiphenylcyclopropenylium fluorosulfate **4** and sodium dicarbonylcyclopentadienylferrate **5**[4a,5]. In this reaction, a complex with the structure **1d** must initially be formed; however, **1d** is not stable, and rearranges immediately, via migration of the methoxy group, to **3b**.



In the reactions described here, pronounced differences are shown in the tendency of formation of complexes **1** and **3**. In general, the complexes **3** are also appreciably more stable than the earlier isolated compounds of type **1**; especially notable is the difference between **3a**[6] and its isomer **1b**, which quickly decomposes even at room temperature. This emphasizes once again the fact that 2-cyclopropenyl metal complexes such as **1** can be viewed as derivatives of the antiaromatic cyclopropenide ions.

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2, 66652-72-0; **3a**, 95218-01-2; **3b**, 95218-02-3; **3c**, 95218-03-4; **4**, 66633-47-4; **5**, 12152-20-4.

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[6] Procedure for **3**: **2** (0.91 g, 2 mmol) [5] was stirred for several hours with $NaBH_3CN$ (0.13 g, 2 mmol) in 20 mL tetrahydrofuran (THF) (**3a**), $NaOCH_3$ (0.22 g, 4 mmol) in 20 mL THF (**3b**), or KCN (0.65 g, 10 mmol) in 20 mL acetonitrile (**3c**). The mixture was evaporated under vacuum; in the case of **3b**, the residue was dissolved in 10 mL dichloromethane, treated with 20 mL hexane, and, after filtration, slowly concentrated. The crystals that separated out were isolated, washed with hexane, and dried under high vacuum. In the case of **3a** and **3c**, the residue was purified by column chromatography on silica gel, the product fraction eluting with toluene or with chloroform/diisopropyl ether (1:1). The eluate was evaporated under vacuum and the residue recrystallized from ether/hexane (cooling of the solution to −40°C) or dichloromethane/hexane. **3a**: decomposition above 60, **3b**: m.p. = 95–97 (decomp.), **3c**: m.p. = 160–162°C (decomp.). Correct C,H,N elemental analyses were obtained for all three compounds.

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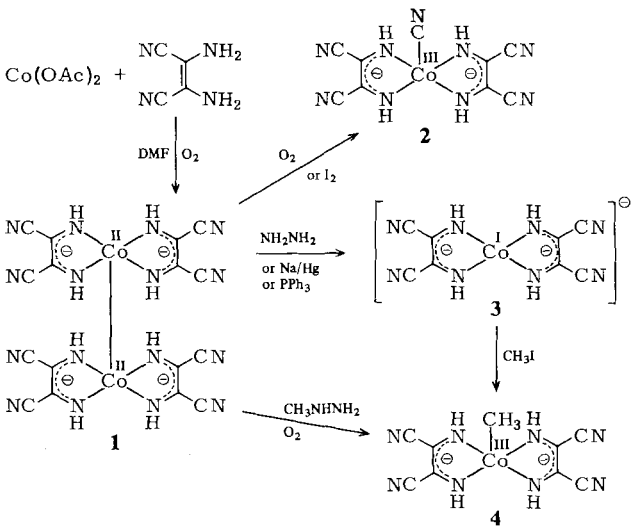
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[9] **3a**: IR (KBr): $\nu = 2020$, 1958 (C≡O), 1753 cm^{-1} (C=C); ^{1}H-NMR ($CDCl_3$): $\delta = 2.47$ (s, 1H), 4.86 (s, 5H), 6.87–7.45 (m, 10H). **3b**: IR (KBr): $\nu = 2020$, 1958 (C≡O), 1729 cm^{-1} (C=C); ^{1}H-NMR ($CDCl_3$): $\delta = 3.29$ (s, 3H), 4.98 (s, 5H), 7.25 (m, 10H). **3c**: IR (KBr): 2205 (C≡N), 2030, 1984 (C≡O), 1787 cm^{-1} (C=C); ^{1}H-NMR ($CDCl_3$): $\delta = 5.09$ (s, 5H), 7.0–7.5 (m, 10H).

Cofacial Dimer of a Diiminosuccinonitrile Complex Containing a Co^{II}–Co^{II} Bond and its Reduction to the Monomeric Co^{I} Complex**

By *Shie-Ming Peng**, *Der-Shin Liaw*, *Yu Wang*, and *Arndt Simon**

As a result of work on metal complexes with delocalized ground states, we report on two novel crystal structures of semidiiminosuccinonitrile (s-disn) complexes of cobalt (Scheme 1).



Scheme 1.

The blue binuclear complex $[Co^{II}(s\text{-}disn)_2]_2$ **1** was synthesized by the reaction of diaminomaleonitrile and $Co(OAc)_2$ in dimethylformamide (DMF), followed by oxidation. Suitable single crystals were grown by slow diffusion of air into the solution for one month. The structure of **1** consists of discrete DMF-solvated dimeric complexes, **1**·$(dmf)_3$ (Fig. 1). The complex **1** has a number of unusual features. First, it contains a short Co^{II}–Co^{II} bond (2.633(3) Å), which is shorter than those in $[Co_2^{II}(CN)_{10}]^{6\ominus}$ (2.794 Å)[2] and $[Co_2^{II}(CNCH_3)_{10}]^{4\oplus}$ (2.734 Å)[3]. The Co atoms are displaced 0.19 Å from the plane formed by the four N atoms toward one another. Both findings indicate a reasonably strong Co–Co σ-bond. Secondly, the two diiminosuccinonitrile ligands are arranged in an eclipsed fashion and are separated by only 2.9 Å. Thirdly, the ligands have more localized double bond character than those in similar complexes, such as $[Ni^{II}(s\text{-}disn)_2]$[4], $[Co^{III}(CN)(s\text{-}disn)_2]$[1] **2**, and $[Co^{I}(s\text{-}disn)_2]^{\ominus}$ **3**. In order to account for all these structural features, it is proposed that, in addition to the Co^{II}–Co^{II} σ-bond, a δ-type bond[5] exists between the two parallel s-disn ligands. These two types of bonds are synergic. The s-disn ligand in **1** has C_{2v} symmetry. Of the five π-electrons, four are in bonding orbitals (b_1, a_2) and one is in an antibonding orbital (b_1). The facial approach of two such monomeric units leads to a splitting of all the π-orbital pairs. Splitting of the antibonding states (b_1^*) and occupation of the lower set would lead to a net stabilization and the formation of one weak δ-type bond between the s-disn ligands. The proposed bonding scheme removes much of the antibonding character from the π* state and results in a more localized double bond arrangement of the s-disn ligands in this complex.

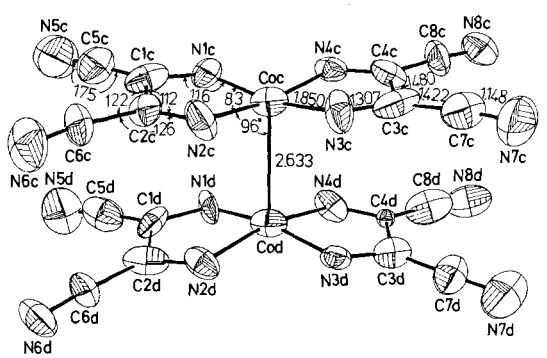


Fig. 1. ORTEP drawing of the crystal structure of **1**. $P\bar{1}$, $a = 13.328(4)$, $b = 27.999(26)$, $c = 9.488(13)$ Å, $\alpha = 85.91(10)$, $\beta = 98.66(8)$, $\gamma = 90.16(6)°$. $Z = 4$. 3527 reflections with $F > 3\sigma(F)$, 833 parameters, $R = 0.082$, $R_w = 0.077$. The crystals easily crack and have poor quality. The bond distances and angles are the average values of 16 chemically equivalent bond parameters. Estimated standard deviations; 0.02–0.04 Å and 1–2°, respectively [8].

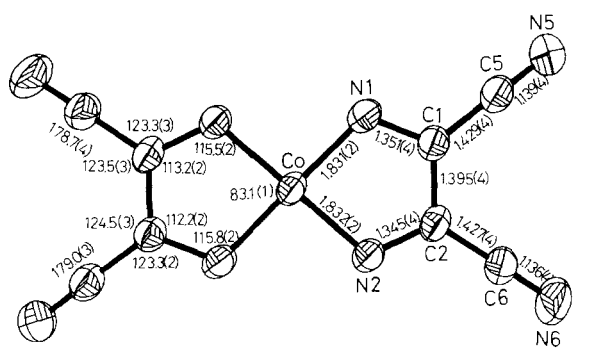


Fig. 2. ORTEP drawing of the anion **3** with 50 percent probability. C2/c, $a = 22.731(4)$, $b = 11.384(2)$, $c = 11.549(3)$ Å, $\beta = 93.23(2)°$. $Z = 4$. 3188 reflections with $I > 2\sigma(I)$, 193 parameters, $R = 0.039$, $R_w = 0.046$.

The reduction of **1** by hydrazine gives the monomeric complex anion $[Co^{I}(s\text{-}disn)_2]^{\ominus}$ **3**, which can be precipitated with the large cation $AsPh_4^{\oplus}$. Suitable single crystals can be grown from the salt **3**·$AsPh_4$. The structure of **3** is shown in Figure 2. The reduction of **1** results in a rupture of the Co–Co bond with formation of the square planar $[Co^{I}(s\text{-}disn)_2]^{\ominus}$ ion. The Co–N bond length, (1.831(2) Å) is short and comparable with that in $[Co^{I}(C_{10}H_{17}N_8)(CO)_6]$ (1.873 Å)[6] and with the M–N distances in complexes with delocalized ground states[1,4,7]. The C–C and C–N distances of the five-membered chelate rings in **3**, $[Co(CN)(s\text{-}disn)_2]$[1], $[Ni(s\text{-}disn)_2]$[4], and $[Pt(s\text{-}disn)_2]$[7] reveal the pronounced electron delocalization in the s-disn ligands of these complexes.

The anion **3** can be converted with CH_3I into the methylcobalt complex **4**, which can also be obtained directly from the dimer **1** by reaction with CH_3NHNH_2/O_2.

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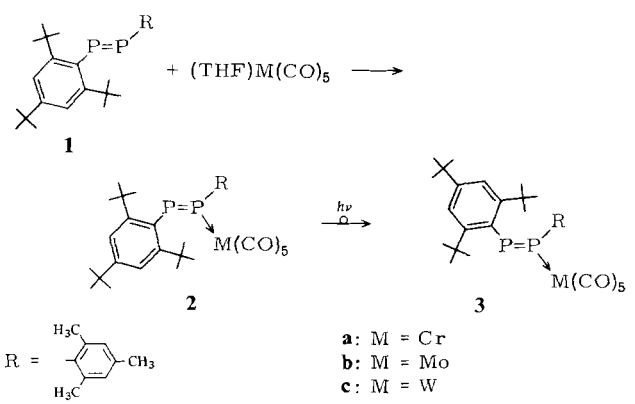
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[8] Further details of the crystal structure investigation may be obtained from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2, on quoting the depository number CSD 51151, the authors names, and full citation of the journal.

E→*Z*-Photoisomerization of a Diphosphene on Carbonylmetal Complexes (M = Cr, Mo, W)**

By *Masaaki Yoshifuji**, *Takashi Hashida*, *Naoki Inamoto*, *Ken Hirotsu**, *Teruhisa Horiuchi*, *Taiichi Higuchi*, *Keiji Ito*, and *Shigeru Nagase**

Recently, diphosphene-transition metal chemistry has developed very rapidly and extensively. We have been successful in the preparation and characterization of carbonylchromium(0), carbonylmolybdenum(0), and carbonyltungsten(0) complexes **2a**–**c** of *E*-mesityl-2,4,6-tri-*tert*-butylphenyldiphosphene **1** (THF = tetrahydrofuran). Transition-metal complexes involving formal P–P double bonds in the (*Z*)-configuration have been reported only very recently[1]. We now wish to report the first photoisomerization of (*E*)-diphosphenes on the pentacarbonylmetal complexes **2**.



In a typical experiment, **2a** (13.7 mg, 0.022 mmol) was dissolved in hexane (5.0 mL) and irradiated with a 100-W medium pressure Hg-lamp at 0°C for 15 min to give the (*Z*) isomer **3a** almost quantitatively. **3a** was purified by chromatography on silica gel at room temperature and recrystallization from pentane[2]. Similarly, upon irradiation, the molybdenum complex **2b** and the tungsten complex **2c** gave **3b** and **3c**, respectively. According to the ^{31}P-NMR spectra, the reaction rate decreases in the series Cr ≫ Mo > W. The FD-MS results were the same before and after irradiation[2].

Neither **2a** nor **1**, R = 2,4,6-tri-*tert*-butylphenyl[3] instead of mesityl, was isomerized on refluxing in $CDCl_3$ for several hours, whereas an *E*/*Z* equilibrium mixture has been formed upon laser irradiation of **1** at low temperature[4].

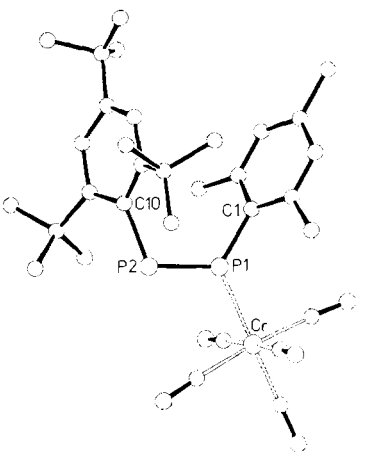


Fig. 1. Structure of **3a** in the crystal. $P2_1/c$, $a = 18.234(1)$, $b = 9.760(1)$, $c = 20.971(1)$ Å, $\beta = 114.72(1)°$, $Z = 4$. $Mo_{K\alpha}$-radiation, $\lambda = 0.7107$ Å, $R = 0.072$ for 2709 reflections with $I > 3\sigma(I)$. Important bond distances and bond angles, and the dihedral angle: P1–P2 2.039(3), P1–Cr 2.354(2) Å; Cr–P1–P2 116.3(1), Cr–P1–C1 124.9(3), P2–P1–C1 118.7(3), P1–P2–C10 109.6(3)°; *C1–P1–P2–C10 12.1(5)°. Further details of the crystal structure investigation* can be obtained from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2 (FRG), by quoting the depository number CSD 51177, the names of the authors, and the journal citation.

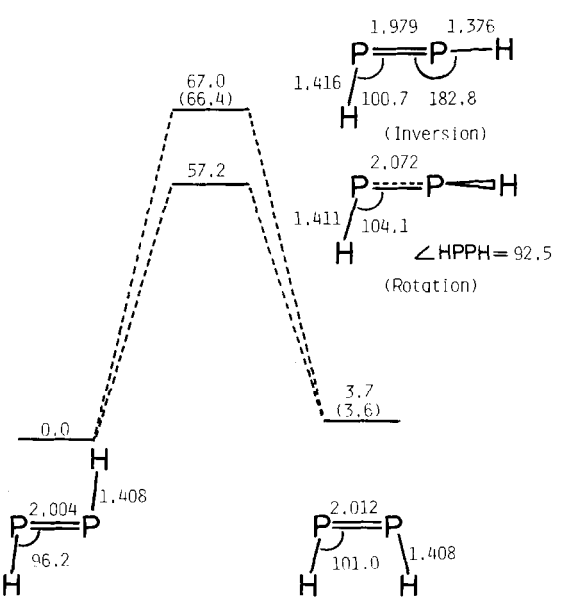


Fig. 2. Energies (kcal/mol) and geometries (Å, degrees) for the isomerization of HP=PH at the MP3/6-31G**//6-31G** level and the CI(S+D+Q)/6-31G**//6-31G** level (in parentheses). The rotational transition state is located by the use of complex molecular orbitals. See also the calculations of geometries optimized at the 3-21G level; T.-K. Ha, M. T. Nguyen, P. Ruelle, *Chem. Phys. 87* (1984) 23.

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The structure of **3a** was determined by X-ray structure analysis (Fig. 1). **3a** is the first example of a (*Z*)-diphosphene as a ligand of a mononuclear carbonylmetal complex. It should be noted that P1, P2, Cr, and Cl are coplanar, whereas the dihedral angle C1–P1–P2–C10 is 12.1°. The bond distance P1–Cr (2.354 Å) is shorter than that for pentacarbonyl(triphenylphosphane)chromium (2.422 Å)[5].

In the absence of these transition metals, the energy barrier for the isomerization of diphosphene (HP=PH) is considerable, the rotational transition state being preferred to the inversion transition state (Fig. 2). On complexation, however, the rotational barrier could be lowered both sterically and electronically.

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CAS Registry numbers:
2a, 95342-12-4; **2b**, 95342-13-5; **2c**, 95342-14-6; **3a**, 95250-88-7; **3b**, 95250-89-8; **3c**, 95250-90-1.

[1] a) M. M. Olmstead, P. P. Power, *J. Am. Chem. Soc. 106* (1984) 1495; b) H. Vahrenkamp, D. Wolters, *Angew. Chem. 95* (1983) 152; *Angew. Chem. Int. Ed. Engl. 22* (1983) 154.

[2] Selected physical data: **2a**: m.p. = 166°C, δ(P) = 500.9, 412.3 (AB, ^1J(PP) = 517.6 Hz), UV (cyclohexane): λ_{max} = 460 nm; **3a**: 136°C, δ = 393.9, 384.9 (603.0 Hz), 473 nm; **2b**: 163°C, δ = 486.3, 395.0 ppm (518.8 Hz), 435 nm; **3b**: 123°C, δ = 398.4, 359.0 (585.9 Hz), 456 nm; **2c**: 177°C, δ = 461.9, 352.4 (528.8 Hz), 436 nm; **3c**: 128°C, δ = 393.1, 322.4 (576.8 Hz), 459 nm. *Note added in proof* (March 22, 1985): We have meanwhile found a new synthesis of **2**: M. Yoshifuji, T. Hashida, K. Shibayama, N. Inamoto, *Chem. Lett.*, in press.

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Synthesis and Dynamic Properties of Chiral Heptalenes**

By *Klaus Hafner**, *Günter L. Knaup*, *Hans Jörg Lindner*, and *Hans-Christian Flöter*

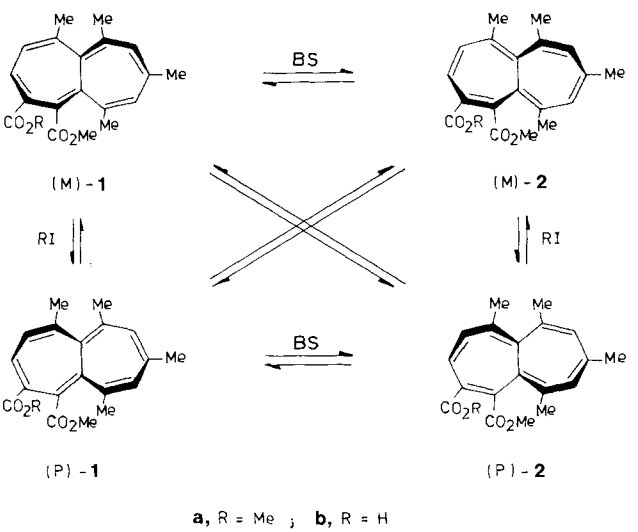
Dedicated to Professor Günther Wilke on the occasion of his 60th birthday

Mono- and bicyclic non-benzenoid systems with a 4n perimeter possess localized double bonds in the ground state. Their antiaromatic structures[1] with delocalized double bonds are transition states on the potential surfaces that connect the localized bond systens with one another. The results of experimental investigations on the 4nπ-electron systems tetra-*tert*-butylcyclobutadiene[2a], 1,3,5-tri-*tert*-butylpentalene[2b], cyclooctatetraene[2c], and heptalene[2d] are in agreement with this.

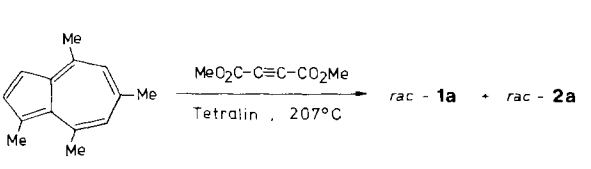
In contrast to cyclobutadiene and pentalene, their higher homologues cyclooctatetraene and heptalene are characterized by a nonplanar structure. X-ray structure analysis[3] of heptalene derivatives confirms a C_2 geometry for the bicyclic system with the two annelated seven-membered rings in boat conformations. For heptalenes, according to *Oth* et al.[4], four axially chiral isodynamic structures should be in equilibrium with one another via two dynamic processes [bond shift (BS) and ring inversion (RI)]. A study of both processes should provide information on their transition states and, therefore, also on the antiaromaticity of the delocalized heptalene system.

For the π-bond shift in heptalenes, *Vogel* et al.[2d, 5] determined an activation energy of 3.5 kcal·mol^{-1} by ^{13}C-NMR spectroscopy; for its 1,6-dialdehyde and dimethyl 1,6-dicarboxylate, a free energy of activation of 9.9 and 14 kcal·mol^{-1}, respectively. *Klärner*[6] found $\Delta G^{\ddagger}_{3°C} = 21.7$ and 21.0 kcal mol^{-1} for the isomerization of the bond-shift isomers of dimethyl 6,8,10-trimethyl-1,2-heptalenedicarboxylate[7], which can be separated by low-temperature chromatography. The kinetic parameters for the ring inversion of the heptalene system have not yet been determined.

We have succeeded for the first time in isolating in pure form all four possible isomers, (M)-**1**, (P)-**1**, (M)-**2**, and (P)-**2**, of a substituted heptalene, dimethyl 5,6,8,10-tetramethyl-1,2-heptalenedicarboxylate[8], and in investigating the kinetics of both dynamic processes for this heptalene derivative.



In analogy to the reaction[7] of azulene with dimethyl acetylenedicarboxylate, the reaction of 1,4,6,8-tetramethylazulene **3** with dimethyl acetylenedicarboxylate in boiling tetralin affords both isomers of *rac*-heptalene **1a** (yellow crystals, m.p. = 130°C) and **2a** (orange crystals, m.p. = 89–91°C) in 38 and 4% yield, respectively; the two compounds could be separated by chromatography on alumina at room temperature[9].



rac-**1a** and *rac*-**2a** differ characteristically in their electron and NMR spectra (Table 1). The position of the double bonds is determined from the ^{1}H-NMR spectra and the

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X-ray structure analyses[10] (Fig. 1), which confirm the double boat structure and thus the chirality of these compounds.

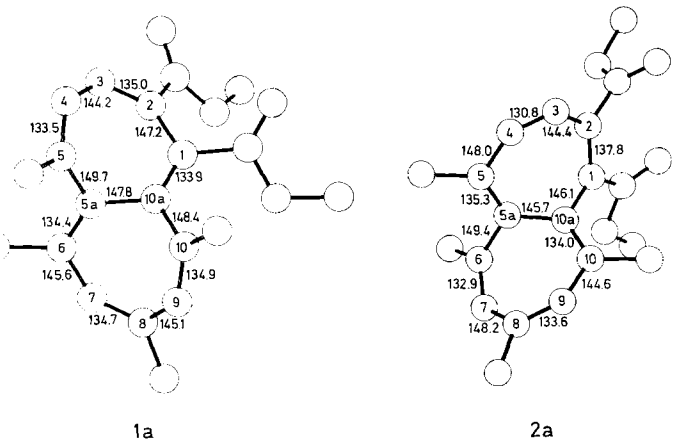


Fig. 1. Molecular structure of **1a** and **2a** with bond lengths [pm] (standard deviation **1a**: $\sigma_r = 0.6$ pm, **2a**: $\sigma_r = 1.0$ pm) [10].

Table 1. Spectroscopic data for racemic heptalenes **1** and **2**.

rac-**1a**: 300-MHz ^{1}H-NMR ($CDCl_3$): $\delta = 1.74$ (s, 3H, 6-Me), 1.96 (d, $J = 1.2$ Hz, 3H, 10-Me), 2.00 (dd, $J = 1.4$, 1.0 Hz, 3H, 5-Me), 2.04 (d, $J = 1.2$ Hz, 3H, 8-Me), 3.69, 3.70 (2s, each 3H, $2CO_2Me$), 6.01 (quint., $J = 1.1$ Hz, 1H, 9-H), 6.14 (s, 1H, 7-H), 6.27 (dq, $J = 6.9$, 1.4 Hz, 1H, 4-H), 7.53 (dq, $J = 6.9$, 1.0 Hz, 1H, 3-H); UV (*n*-hexane): $\lambda_{max}(\lg\varepsilon) = 211$ (4.38), 264 (4.21), 322 sh (3.46) nm.

rac-**1b**: 300-MHz ^{1}H-NMR ($CDCl_3$): $\delta = 1.73$ (s, 3H, 6-Me), 1.95 (d, $J = 1.1$ Hz, 3H, 10-Me), 2.00 (br. s, 3H, 5-Me), 2.03 (d, $J = 1.2$ Hz, 3H, 8-Me), 3.67 (s, 3H, 1-CO_2Me), 6.01 (s, 1H, 9-H), 6.14 (s, 1H, 7-H), 6.28 (dq, $J = 5.9$, 1.4 Hz, 1H, 4-H), 7.61 (dq, $J = 5.9$, 1.1 Hz, 1H, 3-H), 11.10 (s, 1H, 2-CO_2H); UV (dioxane): $\lambda_{max}(\lg\varepsilon) = 265$ (4.20), 318 sh (3.50), 369 sh (2.92) nm.

rac-**2a**: 300-MHz ^{1}H-NMR ($CDCl_3$): $\delta = 1.68$ (s, 3H, 10-Me), 1.77 (s, 3H, 5-Me), 1.99 (d, $J = 1.2$ Hz, 3H, 8-Me), 2.02 (d, $J = 1.3$ Hz, 3H, 6-Me), 3.71, 3.82 (2s, 3H each, $2CO_2$ Me), 6.01 (s, 1H, 9-H), 6.10 (s, 1H, 7-H), 6.55 (d, $J = 11.8$ Hz, 1H, 3-H), 6.59 (d, $J = 11.8$ Hz, 1H, 4-H); UV (*n*-hexane): $\lambda_{max}(\lg\varepsilon) = 210$ (4.34), 230 sh (4.21), 270 (4.31), 308 sh (3.54), 378 (2.74) nm.

rac-**2b**: 300-MHz ^{1}H-NMR ($CDCl_3$): $\delta = 1.72$ (s, 3H, 10-Me), 1.77 (s, 3H, 5-Me), 1.99 (d, $J = 1.0$ Hz, 3H, 8-Me), 2.03 (d, $J = 1.2$ Hz, 3H, 6-Me), 3.73 (s, 3H, 1-CO_2Me), 6.01 (s, 1H, 9-H), 6.10 (s, 1H, 7-H), 6.57 (d, $J = 11.8$ Hz, 1H, 3-H), 6.70 (d, $J = 11.8$ Hz, 1H, 4-H), 11.00 (s, 1H, 2-CO_2H). UV (dioxane): $\lambda_{max}(\lg\varepsilon) = 231$ sh (4.21), 271 (4.30), 309 sh (3.56), 381 (2.75) nm.

The saponification of *rac*-**1a** and *rac*-**2a** with CH_3OH/KOH affords the *rac*-acids **1b** (yellow crystals, m.p. = 150–155 °C (decomp.)) and **2b** (yellow crystals, m.p. 156–157 °C (decomp.)), respectively, which could be reconverted quantitatively into *rac*-diester **1a** and **2a**, respectively, with diazomethane. The resolution of **1b** is achieved by fractional crystallization of the cinchonine and (+)-α-phenylethylamine salts followed by liberation of the acids with 2 N sulfuric acid; that of **2b** in a corresponding way with (+)- and (−)-ephedrine[11].

The enantiomeric purity of the heptalenes so obtained, (+)- and (−)-**1b**, and (+)- and (−)-**2b**, is greater than 98%, as shown on the basis of the signals of the methoxy group in the ^{1}H-NMR spectra of the ephedrine salts. The enantiomerically pure acids, (+)- and (−)-**1b**, and (+)- and (−)-**2b**, and the enantiomerically pure esters obtained from these with diazomethane, (+)- and (−)-**1a** and (+)- and (−)-**2a**, have the high specific optical rotations typical for molecules with chiral chromophores (Table 2).

Table 2. Specific optical rotations of the heptalenes (+)-**1** and (+)-**2** (in $CHCl_3$) [12].

	$[\alpha]_{546}^{20}$	$[\alpha]_{578}^{20}$
(+)-**1a**	+1930 ($c = 1.028$)	+1460 ($c = 1.028$)
(+)-**1b**	+2550 ($c = 1.004$)	+1910 ($c = 1.004$)
(+)-**2a**	+1860 ($c = 0.921$)	+1310 ($c = 0.921$)
(+)-**2b**	+2140 ($c = 0.514$)	+1430 ($c = 1.029$)

The kinetic parameters for the bond shift, starting from *rac*-**2a**, were determined by ^{1}H-NMR spectroscopy in [D_{14}]-diglyme at temperatures between 50 and 80 °C. The rate constants for the reverse reactions were calculated from the equilibrium constants, which were determined in the temperature range of 50 to 170 °C, since the equilibrium ratio *rac*-**1a** : *rac*-**2a** is about 10 : 1 and therefore the measurements starting from *rac*-**1a** afford only very inaccurate data (Table 3).

Table 3. Kinetic parameters for the bond shift (BS) and ring inversion (RI) of the heptalenes **1a** and **2a** [13].

	$\Delta H^{\neq}_{25\,^\circ C}$ [kcal·mol^{-1}]	$\Delta S^{\neq}_{25\,^\circ C}$ [cal·mol^{-1}·K^{-1}]
BS **2a** → **1a**	22.8 ± 0.6	−11.1 ± 2.0
BS **1a** → **2a**	25.7 ± 0.6	− 7.8 ± 1.7
RI (−)-[**1a** ⇌ **2a**] → *rac*-[**1a** ⇌ **2a**]	28.3 ± 0.4	−11.6 ± 0.9

The rates of racemization were determined on the basis of the decrease in optical rotation of solutions of optically active heptalenes **1a** and **2a** in diglyme at 130 to 150 °C. Since the same rate constants are obtained starting from **1a** and **2a**, the bond shift may occur in a preceding equilibrium.

The kinetic data for the dynamic processes of the heptalenes **1a** and **2a** are not in accord with a planar transition state for the bond shift. For the bond shift, which proceeds with retention of configuration, a helical chiral transition state with a delocalized π-electron system must be assumed. In the case of planar transition states, like those assumed by *Paquette*[14] for the analogous processes of substituted cyclooctatetraenes, the energy barrier for the bond shift should be higher than that for ring inversion by the amount of energy required for the delocalization of the anti-aromatic π-electron system.

According to π-SCF force-field calculations[15] for the dynamics of both processes of 1,5,6,10-tetramethylheptalene, which are in agreement with experimental results, the bond shift should proceed via a helical, delocalized transition state ($\Delta H^{\neq}$: 30 kcal·mol^{-1}); the ring inversion, on the other hand, should occur via an only partly planar and localized transition state ($\Delta H^{\neq}$: ca. 31 kcal·mol^{-1}). In contrast to this, the corresponding processes with planar transition states require activation enthalpies of more than 50 kcal·mol^{-1}.

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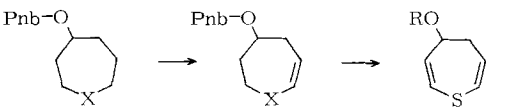
CAS Registry numbers:
(±)-**1a**, 95045-18-4; (+)-**1a**, 95045-19-5; (−)-**1a**, 95045-20-8; (±)-**1b**, 95045-21-9; (+)-**1b**, 95045-22-0; (−)-**1b**, 95045-23-1; **3**, 830-55-7; dimethyl acetylenedicarboxylate, 762-42-5.

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[8] The IUPAC rule A-21.1, according to which the parent system is to be called a heptalene, is not suitable for the correct designation of the bond-shift isomers. Rule A-31.3 makes it possible to give the structures unequivocal names. **1a**: dimethyl 6,8,10,12-tetramethylbicyclo[5.5.0]dodeca-1,3,5,7,9,11-hexaene-2,3-dicarboxylate; **2a** is the corresponding 2,4,6,8,10,12(1)-hexaene.
[9] In addition to *rac*-**1a** and *rac*-**2a**, 2% *rac* dimethyl 5,6,8,10-tetramethyl-2,3-heptalenedicarboxylate (orange needles, m.p. 125–127°C; 300-MHz ^{1}H-NMR ($CDCl_3$): $\delta = 1.78$ (d, $J = 1.0$ Hz, 3H, 10-Me), 1.79 (s, 3H, 5-Me), 1.97 (s, 3H, 6-Me), 2.00 (d, $J = 1.3$ Hz, 3H, 8-Me), 3.76, 3.77 (2s, 3H each, $2CO_2Me$), 5.97 (s, 1H, 7-H), 6.09 (s, 1H, 9-H), 6.75 (s, 1H, 1-H), 7.40 (s, 1H, 4-H); UV (*n*-hexane): λ_{max} (lg ε): 219 sh (4.24), 232 (4.25), 271 (4.30), 328 (3.75) nm) and 23% dimethyl 4,6,8-trimethyl-1,2-azulenedicarboxylate [8] are obtained.
[10] X-ray structure analysis: **1a**: monoclinic, space group $P2_1/c$, $Z = 8$, $a = 2394.5(4)$, $b = 922.9(3)$, $c = 1671.6(9)$ pm; $\beta = 105.04(5)°$, $V = 3567 \times 10^6$ pm^3; $\rho_{calc} = 1.22$ g/cm^3; $5° \leq 2\theta \leq 60°$; ($Cu_{K\alpha}$, $\lambda = 154.18$ pm), 4330 independent reflections, Lorentz and polarization correction, position of the hydrogen atoms calculated and optimized according to ideal geometry, $R_1 = 0.0667$, $R_2 = 0.0509$ for 4322 structure factors ($|F_0| \geq 0.5\,\sigma_F$). **2a**: triclinic, space group $P\bar{1}$, $Z = 4$, $a = 1840.7$, $b = 1197.9$, $c = 860.9$ pm; $\alpha = 102.75(1)$, $\beta = 98.57(2)$, $\gamma = 80.24(4)°$; $V = 1812 \times 10^6$ pm^3; $\rho_{calc} = 1.20$ g/cm^3; $5° \leq 2\theta \leq 60°$; ($Cu_{K\alpha}$, $\lambda = 154.18$ pm); 4830 independent reflections, Lorentz and polarization correction, position of the hydrogen atoms calculated and optimized according to ideal geometry, $R_1 = 0.1417$, $R_2 = 0.0981$ for 4317 structure factors ($|F_0| \geq 0.5\,\sigma_F$). Further details of the crystal structure investigation can be obtained on request from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2, on quoting the depository number CSD-51084, the names of the authors, and the journal citation.
[11] By a similar route (H.-J. Hansen, private communication, 1981), an enantiomeric enrichment was achieved for *rac* dimethyl 7-isopropyl-5,10-dimethyl-1,2-heptalenedicarboxylate (W. Bernhard, H.-R. Zumbrunnen, H.-J. Hansen, *Chimia 33* (1979) 324).
[12] Corresponding optical rotations were found for (−)-**1** and (−)-**2**. Note added in proof (February 6, 1985): Recently the absolute configuration of (+)-**1b** was determined as M by an X-ray structure analysis of the (1*S*,2*R*)-(+)-ephedrine salt of (+)-**1b**.
[13] Details on the kinetic measurements: G. L. Knaup, Dissertation, TH Darmstadt 1985.
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The Homothiopyrylium Ion; Generation and Characterization

By *Kagetoshi Yamamoto, Shoko Yamazaki,* and *Ichiro Murata**

Recently we succeeded in identifying several homothiopyrylium ions generated by protonation of 2,7-di-*tert*-butylthiepines[1] and 1-benzothiepine[2]. We describe now the parent homothiopyrylium ion **7**. Since the use of the protonation sequence to generate **7** requires the hitherto unknown unsubstituted thiepine, which is expected to be an extremely unstable compound[3], we have considered the ionization route for the preparation of **7** and synthesized the precursor 4,5-dihydrothiepin-4-ol **6** using a double Pummerer reaction.



1, X = S
2, X = SO
3, X = S
4, X = SO
5, R = Pnb
6, R = H

Pnb = O_2N–C$_6$H$_4$–CO–

Oxidation of *p*-nitrobenzoyl-protected hexahydro-4-thiepinol **1** (prepared from hexahydro-4-thiepinol[5]) with sodium periodate in aqueous methanol afforded the sulfoxide **2**[4] quantitatively. Interestingly, **2**, on treatment with acetic anhydride, afforded the protected tetrahydro-4-thiepinol **3** as the sole isolable product[4]. The structure of **3** was determined by ^{1}H-NMR (Table 1). After oxidation of **3** with sodium periodate in aqueous methanol or *m*-chloroperbenzoic acid in dichloromethane to the sulfoxide **4**[4], the second double bond was introduced by a modified Pummerer reaction[6]. When **4** was treated with diisopropylethylamine in dichloromethane followed by addition of freshly distilled trimethylsilyl iodide under nitrogen, protected 4,5-dihydro-4-thiepinol **5** was obtained. Finally, the alcohol **6** was smoothly liberated from **5** by hydrolysis with KOH in aqueous *tert*-butyl alcohol.

Table 1. Some physical data for the new compounds. In order to facilitate comparison, the atoms in **3** and **6** are numbered as in **7**.

1, colorless crystals, m.p. = 85.0–85.5°C

3, m.p. = 79.5–80.5°C, 37% yield based on **1**. ^{1}H-NMR (100 MHz, $CDCl_3$): $\delta = 5.36$ (dddd, $J = 9.0$, 7.5, 4.5, 3.0 Hz, H-5); 6.05 (ddd, $J = 9.5$, 7.5, 6.0 Hz, H-3); 6.42 (d, $J = 9.5$ Hz, H-2); 8.26 (AA′BB′, 4 Aryl-H); 2.14–2.56 (m, 2H-6); 2.60–3.14 (m, 2H-4, 2H-7)

5, yellow crystals, m.p. = 107–108°C, 56% yield based on **3**.

6, colorless crystals, m.p. = 42–43°C (hexane/ether). ^{1}H-NMR (360 MHz, $CDCl_3$): $\delta = 2.20$ (bs, OH); 2.66 (dddd, $J(4a,4b) = 13.6$, $J(4a,5) = 8.7$, $J(4a,3) = 6.2$, $J(4a,6) = 1.3$ Hz, H-4a); 2.73 (dddd, $J(4a,4b) = 13.6$, $J(4b,3) = 7.8$, $J(4b,5) = 3.0$, $J(4b,2) = 1.4$ Hz, H-4b); 4.43 (dddd, $J(5,4a) = 8.7$, $J(5,6) = 3.2$, $J(5,4b) = 3.0$, $J(5,7) = 1.5$ Hz, H-5); 5.98 (ddd, $J(7,6) = 11.2$, $J(7,2) = 1.6$, $J(7,5) = 1.5$ Hz, H-7); 6.01 (ddd, $J(3,2) = 9.6$, $J(3,4b) = 7.8$, $J(3,4a) = 6.2$ Hz, H-3); 6.05 (ddd, $J(6,7) = 11.2$, $J(6,5) = 3.2$, $J(6,4a) = 1.3$ Hz, H-6); 6.24 (ddd, $J(2,3) = 9.6$, $J(2,7) = 1.6$, $J(2,4b) = 1.4$ Hz, H-2). IR (KBr): ν(OH) = 3175 cm^{-1}. MS (70 eV): M^+, m/z 128 (100%)

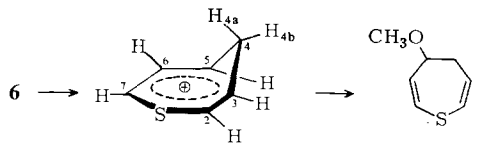
7, ^{1}H-NMR (100 MHz, $CD_2Cl_2 + SO_2 + HFSO_3$, −80°C, standard Me_4Si with $\delta_{CHDCl_2}(Me_4Si) = 5.30$): $\delta = 7.99$ (d, $J(2,3) = 7.5$ Hz, H-2); 6.32 (dt, $J(2,3) = J(3,4a) = J(3,4b) = 7.5$ Hz, H-3); 1.16 (m, H-4a); 4.44 (m, H-4b); 7.15 (dt, $J(5,6) = J(5,4a) = J(5,4b) = 7.9$ Hz, H-5); 7.99 (m, H-6); 10.04 (d, $J(7,6) = 6.1$ Hz, H-7). ^{13}C-NMR (22.5 MHz, $CD_2Cl_2 + SO_2 + HFSO_3$, −70°C, standard Me_4Si with $\delta_{CH_2Cl_2}(Me_4Si) = 53.8$): $\delta = 131.2$ (C-2 or C-6); 133.4 (C-2 or C-6); 129.7 (C-3); 33.76 (C-4); 150.5 (C-5); 178.9 (C-7)

The hydroxy group of **6** can be cleaved off as follows: 10 mg **6** in 0.2 mL CD_2Cl_2 was mixed with 0.2 mL SO_2, containing three drops of fluorosulfuric acid, in an NMR

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tube under nitrogen at −78 °C. This afforded a yellow solution containing a single cationic species, which, as shown by the ^{1}H-NMR spectrum (−80 °C), is the homothiopyrylium ion **7** (Table 1).

The ^{1}H-NMR spectrum of **6** contains two signals assigned to methylene protons at $\delta = 2.66$ and 2.73. In going from **6** to **7**, one signal shifts upfield ($\delta = 1.16$) and the



7 **8**

other downfield ($\delta = 4.44$); the chemical shift difference of these signals in **7** ($\Delta\delta = 3.28$ ppm) is even greater than that observed in the 2,7-di-*tert*-butylthiopyrylium ion[1]. This large value of $\Delta\delta$ is mainly caused by the homoaromatic ring current (H-4a lies above this ring whereas H-4b is situated in the deshielding zone)[7].

Delocalization of positive charge is indicated by the proton chemical shifts in **7**. The average chemical shift of the protons (except for H-4a,b) is $\delta = 7.9$ whereas that of the olefinic protons in **6** is $\delta = 6.07$. Although no valence bond structures of **7** can be written in which the positive charge is localized on either C_6 or C_2, the signals (coincidentally equivalent) of the protons attached to these carbons appear considerably downfield at $\delta = 7.99$. This demonstrates that C_2 and C_3, as well as C_5 and C_7, comprise part of a delocalized six-membered ring cation. The vicinal coupling constants are also informative. Thus, $J_{2,3}$, $J_{5,6}$, and $J_{6,7}$ in **7** are in the range of 6.1—7.9 Hz. In **6**, these are $J_{2,3} = 9.6$ and $J_{6,7} = 11.2$ Hz. This indicates again that the C-atoms at 2, 3, 5, 6, and 7 are part of a six-membered ring.

Retention of the seven-membered ring skeleton during the formation of **7** is confirmed by the fact that quenching of the solution of **7** with a mixture of methanol and $NaHCO_3$ at −78 °C gives 4-methoxy-4,5-dihydrothiepine **8** (colorless oil)[4].

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1, 95069-64-0; **2**, 95069-65-1; **3**, 95069-66-2; **4**, 95069-67-3; **5**, 95069-68-4; **6**, 95069-69-5; **7**, 95069-70-8; **8**, 95069-71-9.

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Pentamethyldiethylenetriamine(phenyl)lithium, a Monomeric Organolithium Compound**

By *Uwe Schümann, Jürgen Kopf*, and *Erwin Weiss**

Dedicated to Professor Günther Wilke on the occasion of his 60th birthday

Organolithium compounds normally occur as oligomers, with a preferred degree of association of 2, 4 or 6[1]. They rarely exist in a monomeric form, as, e.g., in the compounds **1**[2] or **2**[3] in which association is hindered by sterically bulky organic moieties. However, donor ligands can also decisively influence the structure, as is strikingly demonstrated, for example, by phenylethynyllithium. In this instance the species **3**[4] and **4**[5] have been characterized, where the complexing diamine molecules differ only in their chain length.

$[Ph_3CLi(tmeda)]$ — $[(Fluorenyl)Li\{N(C_2H_4)_3CH\}_2]$

1, tmeda = $Me_2N(CH_2)_2NMe_2$ — 2

$[PhC{\equiv}CLi(tmpda)]_2$ — $[(PhC{\equiv}CLi)_4(tmhda)_2]$

3 — 4

$Me_2N(CH_2)_nNMe_2$: tmpda: n = 3, tmhda: n = 6

Also remarkable in this respect is phenyllithium. In the crystalline state it exists in the dimeric form **5**[6]; when dissolved in ether it is dimeric[7] or tetrameric[8], and in the crystalline state with ether of crystallization it is present as the tetramer **6**[9]. A common feature of many structures of this kind is the fourfold coordination of lithium. On using the tridentate ligand pentamethyldiethylenetriamine (PMDTA) only one coordination site remains free for the binding of the organic moiety. Consequently, oligomerization is suppressed. A number of examples of this type have already been reported in the literature, e.g. **7**[10].

$[PhLi(tmeda)]_2$ — $[PhLi(OEt_2)]_4$

5 — 6

$[Li\{CH(SiMe_3)_2\}(pmdta)]$ — [PhLi(pmdta)]

7, pmdta = $[(CH_3)_2NCH_2CH_2]_2NCH_3$ — 8

An attempt to prepare a monomeric phenyllithium in an analogous way met with success. Addition of PMDTA to a suspension of phenyllithium in hexane/pentane mixtures led to formation of [PhLi(pmdta)] **8** (Fig. 1).

The Li atom is located only 2 pm above the plane of the benzene ring with the Li−C(1)−C(2) and Li−C(1)−C(6) angles being almost identical. It is thus strongly monohapto-bonded to an sp^2-hybridized C atom (bond length 213.5 pm). The Li−C distances in **5** and **6** of ca. 221 and 230 pm, respectively, are noticeably longer. This elongation is characteristic for bridge ligands.

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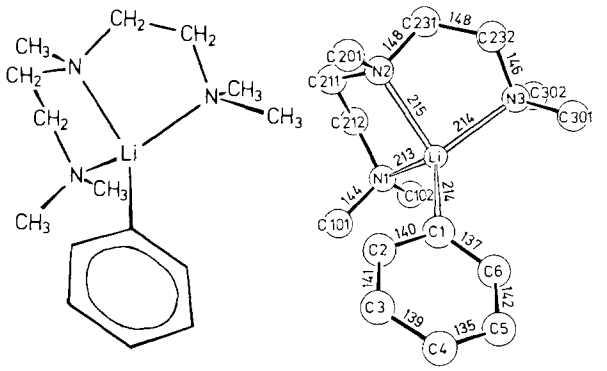


Fig. 1. Structure of **8** in the crystal. Left: line drawing; right: ORTEP diagram with bond lengths [pm]; $P2_1/n$, $a = 859.6(4)$, $b = 1583.2(10)$, $c = 1322.4(9)$ pm, $\beta = 92.72(5)°$, $\rho_{calc} = 0.9509$ g cm^{-3}, $Z = 4$; $Mo_{K\alpha}$ radiation, solution of structure by direct methods (SHELX), refinement to $R = 0.072$ (unweighted) with 746 reflections [$|F| > 4\sigma(F)$], measured to $\theta = 20°$, anisotropic temperature factors, H not determined, refined isotropically with calculated H positions. Important bond lengths ([pm], mean values): Li–C 213.5(16), C–C(phenyl) 138.9, Li–N 214.0(15); angles [°]: N1–Li–N2 87.1(6), N2–Li–N3 87.2(6), N1–Li–N3 115.4(7). Further details of the crystal structure investigation are available on request from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2, on quoting the depository number CSD 51118, the names of the authors, and the full citation of the journal.

The benzene ring is approximately planar; but the hexagon is distinctly distorted (angle at C1 113.1 instead of 120°, while those at C2 and C6 on the other hand, with values of 123.9 and 125.1°, are significantly enlarged). These deformations are likewise characteristic for metal-bound phenyl groups, e.g. in **5**, **6**, or $[Ph_2Mg(tmeda)]$[11].

Phenyllithium is so far the only organolithium system in which three different structures are formed, depending upon the nature of the ligands.

Experimental:

All operations were carried out under an inert gas using dry solvents. Freshly distilled PMDTA (0.83 g, 1 mL, 4.79 mmol), previously dried over potassium, was added dropwise with stirring to a suspension of PhLi (0.5 g, 5.95 mmol), prepared from *n*BuLi and iodobenzene, in 25 mL of a hexane/pentane mixture (1:1). The suspension first became clear then very cloudy again. The mixture was allowed to stand for a while. The supernate was then filtered off, and, after cooling to −30°C, furnished 0.25 g (20%) of **8**. An elemental analysis of the product was fully consistent with that expected for **8**. Crystals suitable for an X-ray structure analysis were obtained on slowly cooling a saturated solution of the product to 8°C followed by drying at 20°C in a stream of argon. The crystals are extremely sensitive and tend to deliquesce after their isolation if excess PMDTA is present.

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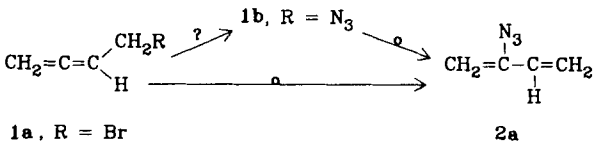
CAS Registry number:
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Synthesis and Reactions of 4-Azido-3-methyl-1,2-butadiene**

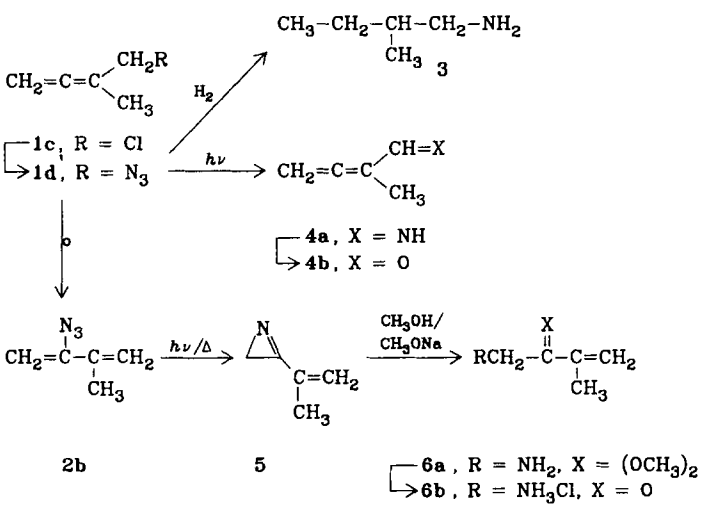
By *Klaus Banert**

Vinyl azides have recently attracted renewed interest, largely because of their manifold reactions[1]. The most common method of synthesis[2]—addition of haloazide to an alkene with subsequent elimination of hydrogen halide—gives only partially satisfactory results in the case of 1,3-butadienes[3,4]. Recently, a synthesis of 2-azido-1,3-butadiene **2a** from 4-bromo-1,2-butadiene **1a** involving an allyl rearrangement has been reported[5]. The postulated intermediate **1b** could not be isolated.



1a, R = Br **2a**

Independently thereof, our own investigations have shown that 4-chloro-3-methyl-1,2-butadiene **1c**[6] reacts with sodium azide in aqueous ethanolic solution quantitatively to give 2-azido-3-methyl-1,3-butadiene **2b** (Table 1)[7]. If, however, the reaction is prematurely terminated and work-up carried out rapidly and carefully, not only **2b** and unreacted **1c** but also the intermediate 4-azido-3-methyl-1,2-butadiene **1d** can be isolated (Table 1). Considerably more efficient is the preparation of **1d**[8] from tributylhexadecylphosphonium azide[9] and **1c**. Apparently the halides **1a** and **1c** do not react in an S_N2'-like fashion, but with direct substitution and subsequent rapid allyl rearrangement. The quantitative rearrangement **1d** → **2b** was monitored by ^{1}H-NMR analysis in chloroform between 20 and 60°C. The activation parameters of the 1st order reaction are: $\lg A = 10.54$, $E_a = 85.9$ kJ/mol, $\Delta H^{\neq}_{298} = 83.5$ kJ/mol, $\Delta S^{\neq}_{298} = -51.5$ J mol^{-1} K^{-1}. The reaction rate increases only slightly with increasing solvent polarity; relative reactivities at 41°C: [D$_{12}$]cyclohexane 1.00, $CDCl_3$ 2.73, 70 wt-% [D$_6$]acetone/D_2O 4.59. Similarly as in the rearrangement of simple allyl azides[10], the large negative



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[**] Reactions of Unsaturated Alkyl Azides, Part 1.

activation entropy and the minimal influence of solvent rule out an ionic mechanism. The reaction **1d** → **2b** could proceed via bicyclic triazolines[10] or be interpreted as a hetero-Cope rearrangement[11].

Table 1. Some physical data of the new compounds **1d**, **2b**, **4a**, **5**, **6a**, and **6b**.

1d: IR (CCl_4): ν = 2990, 2930, 2860, 2100, 1955, 1580, 1430, 1370, 1330, 1300, 1265, 1230, 985, 955, 910, 880, 855 cm^{-1}; ^{1}H-NMR (C_6D_6): δ = 1.43 (t, J = 3.2 Hz, 3H), 3.17 (t, br, 2H), 4.51 (tq, J = 2.3, 3.2 Hz, 2H); ^{13}C-NMR (C_6D_6): δ = 16.1 (q), 54.3 (t), 75.7 (t), 94.7 (s), 207.3 (s); GC-MS (70 eV): m/z 109 ($M^{\oplus}$, 0.4%), 81 ($M^{\oplus} - N_2$, 69), 66 ($M^{\oplus} - HN_3$, 6), 54 (6), 53 (13), 51 (6), 42 (12), 41 (100), 40 (13), 39 (42)

2b: IR (CCl_4): ν = 2990, 2960, 2940, 2180, 2120, 2080, 1580, 1460, 1440, 1390, 1330, 1300, 1265, 1140, 915, 845 cm^{-1}; ^{1}H-NMR (80 MHz, C_6D_6): δ = 1.59 (ddd, J = 1.45, 0.75, 0.25 Hz, 3H), 4.53 (dddq, J = 2.33, 1.69, 0.68, 0.25 Hz, *Z*-1-H), 4.71 (ddd, J = 2.33, 0.73, 0.71 Hz, *E*-1-H), 4.84 (dddq, J = 1.70, 1.69, 0.73, 1.45 Hz, *E*-4-H), 5.49 (dddq, J = 1.70, 0.71, 0.68, 0.75 Hz, *Z*-4-H); ^{13}C-NMR (100 MHz, C_6D_6): δ = 19.7 (q), 98.3 (t), 115.2 (t), 137.2 (s), 146.0 (s); GC-MS (70 eV): m/z 81 ($M^{\oplus} - N_2$, 73%), 66 ($M^{\oplus} - HN_3$, 7), 54 (7), 53 (16), 51 (7), 42 (12), 41 (100), 40 (20), 39 (53), 38 (7)

4a: ^{1}H-NMR ($CDCl_3$): δ = 1.92 (t, J = 2.9 Hz, ca. 3H), 5.03 (m, 2H), 8.02 (s, br, 1H)

5: IR (CCl_4): ν = 3100, 3050, 2980, 2960, 2920, 2900, 1730 (C=N), 1620, 1460, 1440, 1380, 1340, 1195, 990, 930, 630 cm^{-1}; ^{1}H-NMR (C_6D_6): δ = 1.43 (s, 2H), 1.81 (dd, J = 1.0 + 1.6 Hz, 3H), 5.36 (m, 2H); ^{13}C-NMR ($CDCl_3$): δ = 16.9 (q, J = 126 Hz), 20.6 (t, 180 Hz), 128.6 (t, 160 Hz), 132.2 (s), 166.9 (s); GC-MS (70 eV): m/z 81 ($M^{\oplus}$, 100%), 55 (17), 41 (95)

6a: IR (CCl_4): ν = 3400 br, 3100, 2960, 2840, 1450, 1185, 1135, 1090, 1055, 970, 920 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ = 1.20 (br, position concentration-dependent, ca. 2H, 1.70 (m, 3H), 2.75 (s, 2H), 3.17 (s, 6H), 5.19 (m, 1H), 5.30 (m, 1H); ^{13}C-NMR ($CDCl_3$): δ = 18.7 (q), 42.3 (t), 48.6 (q), 103.7 (s), 117.3 (t), 141.3 (s)

6b: White crystals, Fp = 142 °C (methanol/ethyl acetate); IR (KBr): ν = 3420 br, 2980 br, 1670, 1465, 1385, 1365, 1300, 1120, 1090, 1015, 985, 975, 920, 895 cm^{-1}; ^{1}H-NMR (D_2O): δ = 1.84 (dd, J = 1.5 + 0.9 Hz, 3H), 4.35 (s, 2H), 6.08 (m, 2H); ^{13}C-NMR (dioxane/D_2O 1:9): δ = 17.0, 45.2, 130.0, 142.0, 196.0

1d represents the first example of a compound in which an allene system and an azide group are connected via one carbon atom. The structure is confirmed, not only by the spectroscopic data (Table 1), but also by the hydrogenation to **3**. Photolysis of **1d** affords the imine **4a**, hydrolysis of which leads to the aldehyde **4b**[12, 13].

Thermolysis or photolysis of **2b** yields the azirine **5**[14]. This can be cleaved to give the amino acetal **6a** which makes the oxoammonium salt **6b** accessible[15]. The hydrogenation of the CC double bond to give 3-methyl-2-oxobutylammonium chloride[16] supports the constitution of **6b**. If the isolation of intermediates during the reaction sequence **1c** → **1d** → **2b** → **5** → **6a** → **6b** is dispensed with, the yields increase considerably[17].

The reactions **1d** → **4a** and **1d** → **2b** show that **1d** is a typical azide with allyl structure. In contrast, the useful azirine precursor **2b** can be regarded as an "internal"[1] vinyl azide.

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[7] **2b**: A solution of **1c** (3.9 g, 38 mmol) and sodium azide (5.0 g, 77 mmol) in ethanol (10 mL) and water (15 mL) was vigorously stirred at room temperature for 6 d in the absence of light. It was then poured into ice-water and extracted with ether (3×); the ethereal solution was then washed with water (3×), dried over $MgSO_4$, and the ether removed by distillation, leaving **2b** (4.1 g, 99%). Subsequent gas-chromatographic separation (PGC) furnished **2b** as a colorless light-sensitive liquid.
[8] **1d**: 0.22 g (2.1 mmol) **1c** was added dropwise at ca. 30 °C to a supercooled melt of tributylhexadecylphosphonium azide. After 25 min stirring at room temperature the mixture was cooled to −196 °C and recondensed. A mixture of **1d** + **2b** (82:18, 215 mg, 92%) was obtained as a colorless liquid; after PGC, the purity of **1d** was 97%.
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[15] Reaction of **5** with CH_3OH/CH_3ONa and work-up with water/ether afforded 2,2-dimethoxy-3-methyl-3-butenylamine **6a**.—Treatment of a solution of **6a** in CH_3OH/CH_3ONa with 2% hydrochloric acid gave 3-methyl-2-oxo-3-butenylammonium chloride **6b**.
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[17] When concentrated etheral solutions of **2b** (from **1c** → **2b**) are diluted with chloroform and photolyzed, **5** can be obtained in 83% yield (referred to **1c**). The direct photolysis of **2b** (16 h) in CH_3OH/CH_3ONa (ca. 2%) affords, after aqueous work-up, **6a** (96% yield) and, on treatment with dilute hydrochloric acid, **6b** (73% yield).

Bis[(*R*)-(+)-binap]rhodium(I) Perchlorate, a Highly Efficient Catalyst for the Asymmetric Isomerization of Allylamines

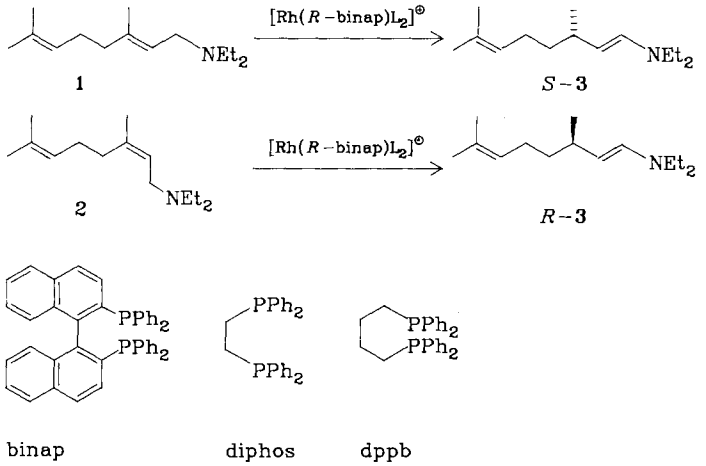
By *Kazuhide Tani**, *Tsuneaki Yamagata*, *Yoshitaka Tatsuno*, *Yuriko Yamagata*, *Ken-ichi Tomita*, *Susumu Akutagawa*, *Hidenori Kumobayashi*, and *Sei Otsuka**

Dedicated to Professor Günther Wilke on the occasion of his 60th birthday

Cationic Rh(I) complexes [Rh(bisphosphane)L_2]$^{\oplus}$ (L_2 = diene or two solvent molecules) catalyze the isomerization of allylamines to the corresponding (*E*)-enamines[1]. With optically pure (*R*)-binap as the bisphosphane ligand, we obtained extremely high optical yields (>99% *ee*) of the enamines *S*-**3** and *R*-**3**, derived from citronellal. Serendipitously we found that the bis(binap) complex **4** also proved to be an excellent catalyst for the asymmetric isomerization.

Consistent with the lack of catalytic activity of the bis(bisphosphane) complex **5**[1c], an addition in situ of an equimolar amount of binap to the catalyst [Rh(binap)(diene)]$^{\oplus}$ caused strong retardation of the reaction below 40 °C. Unexpectedly, however, the catalytic reaction

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proceeded above 80°C at a reasonable rate. We were able to confirm this catalytic activity with the isolated complex *R*-**4**.

$[Rh(binap)_2]ClO_4$ **4** $[Rh(diphos)_2]ClO_4$ **5**

$[Rh(cppb)_2]X$

6a, $X = ClO_4$; **6b**, $X = BF_4$

[Rh(*R*-binap)(norbornadiene)]ClO_4 **7**

The bis(binap) complex *R*-**4** is easily prepared in ca. 70% yield from [Rh(*R*-binap)(cod)]ClO_4 (cod = 1,5-cyclooctadiene) and an equimolar amount of *R*-binap in acetone at room temperature; *R*-**4** forms fairly air-stable, deep red crystals (m.p. = 206°C, decomp.)[2]. Table 1 shows examples for the catalytic activity of *R*-**4** and *S*-**4**. Surprisingly, the same stereoisomer **3** was obtained with mono- and bis(binap) complexes having the same chirality. Furthermore, the stereochemical correlation[1c] between the substrate geometry (*E* or *Z*), the ligand chirality (*R* or *S*), and the product configuration (*R* or *S*) was also the same. Since, in addition, the bis(binap) complex **4** can be used repeatedly without significant loss of catalytic activity, it can be regarded as a better catalyst than the mono(binap) complexes.

Table 1. Representative examples for the isomerization of **1** and **2** [a] to **3** with *R*-**4** and *S*-**4** as catalyst in THF. The selectivity for **3** was higher than 98%.

Substrate	Cat.	*T* [°C]	*t* [h]	[Substrate]/[Rh]	Yield [%]	**3** Conf.	*ee* [%] [b]
2	*R*-**4**	40	23	176	13	*R*	96
1	*S*-**4**	60	2	800	55	*R*	99
1	*S*-**4**	100	15	8000	≈100	*R*	98

[a] Purity of **1**: 99.7%; of **2**: 97.5%. [b] Determined on the basis of the maximum optical rotation of *R*-**3**: $[\alpha]_D^{21} = -77.6$ (*n*-hexane) [1c].

The catalytic activity of several cationic mono- and bis(bisphosphane)rhodium(I) complexes for the isomerization of **2** is compared in Table 2. The bis(diphos) complex **5** is totally inactive (up to 120°C). The bis(dppb) complex **6a** is catalytically active at temperatures as high as 120°C.

The high catalytic activity of **4** may be ascribed to the dissociation of one of the binap ligands, yielding the mono(binap) complex. This inference is supported by the strong compression of the phenyl substituents as revealed by the X-ray structure analysis (Fig. 1)[3]. In the unit cell two crystallographically different types of cation exist; one possesses C_2 symmetry and the other a very similar D_2 symmetry. In the C_2 cation, the Rh is almost rectangular planar coordinated. The angle between planes P1–Rh1–P2 and P1′–Rh1–P2′ is 6.2(2)°. The bis(dppb) complex **6a** has a tetragonal coordination geometry, which is distorted toward tetrahedral, and also possesses two seven-membered chelate rings[4]; the significant tetrahedral distortion was ascribed to the steric crowding. In the bis(binap) complex *R*-**4**, the steric crowding appears to be relieved mainly by elongation of the Rh–P distances (2.368(6)–2.388(6) Å), which are the longest in the known bisphosphane Rh(I) complexes (examples: 2.305(1)–2.321(1) Å in **7**[5]; 2.289(6)–2.313(6) Å in **5**[6]; 2.304(2)–2.361(2) Å in **6b**[4]). The acuter bite angles in the cation of C_2 symmetry (86.3(2)°) and in the cation of D_2 symmetry (86.9(2)°) compared to that in **7** (91.82(5)°) reflect the longer Rh–P distances.

Table 2. Isomerization of **2** with mono- and bis(bisphosphane)rhodium(I)-complex catalysts. A [D_8]tetrahydrofuran solution containing 1.0 mol/L **2** and 0.005 mol/L catalyst was heated in an NMR tube. Yield and selectivity for **3** (>96%) were determined by ^{1}H-NMR spectroscopy at 27°C.

Catalyst	*T* [°C]	*t* [h]	Yield [%]
[Rh(diphos)(cod)]ClO_4	40	23	17
[Rh(dppb)(cod)]ClO_4	90	4	78
[Rh(*R*-binap)(cod)]ClO_4	90	4	~100
$[Rh(diphos)_2]ClO_4$ **5**	90	4	0
	120	18	0
$[Rh(dppb)_2]ClO_4$ **6a**	90	4	0
	120	18	72
$[Rh(R\text{-binap})_2]ClO_4$ *R*-**4**	90	4	95
	120	18	~100

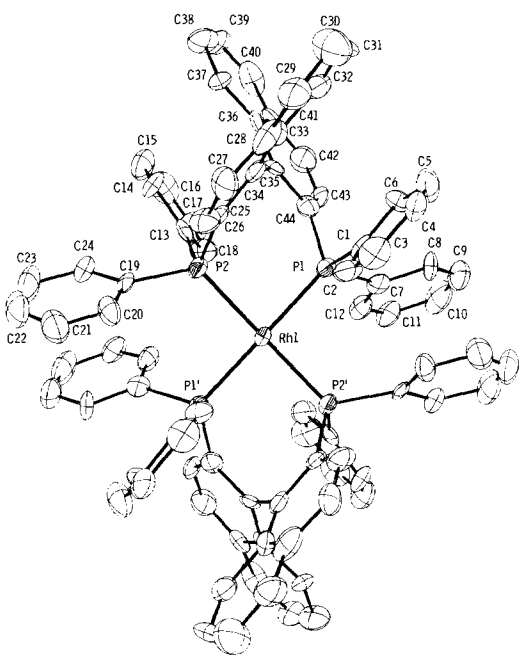


Fig. 1. ORTEP drawing of a cation (C_2 symmetry) of the complex *R*-**4** in the crystal (from CH_2Cl_2–Et_2O). Most important distances [Å] and angles [°]: Rh1–P1 = 2.368(6), Rh1–P2 = 2.388(6), P1–Rh1–P2 = 86.3(2), P2–Rh1–P2′ = 174.0(2), P1–Rh1–P2′ = 93.8(2), P1–Rh1–P1′ = 178.7(2), Rh1–P1–C1 = 114.5(6), Rh1–P1–C7 = 113.7(6), Rh1–P1–C44 = 120.8(6), Rh1–P2–C13 = 116.7(6), Rh1–P2–C19 = 121.2(6), Rh1–P2–C25 = 110.2(6). The angle between the least-squares planes through the two naphthyl rings in a binap ligand is 71.0(3)°. Vibration ellipsoids: 50% probability level.

Isotopic labeling studies on the mono(binap) complex-catalyzed isomerization of allylamines indicated an exclusive 1,3-hydrogen migration[1b], suggesting a mechanism involving a π-allylhydridorhodium(III) intermediate. The identical correlation between the stereochemistries of the product and the chirality of the ligand for mono- and bis(binap)Rh(I) complex-catalyzed isomerizations suggests involvement of very similar π-allyl intermediates. This requires the dissociation of one of the binap ligands in **4**. In the process, however, the conformation of the chelate ring is retained; *R*-binap has a λ-skew configuration[5]. In the exchange between the free and the coordinated binap, the conformation of the chelate ring does not change because the C_2 symmetry is retained tenaciously.

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CAS Registry numbers:
1, 40267-53-6; **2**, 40137-00-6; **3**, 62159-05-1; ***R*-4**, 95156-21-1; ***S*-4**, 95272-23-4; **5**, 47895-57-8; **6**, 70196-22-4; [Rh(diphos)(cod)], 47778-85-8; [Rh(dppb)(cod)], 75752-92-0; [Rh(binap)(cod)]ClO_4, 82864-73-1; ***R*-3**, 95273-03-3; [Rh(*R*-binap)(cod)]ClO_4, 82822-45-5; *R*-binap, 76189-55-4.

[1] a) K. Tani, T. Yamagata, S. Otsuka, S. Akutagawa, H. Kumobayashi, T. Taketomi, H. Takaya, A. Miyashita, R. Noyori, *J. Chem. Soc. Chem. Commun. 1982*, 600; b) K. Tani, T. Yamagata, S. Otsuka, S. Akutagawa, H. Kumobayashi, T. Taketomi, H. Takaya, A. Miyashita, R. Noyori in E. L. Eliel, S. Otsuka: *Asymmetric Reactions and Processes in Chemistry, ACS Symposium Series 185*, ACS, Washington D.C., 1982, p. 187; c) K. Tani, T. Yamagata, S. Akutagawa, H. Kumobayashi, T. Taketomi, H. Takaya, A. Miyashita, R. Noyori, S. Otsuka, *J. Am. Chem. Soc. 106* (1984) 5208.

[2] Analytically pure ***R*-4**·$2H_2O$ was obtained by recrystallization from acetone-ether. The water of crystallization probably comes from the acetone. ^{1}H-NMR (CD_2Cl_2): $\delta = 1.58$ (br. s, H_2O), 6.10–7.70 (m, arom.); $^{31}P\{^1H\}$-NMR ($(CD_3)_2CO$ ext. H_3PO_4, 27°C): $\delta = 24.48$ (d, $J(P-Rh) = 138.5$ Hz); the sharp doublet did not change appreciably between −80°C and 100°C: IR (CsI): $\nu = 3050$ (=CH), 1590 (C=C), 1090 (ClO_4), 815, 745, 700 cm^{-1} (arom.); correct elemental analysis.

[3] ***R*-4**·$\frac{1}{2}CH_2Cl_2$: crystal data: I222, $a = 23.556(14)$, $b = 24.965(13)$, $c = 19.113(13)$ Å, $V = 11240(10)$ Å^3, $Z = 6$, $\rho_{calcd.} = 1.32$ g cm^{-3}, $\rho_{obsd.} = 1.32(1)$ g cm^{-3} (at 16°C), $\mu(Mo_{K\alpha}) = 4.12$ cm^{-1}, $\lambda(Mo_{K\alpha}) = 0.71069$ Å (graphite monochromator), $F(000) = 4242$; 6276 measured reflections (Rigaku-Denki AFC diffractometer, 40 kV, 200 mA), $T = 21 \pm 2$°C, ω-2θ scan, $2.5° < \theta < 55°$, $0 \le h \le 30$, $0 \le k \le 32$, $0 \le l \le 24$; heavy atom method, $R = 0.087$, $R_w = 0.071$ ($w = 1.0/\sigma^2(F_0)$), for 3275 observed reflections ($|F_0| \ge 3\sigma(F_0)$) and 690 parameters, residual electron density (max) = +0.71 e/Å^3. Due to the existence of disorders, the exact positions of the CH_2Cl_2 molecules could not be found. All numerical calculations were carried out on an ACOS 900 computer at the Crystallographic Research Center, Institute for Protein Research, Osaka University. Further details of the crystal structure analysis are available on request from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2 (FRG), on quoting the depository number CSD 51181, the names of the authors, and the journal citation.

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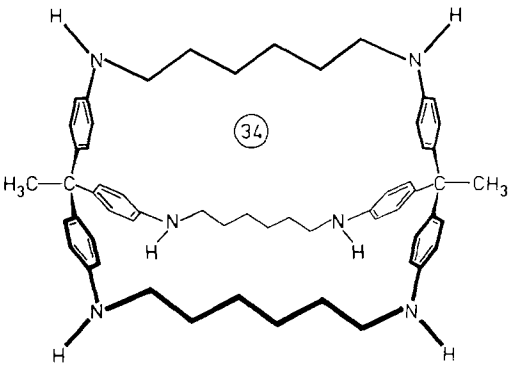
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"In-out"-Isomeric Large Cavities and Their Differing Guest Selectivity**

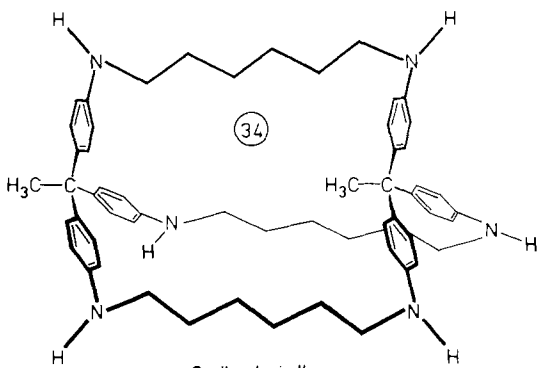
By *Joachim Franke* and *Fritz Vögtle**

Macro*bi*cyclic large cavities (number of ring members about 30) enclosed on several sides have been hardly known up to now[1]. The enclosure of guest molecules on "all sides" should increase the stability and selectivity of the complex due to the better screening of the hydrophobic niches.

We report here the synthesis and properties of two new spherical host compounds **1** and **2** of the speleand type[2], which, despite the same chemical constitution and therefore similar chemical properties, differ in the form and size of their cavities. The water solubility is achieved by protonation of the six amine nitrogens.



1, "out-out"



2, "out-in"

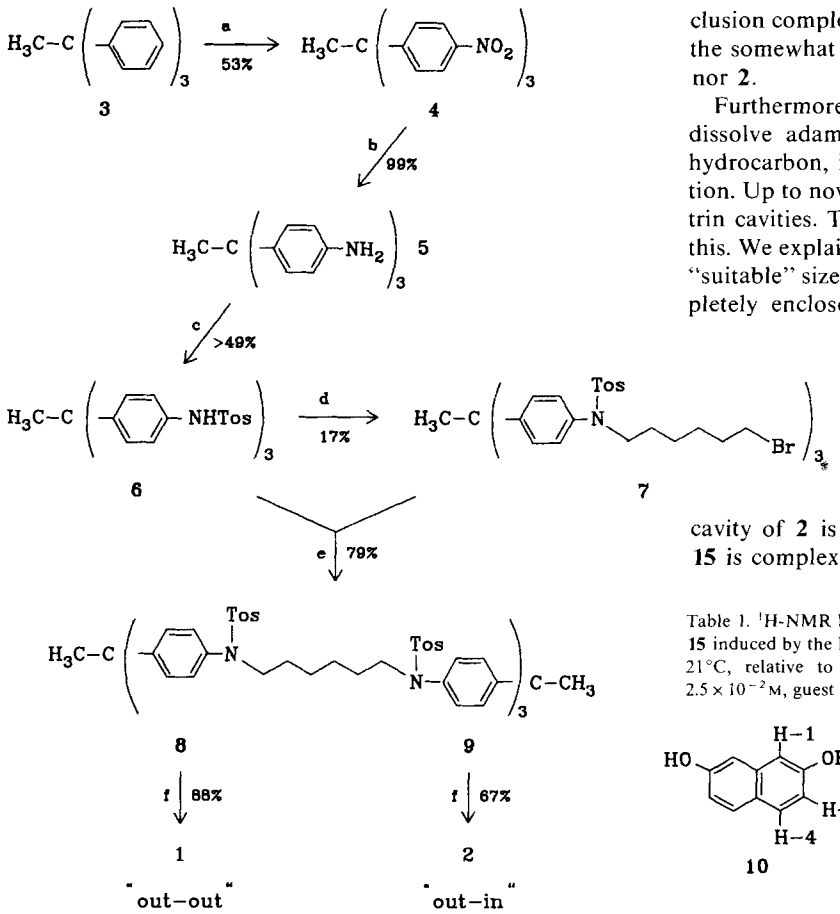
The triphenylethanes[3] **1** and **2**, linked by three chains, were obtained together starting from **3** via **4**—**9** (Scheme 1)[4].

Despite the fact that a loss in yield must be reckoned with during the chain-extension step **6**→**7** due to intramolecular ring closure, the decisive macro-cyclization of **6** with **7** to give **8** and **9** was achieved in the unexpectedly high total yield of 79%! By chromatography of the crude product, the two isomeric macrobicyclic compounds, whose structure we interpret as "out-out" (**8**) and "out-in" (**9**) isomers, could be obtained in a ratio of 1 : 1. The detosylation of **8** and **9** to give **1** and **2**, respectively, was achieved with HBr/phenol in different yields: 88% and 67%, respectively. The assigned structures[4] given for **8** and **9**, and for **1** and **2**, are supported by the ^{1}H- and ^{13}C-NMR spectra, as well as the differing complexation properties.

Table 1 gives some results for the complexation of potential guests with the isomeric host compounds **1** and **2** in deuterated aqueous solution. The corresponding chemical shifts in the ^{1}H-NMR spectrum (δ values) of protons of se-

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Scheme 1. Synthesis of the host compounds **1** and **2**. a) HNO_3, b) H_2/Pt; c) TosCl; d) $Br(CH_2)_6Br$; e) K_2CO_3, dimethylformamide (DMF), the yield given refers to **8** + **9**. Separation of **8** and **9** by chromatography on SiO_2; gradient elution with dichloromethane/petroleum ether 40–60°C/ethyl acetate 1:1:0.2 to 1:1:2; f) HBr, phenol.

lected guest compounds and their changes upon complexation ($\Delta\delta$ values) are also given.

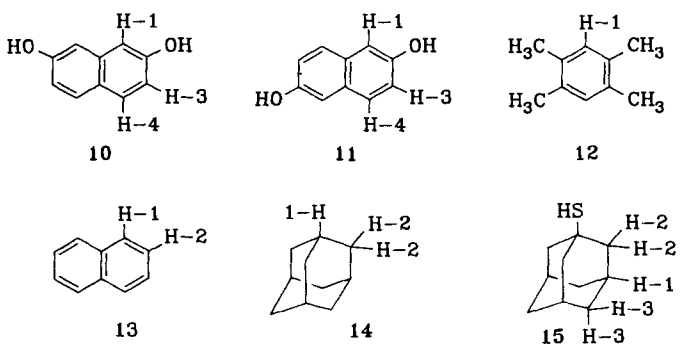
The $\Delta\delta$ values are composed of anisotropy effects between host and guest molecules as well as effects of the positive charges of the ammonium centers. The different shifts of the protons of a single guest molecule we attribute to its spatial orientation with respect to the anisotropy and charge centers of the host.

With **1**, we observe complete H/D exchange for the protons labeled H-1 of guests **10** and **11** within 24 h[6]. Neither **2** nor the comparison compound **16**[7] allow this exchange.

Complexes of synthetic host compounds with arenes lacking functional groups have been seldom up to now[1,5,7,8]. Surprisingly, both hosts **1** and **2** also form inclusion complexes with naphthalene **13** as guest. However, the somewhat larger durene **12** is complexed by neither **1** nor **2**.

Furthermore, with **1**, it was possible for the first time to dissolve adamantane **14**, a non-functionalized aliphatic hydrocarbon, in aqueous medium by selective complexation. Up to now, this has only been possible with cyclodextrin cavities. The isomeric host **2** is not capable of doing this. We explain this marked difference in selectivity by the "suitable" size and form of the cavity of **1**, which can completely enclose the spherically shaped adamantane; the cavity of **2** is too small. Accordingly, 1-adamantanethiol **15** is complexed only by **1** and not by **2**.

Table 1. ^{1}H-NMR high-field shifts of protons of the guest compounds **10**–**15** induced by the host compounds **1** and **2** (400 MHz, D_2O/DCl, pD = 1.2, 21°C, relative to δ = 4.8 for HDO as standard; concentrations: host 2.5×10^{-2} M, guest 1.25×10^{-2} M.



Guest	Guest proton	δ	Guest + **1** $\Delta\delta$ [ppm]	Guest + **2** $\Delta\delta$ [ppm]
10	H-1	7.03	−0.73	−0.5
	H-3	6.93	−0.43	−0.4
	H-4	7.69	−0.69	ca. −0.5 [a]
11	H-1	7.13	−0.4	−0.5
	H-3	7.06	−0.4	−0.43
	H-4	7.61	ca. −0.5 [a]	ca. −0.5 [a]
12	H-1	6.8	—	—
[b]	CH_3	2.13	—	—
13	H-1	7.82	−0.5	−0.5
[b]	H-2	7.45	−0.5	−0.5
14	H-1	1.9	−0.6	—
[b]	H-2	1.8	−0.5	—
15	H-1	2.05	−0.3	—
[b]	H-2	2.12	to	—
	H-3	1.72	−0.5 [c]	—

[a] The chemical shift could not be exactly determined since the signals overlap with those of the host. [b] The complexes were prepared by solid/liquid extraction in D_2O/DCl:CD_3OD (4:1) (cf. [5]). [c] The guest signals could not be exactly assigned.

The fluorescence spectroscopy measurements[9] gave a value of pK = 4.0 for the complex formation of **2** with 8-anilino-1-naphthalenesulfonic acid (ANS) as guest; this value is similar to that for the **16**·ANS complex (pK = 3.8[7]). In this case, too, the **1**·ANS complex (pK = 4.6) is noticably more stable.

Thus, it is shown for the first time that it is possible to obtain two isomeric, structurally very similar host com-

pounds (**1** and **2**), whose differing selectivity can only be attributed to the size of the cavity. Specific deuterations/tritiations appear to be possible in practice with these tailor-made host cavities; moreover, it should be possible to extract organic compounds selectively from a lipophilic phase into the aqueous phase[8].

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[4] Elemental analyses, ^{1}H-, ^{13}C-NMR, and mass spectra are in agreement with the structures given. M.p. [°C]: **1** >250, **2** >250 (both as hydrochlorides); **6** 154–156; **7** 118; **8** 176–178; **9** 137. **1**: ^{1}H-NMR ($CDCl_3$/TMS (int.), 90 MHz): δ = 1.2–1.8 (m, 24H, CH_2), 2.0 (s, 6H, CH_3-*out*), 2.9–3.2 (t, 12H, NCH_2), 3.4–3.6 (s, 6H, NH), 6.3–7.0 (AB system, 24H, aromat. H); $C_{58}H_{72}N_6$, calcd. 852.5818, found 852.5868.—**2**: ^{1}H-NMR ($CDCl_3$/TMS (int.), 90 MHz): δ = 0.89 (s, 3H, CH_3-*in*), 1.2–1.7 (m, 24H, CH_2), 2.0 (s, 3H, CH_3-*out*), 2.9–3.2 (t, 12H, NCH_2), 3.4–3.6 (s, 6H, NH), 6.4–7.0 (AB system, 24H, aromat. H); $C_{58}H_{72}N_6$, calcd. 852.5818, found 852.5842. Fragments with an intensity >2% are not observed (EI; 70 eV). **8**: ^{1}H-NMR (CD_2Cl_2/TMS (int.), 400 MHz): δ = 1.1–1.35 (m, 24H, CH_2), 2.2 (s, 6H, CH_3-*out*), 2.4 (s, 18H, Tosyl-CH_3), 3.3–3.5 (t, 12H, NCH_2), 6.85–6.95 (s, 24H, aromat. H), 7.25–7.45 (AB system, 24H, aromat. H); ^{13}C-NMR ($CDCl_3$/TMS (int.), 90 MHz): δ = 21.56 (tosyl-CH_3), 26.26, 27.12 (CH_2), 28.26 (CH_3-*out*), 50.1 (NCH_2), 127.66, 129.50, 135.17, 137.18, 143.45, 147.70 (aromat. C).—**9**: ^{1}H-NMR (CD_2Cl_2/TMS (int.), 400 MHz): δ = 0.85 (s, 3H, CH_3-*in*), 1.1–1.5 (m, 24H, CH_2), 2.15 (s, 3H, CH_3-*out*), 2.4 (s, 18H, tosyl-CH_3), 3.35–3.55 (m, 12H, NCH_2), 6.85–6.95 (s, 24H, aromat. H), 7.25–7.45 (AB system, 24H, aromat. H); ^{13}C-NMR ($CDCl_3$/TMS (int.), 90 MHz): δ = 21.56 (tosyl-CH_3), 25.15 (CH_3-*in*), 26.02, 28.29 (CH_2), 32.53 (CH_3-*out*), 50.27 (C–N), 127.66, 129.47, 137.24, 143.49, 147.92 (aromat. C). The ^{13}C-NMR absorptions of the quaternary carbon atoms could not be unequivocally identified owing to the limited solubility of the sample.

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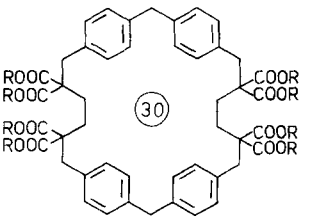
[8] F. Diederich, K. Dick, *Angew. Chem. 95* (1983) 730; *Angew. Chem. Int. Ed. Engl. 22* (1983) 715; *Angew. Chem. Suppl. 1983*, 957.

[9] Fluorescence spectrometer, Hitachi Model 204-A; excitation wavelength: λ = 375 nm, emission measured at 505 nm, medium 0.5 M KCl/0.015 M HCl buffer. Concentration of 1,8-ANS: $2 \cdot 10^{-6}$ M; the concentration of **1** and **2** was varied from 0 to 10^{-3} M.

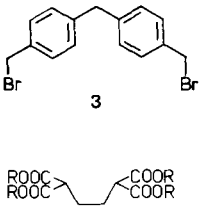
Large Carbocyclic Cavities for the Selective Inclusion of Organic Guest Molecules in Aqueous Solution**

By *Fritz Vögtle**, *Thomas Merz*, and *Herbert Wirtz*

The inclusion of guest molecules in aqueous solution has, up to now, only been achieved with certainty for heterocyclic host compounds[1,2]. Large carbon rings would have the advantage of being chemically more stable and, via reactions of the side chains, more variable. We report for the first time a water-soluble, *carbo*macrocyclic host compound **2** with a 30-membered cavity.



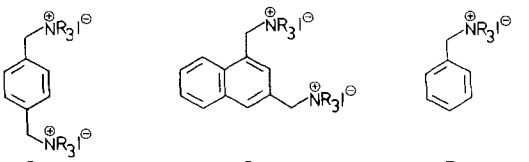
1: R=C_2H_5
2: R=H



4: R=C_2H_5

Reaction of the diphenylmethane derivative **3** with the disodium salt of the 2,2′-ethylenebis(malonic)tetraester **4** under high-dilution conditions affords the desired "dimeric" octaester **1** (m.p. = 190°C) in 1.8% yield[3,4]. Alkaline hydrolysis leads to the macrocyclic octacarboxylic acid **2** (m.p. >320°C), which, as desired, is soluble as the anion[1,2] in alkaline water.

Upon addition of guest compounds—which spatially fit the cavity—such as 1,4-xylylenebis(trimethylammonium)diiodide **5** to solutions of **2** in D_2O/NaOD, all the protons of the guest molecule experience characteristic, strong high-field shifts[5] (cf. Table 1).



5 **6** R=CH_3 **7**

Table 1. ^{1}H-NMR high-field shifts of protons of the guest compounds **5**–**7** due to the host compound **2** (400 MHz, D_2O/NaOD, pD = 14, 21°C; standard defined as HDO at δ = 4.8; concentrations: host 5×10^{-2} M, guest 2.5×10^{-2} M).

Guest	δ(Aryl-H)	$\delta(CH_2)$	$\delta(N-CH_3)$
5	7.75	4.6	3.16
6	7.95	4.93, 4.71	3.2
7	7.55	4.66	3.06
	$\Delta\delta$(Aryl-H)	$\Delta\delta(CH_2)$	$\Delta\delta(N-CH_3)$
5 + **2**	−0.5	−0.6	−0.3
6 + **2**	−0.13	−0.1	−0.25
7 + **2**	−0.16	−0.2	−0.18

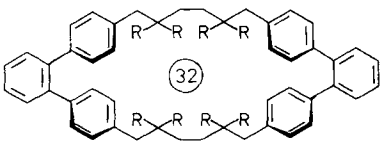
The inclusion of organic guest molecules, in this case, quaternary ammonium compounds, in the cavity of the new type of host **2** is thus demonstrated. In contrast to all receptor model substances so far described for which the inclusion of the guest in the host cavity is certain, **2** contains no donor centers in the ring skeleton; hydrogen-bond bridges between host and guest are largely ruled out. The shift of *all* protons of the guest **5** indicates the enclosure of all parts of **5** by the host compound on a time average. That the host **2** forms different inclusion complexes is shown qualitatively by the finding that the high-field shifts are very different, depending on the guest molecule. Whereas the naphthalene derivative **6**, apparently due to its large spatial demands, is not enclosed like **5**, the quaternary monoammonium salt **7** apparently fits somewhat better; however, the shifts are not so pronounced as those of **5**. In contrast, naphthalene could not be transferred into the aqueous phase with **2**.

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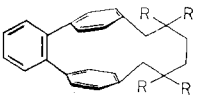
[**] This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.

Fluorescence spectroscopy measurements give a value of $pK = 2.35$ in water for the complex formation of **2** with 8-anilino-1-naphthalenesulfonic acid (ANS). This is higher than the value for the β-cyclodextrin·ANS complex in neutral aqueous solution.

The ease with which the new host system **2** can be structurally varied is shown by the successful synthesis in an analogous way of the 32-membered host compounds **8** and **9**, derived from *o*-terphenyl, as well as of the 16-membered "monomers" **10** and **11**, respectively[6].



8: R=CO_2Et
9: R=CO_2H



10: R=CO_2Et
11: R=CO_2H

Carbomacrocycles as host compounds have the advantage that their large ring cannot be hydrolytically cleaved. This is especially important if functional groups other than the carboxy group are attached to the large ring in order to effect host reactions that are analogous to enzymatic reactions[1,7]. Accordingly, compounds of the types **1** and **8** can be derivatized under harsh conditions, e.g., to give *uncharged*, but nonetheless water-soluble, host compounds with oligoamide, urea, or barbiturate side chains. Oligocarboxylic acids of the types **2** and **9** are, moreover, also (acid) complex formers for *cations*. If the carboxy groups point inward, a smaller cavity is formed, which is more suitable for metal cations.

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CAS Registry numbers:
1, 95046-03-0; **2**, 95046-04-1; **2**·**5**, 95046-09-6; **2**·**6**, 95046-10-9; **2**·**7**, 95046-12-1; **2**·ANS, 95046-13-2; **3**, 16980-01-1; **4**, 95046-02-9; **5**, 88791-91-7; **6**, 95046-05-2; **7**, 4525-46-6; **8**, 95069-30-0; **9**, 95069-31-1; **10**, 95046-06-3; **11**, 95046-07-4; ANS, 82-76-8.

[1] Cf. M. Dhaenens, L. Lacombe, J. M. Lehn, J.-P. Vigneron, *J. Chem. Soc. Chem. Commun. 1984*, 1097, and references cited therein.

[2] Recently, a carbocyclic host-hexasulfonic acid of the calixaren type was reported, but without evidence of a ^{1}H-NMR high-field shift: S. Shinkai, S. Mori, T. Tsubaki, T. Sone, O. Manabe, *Tetrahedron Lett. 25* (1984) 5315. Cf. also S. P. Adams, H. P. Whitlock, *J. Am. Chem. Soc. 104* (1982) 1602.

[3] In addition, a product that has not been exactly identified is formed, possibly an oligomer of higher molecular weight 2500–6500 (osmometric).

[4] Elemental analyses and spectra of the new compounds are in agreement with the structures given. **1**: ^{1}H-NMR ($CDCl_3$/TMS(int.), δ values, 90 MHz): 1.2 (t, OCH_2CH_3), 1.76 (s, CH_2CH_2), 3.1 (s, Aryl-CH_2), 3.86 (s, Aryl-CH_2-Aryl), 4.1 (q, OCH_2CH_3), 6.74 (d, Aryl-H), 7.0 (d, Aryl-H); *m/z* (M^+) = 1077 (EI).—**2**: ^{1}H-NMR (same conditions as those for **1**): 1.53 (s, CH_2CH_2), 2.8 (s, Aryl-CH_2), 3.9 (s, Aryl-CH_2-Aryl), 6.7 (d, Aryl-H), 7.1 (d, Aryl-H); *m/z* (M^+) = 852 (FAB).

[5] Measured with an external standard: Cf. J. Franke, F. Vögtle, *Angew. Chem. 97* (1985) 224; *Angew. Chem. Int. Ed. Engl. 24* (1985) 219.

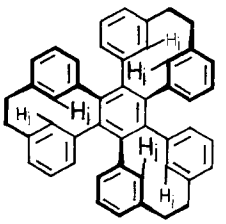
[6] **8** and **10**: viscous liquids, both $R_f = 0.35$ ($CHCl_3$).—**9**: complete purification is difficult.—**11**: m.p. 164–166°C (decomp., CO_2 evolution), 235–242°C.

[7] Cf. J. Winkler, E. Coutouli-Argyropoulos, R. Leppkes, R. Breslow, *J. Am. Chem. Soc. 105* (1983) 7198; Y. Murakami, *Top. Curr. Chem. 115* (1984) 107; I. Tabushi, K. Yamamura, *ibid. 113* (1984) 145, and references cited therein.

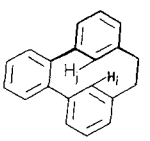
A Three-Blade Propeller Compound with Seven Bracketed Benzene Rings**

By *Wolfram Kissener* and *Fritz Vögtle**

In contrast to heptahelicene[2], which has a twofold symmetry axis, a three-blade propeller symmetry[3] is predicted for the hydrocarbon $C_{48}H_{36}$ **1**, derived from hexaphenylbenzene. This requires that the outer benzene rings be arranged in a stepwise displaced fashion, in analogy to the isolated "propeller blade" **2**[4], alternately above and below the plane of the central benzene ring[5].

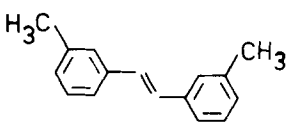


1 (all-*anti*)

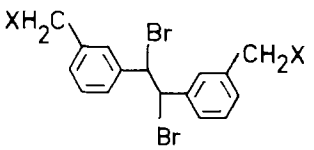


2 (*anti*)

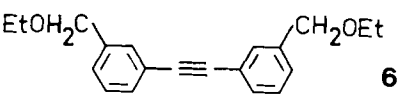
The synthesis of the helically chiral hydrocarbon **1**[6], for which, based on the results for **2**[4], high optical rotation could be expected, has now been achieved by us starting from stilbene **3** via the intermediates **4**—**8**[7]. The cyclization of the hexakis(bromomethyl) compound **8** with phenyllithium could only be achieved at unusually high temperatures (boiling tetrahydrofuran).



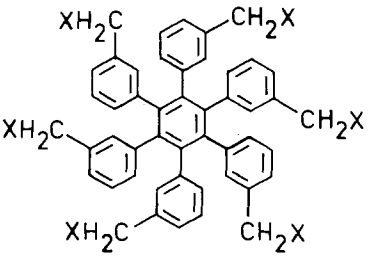
3



4: X = H
5: X = Br



6



7: X = OEt
8: X = Br

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[**] New helical molecules, Part 11. This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie. We also thank Dipl.-Chem. *A. Aigner* and *K.-H. Duchêne* for their cooperation.—Part 10: [1].

Via this reaction, we surprisingly directly obtained not only **1** but, in addition, two isomers, which we assign[8] to the unexpectedly stable *syn,syn,anti-* and *syn,anti,anti*-conformations **9** and **10**[7] (Fig. 1) on the basis of their ^{1}H-NMR spectra and their thermal rearrangement to give **1**.

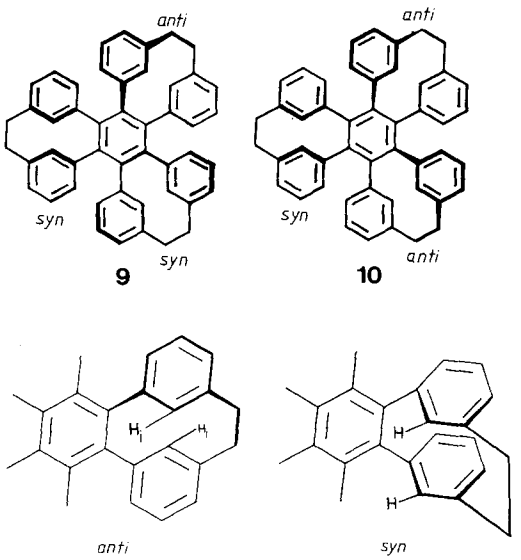


Fig. 1. *anti-* and *syn*-Arrangements (selected) in **1**, **9**, and **10**.

Upon heating of the products of the phenyllithium cyclization to 350 °C, a *syn*→*anti* rearrangement takes place, which is at first apparent by change in the crystal structure under the hot-stage microscope, but also in the completely changed ^{1}H-NMR spectrum (Fig. 2). Whereas the *syn* conformers **9** and **10** exhibit arene signals at $\delta = 5.15$, 5.22, and 5.45 as well as CH_2 signals centered at $\delta = 2.1$ and 3.2, the ^{1}H-NMR spectrum of **1** proves its structure on the basis of the strong high-field shifts of the inner protons [$\delta(H_i) = 5.4$]. The inner protons of the comparison compound **2** absorb at the same field strength ($\delta = 5.44$).

Racemic **1** (all-*anti*) is almost colorless; above 380 °C, it turns brown[9]. A base-line separation of the racemic mixture of **1** was achieved by HPLC on (+)-poly(triphenylmethylmethacrylate) [(+)-PTrMA][10]. As expected, the optical rotations are high: $M^{22}_{436} = +5235$[9].

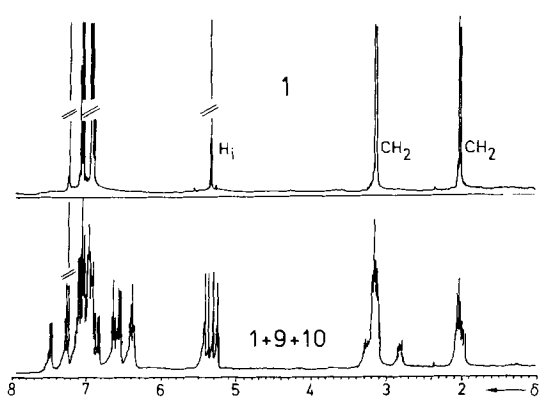


Fig. 2. ^{1}H-NMR spectra of the synthetically obtained mixture of **9**, **10**, and **1** (below) and of pure **1** (above): 400 MHz, in $CDCl_3$.

As expected, the optical stability of the new molecular propeller **1**, which is important for practical applications[11], is considerable; it is even higher than that of the helicenes. **1** even sustains heating at 310 °C for several minutes—conditions that lead to the racemization of the helicenes as well as of **2**. This is plausible since the inversion of a phenylene group in the *anti*-position is coupled with that of each of the other five, in contrast to the independent ring inversion in **2**.

By analogous synthetic strategy, other helices, with high optical rotation and stability, might be accessible[12]. The dehydrogenation product of **1**, a diphenanthroovalene, is also of interest due to its polycyclic aromatic structure.

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CAS Registry numbers:
(±)-**1**, 95216-91-4; (+)-**1**, 95340-76-4; (−)-**1**, 95340-77-5; **3**, 35286-92-1; **4**, 74844-03-4; **5**, 95216-92-5; **6**, 95216-93-6; **7**, 95216-94-7; **8**, 95216-95-8; (±)-**9**, 95340-78-6; (±)-**10**, 95342-08-8.

[1] A. Aigner, F. Vögtle, S. Franken, H. Puff, *Chem. Ber. 118* (1985), in press.
[2] Review: W. H. Laarhoven, W. J. C. Prinson, *Top. Curr. Chem. 125* (1984) 63.
[3] References: K. Mislow, J. Siegel, *J. Am. Chem. Soc. 106* (1984) 3319; K. Meurer, F. Vögtle, *Top. Curr. Chem.* (1985), in press.
[4] E. Hammerschmidt, F. Vögtle, *Chem. Ber. 113* (1980) 1125; M. Wittek, F. Vögtle, G. Stühler, A. Mannschreck, B. M. Lang, H. Irngartinger, *ibid. 116* (1983) 207.
[5] This may be compared with the *achiral para*-bridged "trifoliaphane": M. Psioz, H. Hopf, *Angew. Chem. 94* (1982) 639; *Angew. Chem. Int. Ed. Engl. 21* (1982) 623.
[6] Name according to IUPAC nomenclature:
Decacyclo[37.3.1.1^{4,8}.1^{11,15}.1^{18,22}.1^{25,29}.1^{32,36}.0^{2,31}.0^{3,16}.0^{17,30}]octatetraconta-1(42),2,4(48),5,7,11(47),12,14,16,18(46),19,21,25(45),26,28,30,32(44),33,35,39(43),40-henicosaene.
[7] M.p. [°C]: **5** 206; **6** 64; **7** liquid, R_f value = 0.39 ($CHCl_3$/acetone 9 : 1); **8** 266; **9** rearrangement to **1** above ca. 300; **10** rearrangement to **1** above ca. 300.
[8] Examination of molecular models plausibly explains the lack of formation of the all-*syn* conformer, in which a sterically less-favorable arrangement of the six peripheral benzene rings should be present.
[9] Elemental analyses and spectra of the new compounds are in agreement with the structures given. The weighing of small amounts of **1** poses some difficulties owing to its strong electrical charge. The optical rotation of the (−)-enantiomer is of the same order of magnitude as that of the (+)-enantiomer.
[10] We thank Prof. Dr. *Y. Okamoto* for column material. See also: Y. Okamoto, K. Suzuki, K. Ohta, K. Hatada, H. Yuki, *J. Am. Chem. Soc. 101* (1979) 4763; H. Yuki, Y. Okamoto, I. Okamoto, *ibid. 102* (1980) 6356.
[11] Cf. G. Solladié, R. G. Zimmermann, *Angew. Chem. 96* (1984) 335; *Angew. Chem. Int. Ed. Engl. 23* (1984) 348.
[12] Cf. a) F. Vögtle, M. Palmer, E. Fritz, K. Meurer, U. Lehmann, A. Mannschreck, F. Kastner, U. Huber-Patz, H. Puff, E. Friedrichs, *Chem. Ber. 116* (1983) 3112; b) M. Wittek, F. Vögtle, *ibid. 115* (1982) 1363.

"Stereochemical Activity" of a Lone Pair of Electrons on Low Valent Elements of the 4th Main Group: $(GeN\mathit{t}Bu)_4 \cdot 2\,AlCl_3$ and $(SnN\mathit{t}Bu)_4 \cdot 2\,AlCl_3$**

By *Michael Veith** and *Walter Frank*

Dedicated to Professor Gerhard Fritz on the occasion of his 65th birthday

The "stereochemical activity" of a lone pair of electrons on heavy main group elements has often been discussed

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[**] Cyclic Diazastannylenes, Part 21. This work was supported by the Fonds der Chemischen Industrie.—Part 20: M. Veith, W. Frank, *Angew. Chem. 96* (1984) 163; *Angew. Chem. Int. Ed. Engl. 23* (1984) 158.

with resort to bond theory and structural and chemical aspects for evidence of the existence or non-existence of such an activity. In the case of molecular compounds of divalent elements of the fourth main group (especially of Ge^{II} and Sn^{II}), primarily the existence of transition-metal complexes of the type X_nM-ElY_2[2] or $[X_nM-ElY_3]^{\ominus}$[2] (El = Ge, Sn) has been taken as supporting evidence for these elements being able to function as bases by virtue of the lone pair of electrons; however, the particular electronic structure of the transition metal was ignored (back-bonding etc., cf. also carbene complexes[3]). Even though a whole series of acid-base adducts such as $(Cp)_2Sn \cdot AlX_3$[2] (Cp = cyclopentadienyl, X = halogen) and $X_2Sn \cdot BF_3$[2] have been reported, neither the exact structures are known, nor is the formulation of the compounds as adducts confirmed. According to most recent structure investigations even the species $(\eta^5\text{-}C_5H_5)_2Sn-BF_3$ designated as adduct must be described as $[(BF_4)^{\ominus}\{(\mu\text{-}\eta^5\text{-}C_5H_5)_2Sn(\mu\text{-}\eta^5\text{-}C_5H_5)\}^{\oplus} \cdot thf]_n$[4]. By reaction of the cubane-like compounds $(GeNtBu)_4$[5] and $(SnNtBu)_4$[5] with aluminum trichloride we have now succeeded in preparing adducts which contain Ge–Al and Sn–Al bonds, respectively. By varying the molar ratio of the reaction partners, we have tried to prepare the adducts $(t\text{BuNEl})_4 \cdot (AlCl_3)_x$ with x = 1–4; however, on crystallization only those adducts with x = 2 could be isolated.

$$(t\text{BuNEl})_4 + Al_2Cl_6 \xrightarrow[\text{toluene}]{\Delta} (t\text{Bu}-\text{NEl})_4 \cdot 2\,AlCl_3$$
1, El = Ge; **2**, El = Sn

The ^{1}H-NMR spectra of the reaction solutions surprisingly contain (see molecular structure in Fig. 1) only one singlet, whose chemical shift depends upon the ratio of the reaction partners (when x = 2, **1**: $\delta = 1.30$ (s); **2**: $\delta = 1.32$ (s), 60 MHz, 28 °C, toluene)[6]. This finding could be explained in terms of the presence of various adducts and a rapid exchange of the $AlCl_3$ groups in solution. An X-ray structure analysis on single crystals of **2** confirmed the adduct structure. **1** and **2** are relatively unstable; they decompose into the starting components, slowly in solution and rapidly under reduced pressure (in the mass spectrometer).

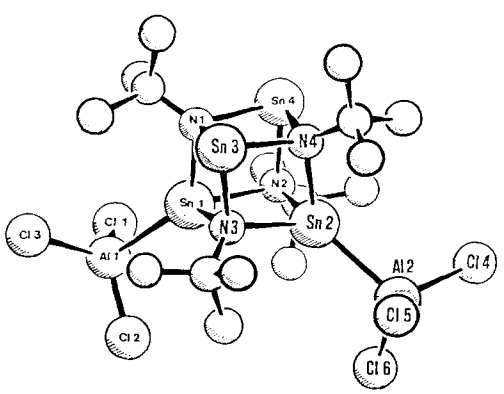


Fig. 1. Structure of **2** in the crystal. The unnamed atoms are carbon atoms; the hydrogen atoms of the methyl groups are not shown. The Sn_4N_4 skeleton is retained on adduct formation, the point symmetry of **2** is almost C_{2v} (mm2). Cell dimensions: $a = 1032.5(5)$, $b = 2311.2(9)$, $c = 1981.4(8)$ pm, $\beta = 124.3(1)°$. Space group: $P2_1/c$; $Z = 4$. Four-circle diffractometer, $R = 0.074$ with a reflection-parameter ratio of 14.07 : 1. Some selected (averaged) bond lengths: Sn–Al 278(1), Al–Cl 212.4(8), Sn–N 219(2), N–C 150(1) pm. Further details of the crystal structure investigation are available on request from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2, on quoting the depository number CSD 51183, the names of the authors, and the full citation of the journal.

The structure analysis of **2** (Fig. 1) proves for the first time that low-valency elements such as Sn^{II} can function as donors in Lewis acid-base adducts. The Sn–Al bond length corresponds exactly to that expected from the atomic radii[7]; the aluminum atoms coordinate in a distorted tetrahedral fashion, with the Cl–Al–Cl angle of 113.9° (mean) lying in the range typical for $AlCl_3$ adducts[8]. On comparing the structure of **2** with the structure of the uncoordinated $(SnNtBu)_4$[9] the following differences emerge: a) the distance between the fourfold coordinated tin atoms in **2** is reduced (Sn1 ··· Sn2 = 323.6(2) pm, in $(SnNtBu)_4$: 333 pm[9]), while the other intramolecular distances all remain, within the standard deviations, the same. b) As a direct consequence of this closing-up, the N–Sn–N angles in the four membered ring N2–Sn1–N3–Sn2 (84° in **2** compared to 80° in $(SnNtBu)_4$) are widened and the Sn–N–Sn angles compressed. A very superficial interpretation of this effect could lead to the conclusion that the distance between the respective tin atoms becomes smaller by withdrawal of the electron density of the lone electron pairs. The adducts **1** and **2** support the hypothesis that the $(t\text{BuNEl})_4$ molecules (El = Ge, Sn) may better be described as cage molecules with oriented bonding[9]. But it is still unclear why only the adducts with two $AlCl_3$ moieties crystallize and not also those with another Al : Sn ratio.

Experimental:

Newly sublimed aluminum trichloride (0.152 g, 1.14 mmol) was treated with a solution of $(t\text{BuNGe})_4$[5] or $(t\text{BuNSn})_4$[5] (0.58 mmol) in toluene (30 mL) in the strict absence of moisture. On heating the mixture to boiling the $AlCl_3$ dissolved. The resulting solution was concentrated by evaporation and allowed to stand. After a few hours, rhombus-shaped crystals separated out. Yields: **1**, 0.36 g (75.6%); **2**, 0.38 g (65%). The crystals gave correct elemental analyses.

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CAS Registry numbers:
1, 95156-17-5; **2**, 95156-18-6; (*t*-BuNGe)$_4$, 84805-53-8; (*t*-BuNSn)$_4$, 95156-19-7; Al, 7429-90-5; Sn, 7440-31-5.

[1] J. D. Donaldson, *Prog. Inorg. Chem. 24* (1967) 251.
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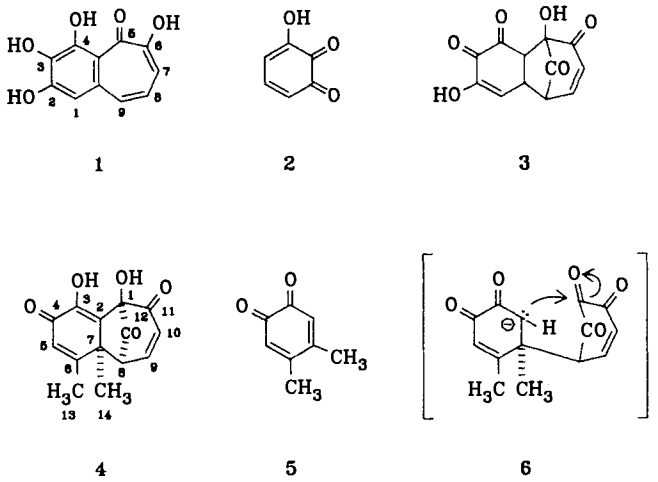
Mechanism of Purpurogallin Formation: An Adduct from 3-Hydroxy-*o*-benzoquinone and 4,5-Dimethyl-*o*-benzoquinone

By *Walter Dürckheimer** and *Erich F. Paulus*

Dedicated to Professor Rolf Sammet on the occasion of his 65th birthday

Purpurogallin **1**, found in nature as a glycoside, is formed upon oxidation of pyrogallol in water. The mechanism of this reaction is still largely speculative. *Salfeld*[1] and *Horner* et al.[2] postulated an intermediate **3** formed

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1 2 3

4 5 6

from two molecules of 3-hydroxy-*o*-benzoquinone **2**; however, **3** has not yet been isolated. Previous studies[3] showed that pyrogallol forms 3-hydroxy-*o*-benzoquinone **2** upon oxidation with a variety of oxidizing agents in water; **2** quickly reacts in situ with itself or with an *o*-quinone, containing at least one unsubstituted double bond, to form dihydroxybenzotropolones of the purpurogallin type[2].

We have now been able to synthesize the adduct **4** from **2** and 4,5-dimethyl-*o*-benzoquinone **5**. **4** exhibits extensive structural analogy to the postulated intermediate **3** and therefore supports the previous conceptions regarding the mechanism of formation of purpurogallin[4]. The structure of **4** was determined on the basis of its spectra[5] and by an X-ray crystal structure analysis (Fig. 1). The relatively small standard deviation of the bond lengths reflects a high quality X-ray structure analysis and allows one to conclude that the bond C07–C08 (1.568(2) Å) is especially labile and that its cleavage could lead to further reactions.

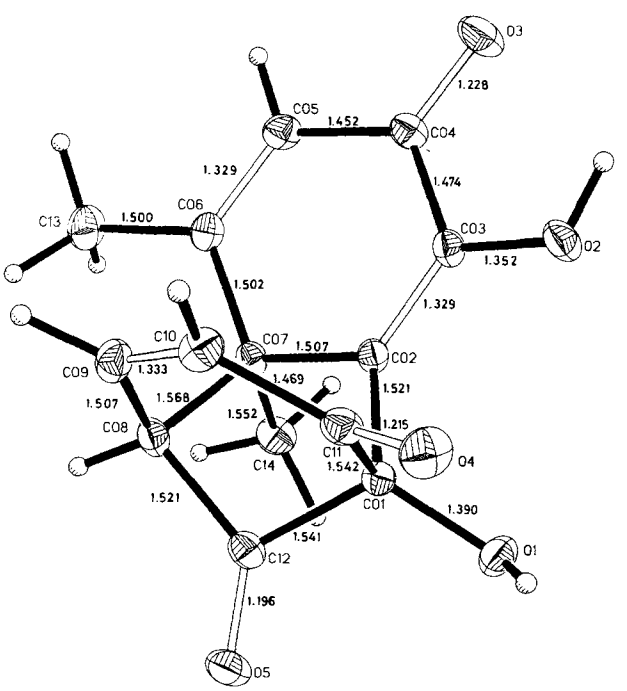


Fig. 1. Crystal structure of **4** with thermal vibration ellipsoids [6]. Bond lengths in Å.

It is assumed that the formation of this unusual carbonyl-bridged seven-membered ring system takes place in several steps. First, pyrogallol is dehydrogenated by **5** to give the highly reactive **2**, which is a vinylogous carboxylic acid. **5** and **2** have similar redox potentials in water. In the next step, the anion of **2** reacts with **5** in a Michael-type addition to give intermediate **6**, which cyclizes via nucleophilic attack of the carbanion on the central carbonyl group of the 1,2,3-tricarbonyl system. This carbonyl group is the most electrophilic due to the inductive effect of the neighboring carbonyl groups.

Procedure:

1,3-Dihydroxy-6,7-dimethyltricyclo[6.3.1.$0^{2,7}$]dodeca-2,5,9-triene-4,11,12-trione **4**: 2.7 g (0.02 mol) **5** is suspended in 20 mL anhydrous dioxane and a solution of 1.3 g (0.01 mol) pyrogallol in 10 mL dioxane is slowly added dropwise while shaking. **5** quickly dissolves, and, after the solution has stood for a short time at room temperature, 2.4 g (92%) **4** precipitates as pale yellow crystals. These are suctioned off and washed with a small amount of dioxane. Recrystallization from ethyl acetate gives 2.1 g (81%) **4**, with a point of decomposition of 165 °C. With iron(III) chloride, **4** gives a strong enol reaction. A colorless diacetate, which has a point of decomposition of 214–216 °C, is formed with acetic anhydride.

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2, 15258-70-5; **4**, 95070-14-7; **5**, 4370-50-7; pyrogallol, 87-66-1; dioxane, 123-91-1; oxygen, 7782-44-7.

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[5] **4**, IR (KBr): ν = 1780 (C12=O), 1690 (C11=O), 1650 cm (C4=O); UV (CH_3CN): λ = 215 ($\log\varepsilon$ = 4.10), 254 (3.89), 302 (3.28), 344 nm (3.15); ^{1}H-NMR (Me_2SO, Me_4Si): δ = 1.42 (s, 3 H-14), 2.12 (d, 3 H-13), 3.7 (d, H-8), 6.08 (d, H-5), 6.22 (d, H-10), 6.62 (s, OH-1), 7.42, 7.45 (dd, H-9), 9.15 (OH-3).
[6] Program system: G. M. Sheldrick: *SHELXTL, an Integrated System for Solving, Refining, and Displaying Crystal Structures from Diffraction Data*, Universität Göttingen 1983. a = 7.106(1), b = 11.082(1), c = 14.217(1) Å, β = 92.49(1)°; $P2_1/n$; Z = 4; $\rho_{calc.}$ = 1.417 g/cm^3; $\rho_{obs.}$ = 1.44 g/cm^3; R3-Diffractometer (Nicolet): 2ϑ/ϑ-Scan; $Mo_{K\alpha}$; 2724 [$F > \sigma(F)$] from 3123 independent reflections (ϑ_{max} = 28°); R_1 = 0.046; R_2 = 0.033 [$w = 1/\sigma^2(F)$]; standard deviation of the CC bond lengths: 0.002 Å. Further details of the crystal structure elucidation can be obtained from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen by quoting the number CSD 51240, the names of the authors, and the journal citation.

Cleavage of Tris(cyclopentadienyl)lanthanide Complexes with Alkyllithium Compounds—a New Route to Alkylbis(cyclopentadienyl)lanthanides**

By *Herbert Schumann** and *Gerald Jeske*

Alkylbis(cyclopentadienyl)lanthanide complexes are accessible by reaction of bis(cyclopentadienyl)lanthanide

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[**] Organometallic compounds of the lanthanides, Part 26. This work was supported by the Fonds der Chemischen Industrie and by special funds of the TU Berlin.—Part 25: I. Albrecht, E. Hahn, J. Pickardt, H. Schumann, *Inorg. Chim. Acta*, in press.

halides with Grignard reagents or alkyllithium[1]. However, this method is limited to the synthesis of such compounds containing the lanthanides samarium to lutetium. It has not yet been possible to prepare bis(cyclopentadienyl)lanthanide halides of lanthanum, cerium, and praseodymium[2,3]. Proton acids, such as 1-alkyne[4], hydrogen cyanide[5], or formic acid[2], react with tris(cyclopentadienyl)neodymium to form the bis(cyclopentadienyl)neodymium derivatives $[(C_5H_5)_2NdX]$ ($X = C{\equiv}CR$, CN, O_2CH); these do not afford the possibility, however, of synthesizing bis(cyclopentadienyl)neodymium hydride, which has promise as a hydrogenation catalyst[6].

We have now found that, even below room temperature, tris(cyclopentadienyl)lanthanides react with *sec*-butyl- and *tert*-butyllithium to form butylbis(cyclopentadienyl)lanthanide complexes **1** and **2** along with cyclopentadienyllithium[7]. **1a** and **1b** already decompose at $-30\,^{\circ}C$ and $0\,^{\circ}C$, respectively, to form butene and, respectively, bis(cyclopentadienyl)neodymium hydride and bis(cyclopentadienyl)lutetium hydride, **3a** and **3b**[8].

$$[(C_5H_5)_3Ln(thf)] + LiR \xrightarrow[-78\,^{\circ}C]{THF} [(C_5H_5)_2Ln{-}R(thf)] + LiC_5H_5$$

1a, Ln = Nd, R = *sec*-C_4H_9
1b, Ln = Lu, R = *sec*-C_4H_9
2a, Ln = Nd, R = *tert*-C_4H_9
2b, Ln = Lu, R = *tert*-C_4H_9

$$2\,\mathbf{1a,1b} \xrightarrow{THF} [(C_5H_5)_2LnH(thf)]_2 + 2\,C_4H_8$$

3a, Ln = Nd,
3b, Ln = Lu

THF: tetrahydrofuran

2a and **2b** react with hydrogen in toluene at room temperature, resulting in cleavage of *iso*-butane and formation of **3a** and **3b**, respectively, the latter of which is also obtainable via other routes[9,10]. **3a**[11], which precipitates in 82% yield in the form of blue needles, is a superb hydrogenation catalyst for alkynes[6].

$$2\,\mathbf{2a,2b} \xrightarrow[1\,atm.]{H_2} \mathbf{3a,3b} + 2\,iso\text{-}C_4H_{10}$$

Tris(cyclopentadienyl)neodymium does not react with $LiCH_3$, Li–*n*-C_4H_9[12], $LiCH_2SiMe_3$, and $LiCH(SiMe_3)_2$ to form alkylbis(cyclopentadienyl)neodymium complexes. Tris(cyclopentadienyl)praseodymium reacts with *n*-butyllithium in THF to form $[(C_5H_5)_3Pr{-}C_4H_9]^-$[13]; the replacement of the second cyclopentadienyl ligand by excess *tert*-butyllithium has not yet been achieved.

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CAS Registry numbers:
1a, 95274-92-3; **1b**, 95274-93-4; **2a**, 95274-94-5; **2b**, 76207-08-4; **3a**, 95251-28-8; **3b**, 80680-04-2; $[(C_5H_5)_3Nd(thf)]$, 84270-65-5; $[(C_5H_5)_3Lu(thf)]$, 91986-28-6; Li(*sec*-C_4H_9), 598-30-1; Li(*tert*-C_4H_9), 594-19-4.

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[5] B. Kanellakopulos, E. Dornberger, H. Billich, *J. Organomet. Chem. 76* (1974) C42.
[6] G. Jeske, H. Lauke, T. J. Marks, H. Mauermann, H. Schumann, unpublished.
[7] 2.2 g (5.3 mmol) $[(C_5H_5)_3Nd(thf)]$ is suspended in 50 mL THF at $-78\,^{\circ}C$ and treated with 3.6 mL of a 1.5 M solution of *tert*-butyllithium in hexane. The reaction mixture is allowed to warm up to room temperature over the course of 6 h and then stirred for 6 h. This solution is concentrated to 10 mL and treated with 70 mL ether. The undissolved LiC_5H_5 is filtered off and the solution cooled to $-30\,^{\circ}C$; 1.6 g (74%) **2a** crystallizes as green needles; m.p. = 42 °C (decomp.). Characterized by complete elemental analysis. ^{1}H-NMR (C_4D_8O, 25 °C): $\delta(CH_3) = 8.84$ (s, 9H), $\delta(C_5H_5) = -2.76$ (s, 10H). IR (KBr): 3092 m, 2980 s, 2930 s, 2900 s, 2870 s, 2740 vs, 2720 vs, 2660 s, 1450 m, 1385 m, 1370 w, 1345 w, 1295 w, 1180 w, 1152 w, 1120 w, 1090 m, 1040 s, 1010 s, 915 m, 890 s, 760 vs, 667 w, 470 w, 400 w.
[8] For **3b**, the dimeric structure was verified by an X-ray structure analysis (H. Schumann, W. Genthe, E. Hahn, unpublished).
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[11] 1.3 g (3.2 mmol) **2a** was dissolved in a mixture of 20 mL THF and 50 mL toluene and stirred for 12 h under H_2 atmosphere at room temperature. The solvent is subsequently removed and the residue dissolved in a small amount of THF. The solution is cooled overnight at $-50\,^{\circ}C$, resulting in the crystallization of 0.9 g (82%) **3a** as blue needles. Characterization by complete elemental analysis. M.p. = 84 °C (decomp.). ^{1}H-NMR (C_4D_8O, 25 °C): $\delta(C_5H_5) = -3.71$ (s, 10H). IR (KBr): 3080 m, 2950 s, 2870 s, 2700 w, 2400 w, 1440 s, 1380 s, 1310 m, 1200 m, 1040 s, 1010 s, 880 s, 750 s, 615 w, 565 m, 400 m.
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Symmetrical and Unsymmetrical Triphosphenium Ions**

By *Alfred Schmidpeter**, *Siegfried Lochschmidt*, and *William S. Sheldrick*

The isoelectronic molecules and ions $(Ph_3P)_2E^{(n-4)+}$ can be regarded as triphenylphosphane complexes of the nonmetals E, main group n, and are known for E = C, N, O. In the case of E = P, such an ion with an element of the third period is now also accessible.

Neither triphenylphosphane nor aluminum chloride react alone with phosphorus trichloride; together, however, they effect the reductive break-up of PCl_3 with formation of a chlorophosphonium and a triphosphenium ion[1] [eq. (1)].

$$PCl_3 + 3\,Ph_3P + 2\,AlCl_3 \longrightarrow [Ph_3P{-}P{-}PPh_3^+]AlCl_4^- + Ph_3PCl^+AlCl_4^- \quad (1)$$

1

1,1,1,3,3,3-Hexaphenyltriphosphenium tetrachloroaluminate **1**[2] (Table 1) crystallizes with half a molecule of CH_2Cl_2. Its X-ray structure analysis[3] shows two independent, yet not significantly different cations (Fig. 1). The average PP distance lies between that of a PP single bond and a PP double bond (220–225 and 200–205 pm, respectively); the PPP angle is, nevertheless, small[4]. A PNP

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angle of between 135 and 180° is found for the homologous $(Ph_3P)_2N^+$ ion.

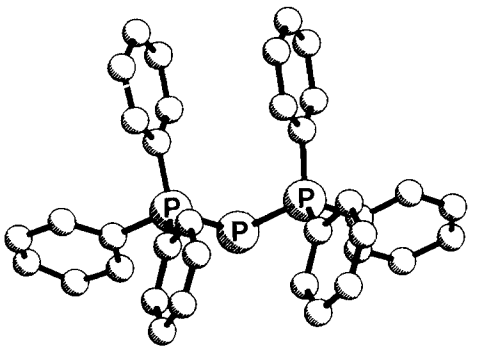


Fig. 1. Structure of one of the two independent cations of $1 \cdot 1/2 CH_2Cl_2$ in the crystal. PP distances: 213.7(6), 212.8(6) in the cation shown, and 214.1(6), 212.4(6) pm in the cation not shown; PPP angle: 102.2(2) and 103.0(3)°, respectively.

Table 1. ^{31}P-NMR data of the triphosphenium ions of the salts **1**, **3** (A_2X), **4** (ABX), and of the triphosphanediium ion of **2** (A_2X); $O(CH_2)_4N-$ = morpholino.

	L	$\delta(^{31}P)$			J [Hz]		
		P^X	PPh_3	P_L	P^XPPh_3	P^XP_L	P_LPPh_3
1	Ph_3P	−174	30		502		
2		−119	23		288		
3a	$MePh_2P$	−180	30	24	482	480	25
3b	Me_2PhP	−173	31	16	481	463	26
3c	Bu_3P	−199	32	32	503	458	41
3d	Et_2NPh_2P	−167	30	64	510	501	30
3e	$(Et_2N)_2PhP$	−170	30	77	524	479	27
3f	$PhNHPh_2P$	−178	29	49	479	524	27
3g	$(Me_2N)_3P$	−180	29	84	523	493	30
3h	$[(CH_2)_5N]_3P$	−173	29	77	542	497	32
3i	$[O(CH_2)_4N]_3P$	−181	28	76	526	528	32
3k	$(EtO)_3P$	−196	32	80	437	562	15
4a	$MePh_2P$	−176		23		464	
4b	Me_2PhP	−159		12		451	
4c	Bu_3P	−229		33		473	
4d	Et_2NPh_2P	−164		79		508	
4e	$(Et_2N)_2PhP$	−163		64		510	
4f	$PhNHPh_2P$	−182		47		498	
4g	$(Me_2N)_3P$	−194		85		518	
4h	$[(CH_2)_5N]_3P$	−193		79		560	
4i	$[O(CH_2)_4N]_3P$	−207		78		566	
4k	$(EtO)_3P$	−218		82		508	

On redissolving in CH_2Cl_2, **1** decomposes, whereby Ph_3P is liberated and more $Ph_3PCl^+AlCl_4^-$ is formed. The amorphous orange-yellow precipitate that separates is a phosphorus subchloride in which chlorine is partially replaced by triphenylphosphonio moieties; the replaced Cl^- reacts with $AlCl_3$ to give $AlCl_4^-$. In the decomposition reaction, the redox reaction between PCl_3 and Ph_3P which started in equation (1) thus continues further. This is initiated by the chloride ions that become available from the dissociation of $AlCl_4^-$, which increases with dilution. The decomposition can consequently be suppressed by the addition of $AlCl_3$ (about 0.3 mol/mol **1** for a 0.5 M solution of **1**).

In the presence of 1.5 mol $AlCl_3$/mol **1**, reaction of **1** with HCl or *tert*-butyl chloride proceeds according to Eq. (2) to give the hexaphenyltriphosphanediium salt **2** (Table 1). The ^{31}P-NMR spectrum of **2** is characterized by a high PH coupling constant ($J_{PH} = 235$ Hz), otherwise observed for diacyl- or bis(perfluorophenyl)phosphanes

$$\mathbf{1} + HCl + AlCl_3 \longrightarrow \underset{\mathbf{2}}{[Ph_3P{-}PH{-}PPh_3^{2+}](AlCl_4^-)_2} \quad (2)$$

With other alkyl chlorides RCl, **1** reacts under the same conditions to give the 2-alkylhexaphenyltriphosphanediium salts **2**, R instead of H[5].

Consistent with **1** being regarded as a phosphane complex, its PPh_3 moieties can be stepwise replaced by more basic phosphanes L according to Eq. (3) (Table 1).

$$\mathbf{1} \xrightarrow[-Ph_3P]{+L} \underset{\mathbf{3}}{[L{-}P{-}PPh_3^+]AlCl_4^-} \xrightarrow[-Ph_3P]{+L} \underset{\mathbf{4}}{[L{-}P{-}L^+]AlCl_4^-} \quad (3)$$

The salts of the unsymmetrical triphosphenium ions **3** are also formed on reaction of the salts with the symmetrical ions **1** and **4** [Eq. (4)]. The equilibria (4) usually lie distinctly on the side of **3** ($K > 100$). Exceptions are found with phosphanes that exhibit only slightly higher basicity towards P^+ than does triphenylphosphane: $MePh_2P$, $K = 93$; Et_2NPh_2P, $K = 59$; $PhNHPh_2P$, $K = 1.8$.

$$\mathbf{1} + \mathbf{4} \rightleftharpoons 2\,\mathbf{3} \quad (4)$$

The PP coupling constants of the unsymmetrical ions in **3** correspond on the average quite well with the mean of J_{PP} in **1** and **4** (with the same L), but may (as in the case of **3k**) deviate rather strongly from it (Table 1).

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[1] We have already reported on a particular cyclic triphosphenium ion and the reaction of a hexaaminotriphosphenium ion with an electron-rich olefin: a) A. Schmidpeter, S. Lochschmidt, W. S. Sheldrick, *Angew. Chem.* 94 (1982) 72; *Angew. Chem. Int. Ed. Engl.* 21 (1982) 63; b) A. Schmidpeter, S. Lochschmidt, A. Willhalm, *Angew. Chem.* 95 (1983) 561; *Angew. Chem. Int. Ed. Engl.* 22 (1983) 545; *Angew. Chem. Suppl. 1983*, 710.

[2] A solution of Ph_3P (53.0 g, 204 mmol) in $CHCl_3$ (500 mL) is treated at 20°C with 22.0 g (163 mmol) $AlCl_3$ and then directly afterwards dropwise with 6.0 mL (68 mmol) PCl_3 within 5 min. The solution is kept at 3°C and gradually evaporated down to half its original volume within 2 weeks. The bright-yellow cubic-like crystals of $1 \cdot 1/2 CH_2Cl_2$ that separate are recovered by filtration on a frit, washed with $CHCl_3$, and dried in a vacuum, m.p. 78°C, yield 36.1 g (69%); correct C,H analysis. The crystals can be stored for many months at 0°C without decomposition, but decompose at room temperature within 1–2 weeks to give a yellow amorphous substance.

[3] $Pna2_1$, $a = 3369.0(7)$, $b = 930.9(1)$, $c = 2420.4(2)$ pm, $Z = 8$, $\rho_x = 1.34$ g·cm^{-3}; direct methods (MULTAN, *P. Main*), $R = 0.091$, $R_w = 0.08$ for 3222 independent reflections $Cu_{K\alpha}$, $2\theta \leq 115°$, $F_0^2 \geq 2.5\sigma(F_0^2)$, empirical absorption correction). Only Cl, P, and Al atoms could be anisotropically refined. The positions of the H atoms of ten benzene rings were geometrically calculated, with the remaining two not being taken into account. Further details of the crystal structure investigation are available on request from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2, on quoting the depository number CSD 51241, the names of the authors, and the full citation of the journal.

[4] The PP angle is, however, greater than in the ion $[(OPh_2P)_2P]^-$ (95°), which is formally derived from the ion in **1** by double Ph/O$^-$ exchange: A. Schmidpeter, G. Burget, H. G. von Schnering, D. Weber, *Angew. Chem.* 96 (1984) 795; *Angew. Chem. Int. Ed. Engl.* 23 (1984) 816.

[5] A. Schmidpeter, S. Lochschmidt, K. Karaghiosoff, W. S. Sheldrick, *Chem. Ber.*, in press.

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Sulfur Monoxide as 4-Electron Bridge-Ligand in the Complex $[\{(\eta^5\text{-}C_5H_5)(CO)_2Mn\}_2SO]$**

By *Ingo-Peter Lorenz*, Johannes Messelhäuser, Wolfgang Hiller,* and *Klaus Haug*

In the free state, sulfur monoxide is extremely unstable; its stabilization by complexation was first described by *G. Schmid* et al. and *M. Höfler* et al.[1]. We have now succeeded in synthesizing the first SO-complex **3** with symmetrical SO-bridge and sp^2-hybridized sulfur (3c4e system).

Sulfur monoxide is generated in solution in the presence of the substitution-labile solvent complex **1a** by thermolysis of thiirane *S*-oxide **2** at room temperature[2] and is trapped by complexation in **3** (ca. 10%), a black-violet, crystalline solid that is sensitive to light and air in solution; more productive is the irradiation of the carbonylcyclopentadienylmanganese complex **1b** and **2** in petroleum ether (ca. 30%)[3].

$$2\ [(\eta^5\text{-}C_5H_5)(CO)_2MnL] + \underset{O}{\overset{}{S}} \xrightarrow[-2\ L]{\text{room temperature or } h\nu} [\{(\eta^5\text{-}C_5H_5)(CO)_2Mn\}_2SO] + C_2H_4$$

1a, L = thf; **1b**, L = CO; **2**; **3**

The mechanism of formation of **3** is still unclear. We postulate initial adduct formation of **2** with **1** to give an unstable intermediate, which is converted via C_2H_4- and L-elimination and addition of the Lewis acid **1**-L into **3**. The composition and structure of the complex was confirmed by elemental analysis, ^{1}H-NMR, IR, UV, and mass spectra, and by an X-ray structure analysis. The FD mass spectrum shows the molecular ion at $m/z = 400$. The IR spectrum (KBr) shows, in addition to the C_5H_5- and CO-bands (ν(CO) = 2010 s, 1995 m-s, 1948 vs, 1923 vs, 1908 w, cm^{-1}; (pentane): 2027 s, 2019 w, 1965 m, 1947 vs, cm^{-1}), three further absorptions at 1037 m, 475 w-m and 454 w, cm^{-1}, which are assigned to the S=O- and SMn_2-stretching vibrations, respectively. The ^{1}H-NMR spectrum shows only one singlet at $\delta = 4.77$ for the ring protons, even at -40 °C ($CDCl_3$). The deep violet color of **3** is attributed to the very intense band at 18450 cm^{-1} in the UV/VIS spectrum ($^1A_1$-$^1B_2$ transition in the 4π-SMn_2 skeleton, C_{2v}).

According to a single-crystal X-ray structure analysis[4], the complex **3** contains the SO-ligand as a 4-electron donor oriented in a symmetrical bridge position (Fig. 1). The S-atom is bound to the two Mn atoms via two short bonds (Mn1–S 212.6(2), Mn2–S 212.1(2); the S–O9 distance of 150.4(4) pm is negligibly longer than in the free molecule. The bond angles M1–S–Mn2, Mn1–S–O9, and Mn2–S–O9 are 130.78(7), 114.4(2), and 114.8(2)°, respectively, thus the four atoms of the central SOMn skeleton lie exactly in a plane. The Mn1–Mn2 distance of 386.2(1) pm rules out any bond interaction[5]. The CO ligands are rotated pairwise through an angle of 34.8° with respect to each other.

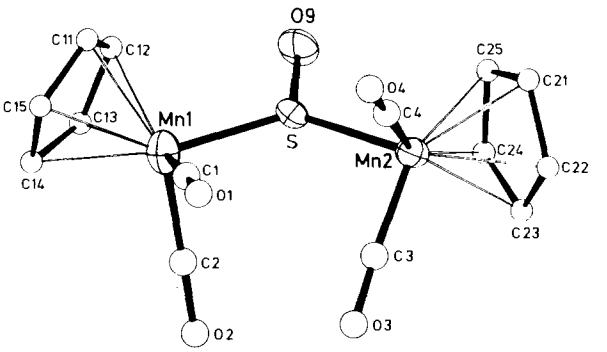
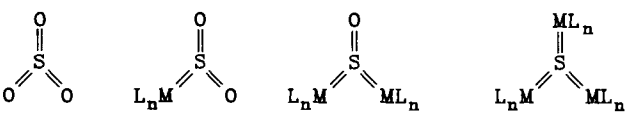


Fig. 1. Crystal structure of **3**. Selected bond lengths [pm] and angles [°]: S–O9 150.4(4), Mn1–S 212.6(2), Mn2–S 212.1(2), Mn1–C1 176.3(7), Mn1–C2 178.6(7), C1–O1 116.3(7), C2–O2 115.2(7); Mn1–S–Mn2 130.78(7), Mn1–S–O9 114.4(2), Mn2–S–O9 114.8(2), S–Mn1–C1 94.9(2), S–Mn1–C2 93.1(2), Mn1–C1–O1 177.5(6), Mn1–C2–O2 179.0(6). The two independent molecules of **3** show, within the limits of error, the same geometry.

It follows from the trigonal-planar arrangement and Mn=S double bonding of **3** that it is not to be regarded as an organometallic derivative of sulfoxides, but, because of the isolobal relationship $O \rightarrow \overline{O} \leftarrow (\eta^5\text{-}C_5H_5)(CO)_2Mn$, as a derivative of sulfur trioxide **I**. Since a trigonal-planar sulfur environment is also present in the complex **II**[6] an isotypic series of the known compounds **I**—**IV** can be formulated.



$L_nM = (\eta^5\text{-}C_5H_5)(CO)_2Mn$

Höfler et al.[1b] have described the oxidation of the sulfido complex $[\{(\eta^5\text{-}C_5H_5)(CO)_2Mn\}_2S]$ with atmospheric oxygen to give **3**. Aside from color and molar mass, our findings are not reconcilable with those already published[1b]; rather, it would seem that **3** can form two structural isomers, depending on the synthetic route used; that is, two structures which differ in the electron-donor ability of their SO bridge (3c2e system).

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1b, 12079-65-1; **2**, 7117-41-1; **3**, 95218-04-5.

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[**] This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.

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[3] Preparation of **3**: A solution of **1b** (814 mg, 4 mmol) and **2** (304 mg, 4 mmol) in petroleum ether (60/90°C) was irradiated in a photolysis apparatus for 40 min. The solution turned from yellow to deep-violet in color. After filtration and removal of solvent from the filtrate, **1b** could be separated from the resulting residue by sublimation in a high vacuum. Recrystallization of the remaining residue from petroleum ether at −30°C afforded analytically pure **3**, m.p. 142°C (decomp.).

[4] $P2_1/n$, $Z=8$; $a=1403.4(3)$, $b=1081.3(2)$, $c=2044.8(4)$ pm, $\beta=100.87(4)°$, $V=3047.5\times10^6$ pm^3; $\rho_{calc}=1.744$ g/cm^3, $\theta=3-24°$ ($Mo_{K\alpha}$ radiation, graphite monochromator, $T=-80°C$). 4490 reflections measured, LP correction, empirical absorption correction. Direct methods. Refinement [2265 reflections with $I\geq3\sigma(I)$] of all atom positions with anisotropic temperature parameters, cyclopentadienyl C-atoms isotropic; $R_1=0.053$, $R_2=0.056$, 298 parameters. Further details of the crystal structure investigation are available on request from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2, on quoting the depository number CSD 51 128, the names of the authors, and the full citation of the journal.

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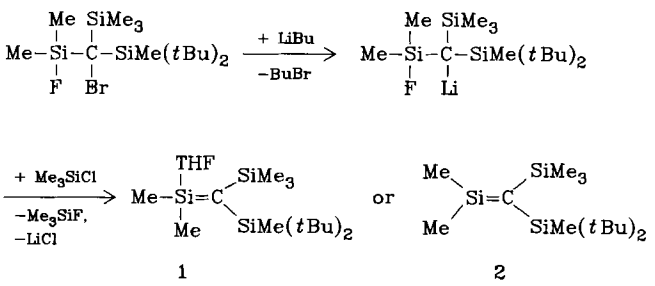
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Isolation and Structure of a Stable Molecule Containing a Silicon-Carbon Double Bond**

By *Nils Wiberg**, *Gerhard Wagner*, and *Gerhard Müller**

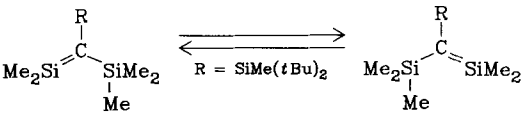
The stable, tetrahydrofuran (THF)-containing silaethene **1** is obtained in crystalline form in THF[1a]. By the same reaction sequence, the THF-free **2** is formed in diethyl ether in ca. 60% yield. It could not, however, be isolated



from the reaction mixture in crystalline form[1b]. Its existence was demonstrated by characteristic trapping experiments[1b, 1c] as well as by the formation of **1** upon addition of THF to **2**:

$$\mathbf{2} + \text{THF} \rightleftharpoons \mathbf{1}$$

We have now succeeded in converting **1** into crystalline **2** by removing THF from **1** by azeotropic distillation with benzene (see Experimental Procedure). The silaethene **2** ($M^{\oplus}$: m/z 300) forms colorless prisms which are stable at room temperature but decompose above 65°C over the course of several days. The ^{1}H-NMR spectrum (90 MHz, $C_6D_5CD_3$, 30°C: $\delta=0.55$ (very broad, Me_2Si, Me_3Si, MeSi), 1.26 (sharp, tBu_2Si)) indicates a rapid methyl exchange, which was also observed for the silaethene $Me_2Si{=}C(SiMe_3)_2$[1c, 2].



The X-ray structure analysis (Fig. 1)[3] shows an essentially planar $C_2Si{=}CSi_2$ skeleton for **2** (the sums of the valence angles at Si1 and C1 each 360.0°[4]). The torsional distortion along the Si=C bond amounts to only 1.6° (Fig. 2). The deviations of the valence angles at the unsaturated centers Si1 and C1 from standard sp^2 values may be easily explained by the steric strain exerted by the $SiMe_3$ and especially the $SiMe(tBu)_2$ groups at C1.

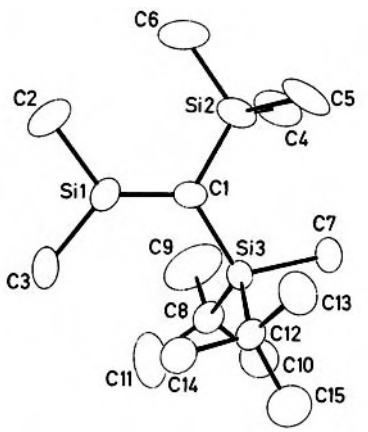


Fig. 1. Structure of **2** in the crystal (ORTEP, thermal ellipsoids 50%). Important distances [Å] and angles [°]: Si1–C1 1.702(5), Si1–C2 1.851(5), Si1–C3 1.842(5), C1–Si2 1.865(5), C1–Si3 1.890(5), C1–Si1–C2 127.0(3), C1–Si1–C3 129.0(2), C2–Si1–C3 104.0(3), Si1–C1–Si2 119.5(3), Si1–C1–Si3 122.8(3), Si2–C1–Si3 117.7(2).

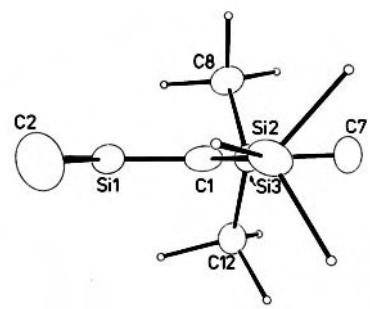


Fig. 2. View of **2** perpendicular to the plane of the double bond (methyl groups at Si2, C8, C12 with arbitrary radii). Angle of planes Si1C1C2C3–C1Si1Si2Si3 = 1.6°.

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[**] Part 9, Unsaturated Silicon Compounds; Part 60, Compounds of Silicon. For Part 8 (Part 59) see [1c].

The length of the Si=C bond, the subject of considerable controversy[5a], is 1.702(5) Å in **2**. Thus, it fits astonishingly well into the range of 1.69–1.71 Å predicted theoretically by ab initio calculations[5]. Compared to a typical Si–C bond (1.87 Å), the observed Si=C distance is shortened by ca. 0.17 Å (shortening C–C→C=C: 0.19 Å). It is drastically shorter than the Si=C bond in the silaenol ether $(Me_3Si)_2Si{=}C(OSiMe_3)$(1-adamantyl) (1.764(3) Å[6]), which is twisted by 14.6°. The reason for the bond length and torsional distortion of this Si=C bond is thought to be the bulkiness of the substituents as well as the high electronegativity of the $OSiMe_3$ group[5,6]. Since the silaethene **2** contains less bulky and not particularly electronegative substituents, the observed Si=C bond length in **2** should be representative for silaethenes $R_2Si{=}CR_2$ with moderately bulky substituents R = H, alkyl, silyl. The previously found Si=C bond length of 1.747(5) Å in the THF adduct **1**[1a] had already indicated that the Si=C distance in unsaturated systems like **2** should be shorter than in the aforementioned silaenol ether. The observed double bond geometry of the silaethenes shows close resemblances to that of ethenes. This implies a similar bonding situation in both systems.

Experimental Procedure:

The benzene from a solution of 1.5 mmol of crystalline **1** (prepared according to [1a]) in 25 mL of anhydrous benzene contained in a flask A was distilled in high vacuum into a flask B which had been cooled to −78°C and contained 10 mmol of pure LiBu as a THF scavenger. By cooling A to −78°C and warming B to room temperature, the benzene was distilled back into A. After repeating this process 40 times, 1 mL of anhydrous pentane was distilled onto the benzene-free residue in A. The pentane solution thus obtained was cooled to −90°C for 2–3 d (formation of seed crystals) and subsequently to −78°C. The pentane was decanted off and the crystals were dried in vacuo.

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[2] ^{13}C-NMR (−70°C, $C_6D_5CD_3$): δ = 30.11 (CMe_3), 21.80 (CMe_3), 7.06 ($SiMe_3$), −2.10 ($SiMe(tBu_2)$), 10.81 and 5.85 (C=$SiMe_2$), 77.20 (C=Si).— ^{29}Si-NMR (−70°C, $C_6D_5CD_3$): δ = −4.60 ($SiMe_3$), 6.00 ($SiMe(tBu_2)$), 144.2 (Si=C). The spectra were recorded in cooperation with Dr. *B. Wrackmeyer*.

[3] Crystal structure data of **2**: $C_{15}H_{36}Si_3$ M_r = 300.71, space group $P2_12_12_1$, a = 8.109(1), b = 14.886(2), c = 16.470(2) Å, V = 1988.10 Å^3, $\rho_{calcd.}$ = 1.005 g/cm^3 for Z = 4. 3378 measured reflexions of which 2928 were unique ($+h+k+l$ and Friedel reflections, $(\sin\theta/\lambda)_{max.}$ = 0.572, ω-scan, Δω = 1°, $Mo_{K\alpha}$, λ = 0.71069 Å, $F(000)$ = 672, T = −35°C). Direct methods (MULTAN 80); R = 0.055, R_w = 0.053 ($w = k/\sigma^2(F_0)$, k = 1.8 in last cycle) for 163 refined parameters and 2447 structure factors with $F_0 > 4.0\sigma(F_0)$ (full matrix, non-H atoms anisotropic, H atoms constant, $\Delta\rho_{max}$ (final) = +0.45/−0.36 e/Å^3, SHELX 76). The refinement of the enantiomorphous structure did not result in significant differences. Further details of the crystal structure analysis are available on request from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2 (FRG), on quoting the depository number CSD 51178, the names of the authors, and the journal citation.

[4] The relatively large thermal parameters of atoms C2/C3 at Si1 (Fig. 2) do not exclude a slight pyramidalization of Si1 with disordered methyl groups. Alternatively, they point to a relatively shallow minimum of the equilibrium conformation of Si1.

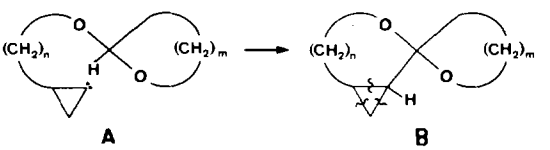
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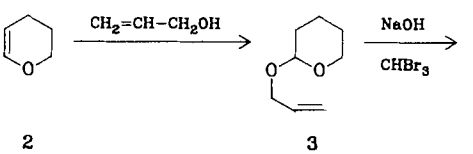
Spiroacetal Formation by Carbene (Carbenoid) Insertion Reaction: Synthesis of the Major Constituent of the Sex Attractant of the Olive Fly *(Dacus oleae)***

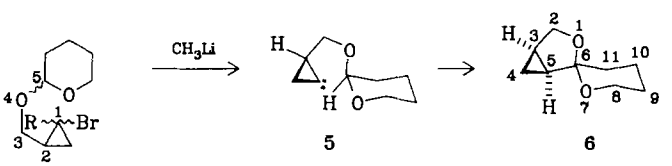
By *Udo H. Brinker*, Ali Haghani,* and *Klaus Gomann*

The spiroacetal unit is a frequently occurring structural element in antibiotics and insect pheromones[2]. Herein we present a novel strategy for the synthesis of spiroacetals[3], the key step of which is an intramolecular C–H insertion reaction of a cyclopropylidene (cyclopropylidenoid) (**A** → **B**). Subsequent selective opening of the three-membered ring in **B** should enable the synthesis of methylated spiroacetals and(or) spiroacetals with expanded rings.

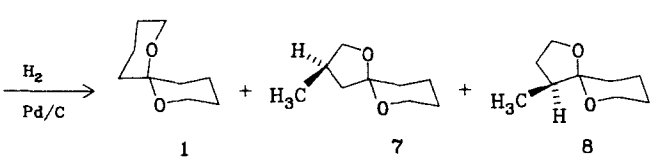


To test this synthetic concept we chose 1,7-dioxaspiro-[5.5]undecane **1**, the prototype of some spiroacetals isolated from natural products. **1** is the major constituent of the sex attractant of the female olive fly *Dacus oleae* (Gmelin); the biological activity of the racemate has been confirmed by field experiments[4].





4a, R = Br; **4b**, R = Li
4c, R = H; **4d**, R = CH_3



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[**] Carbene Rearrangements, Part 18. This work was supported by the Fonds der Chemischen Industrie. We thank Dr. *W. Dietrich*, Priv.-Doz. Dr. *H. Duddeck*, and Dr. *M. Kaiser* for recording the 2D-^{1}H-NMR (NOESY and COSY) spectra of **6** and Dr. *D. Müller* for the GC-MS determinations.—Part 17: [1].

Addition of allyl alcohol to 3,4-dihydro-2*H*-pyran **2** in the presence of traces of hydrochloric acid[5] affords the acetal **3** (yield: 85%). Dibromocarbene, generated by phase-transfer catalysis, adds to the double bond of **3**[6] with formation of two diastereomers **4a** (ratio ca. 1:1, yield: 64%). Reaction of **4a** with methyllithium in ether at $-75\,^{\circ}C$ leads to formation of the tricyclic spiroacetal **6**[6] as main product (20%, not yet optimized), along with the bromocyclopropane compounds **4c** (ca. 15%)[6,7] and the methylated diastereomers **4d** (ca. 5%).

The tricycle **6** is the product of an intramolecular insertion of the cyclopropylidene(oid) into the tertiary C–H bond of **5**. Dreiding models show that this "activated"[8] C–H bond, flanked by two oxygen atoms, is located in a favorable position for the insertion. Insertions into C–H bonds adjacent to a heteroatom (O[9], N, S) with formation of a five-membered ring are well-known[8]. Compounds resulting from insertion into secondary C–H bonds in the α-position to the oxygen atoms are, according to the mass spectrum of the crude mixture (coupled GC-MS), not formed. Accordingly, **6** is the only product formed on reaction of the carbene(oid) **5**[10]. The exclusive formation of **6**, in which the cyclopropane ring and the oxygen atom of the six-membered ring are located on the same side of the molecule[10], could be due to the fact that no steric interaction of the geminal three-membered ring protons on C-4 with the protons on C-11 takes place in the transition state of the insertion reaction. This stereoselectivity could also be favored by an intramolecular complexation in **4b**. After coordination of the lithium by the oxygen atoms in **4b** and subsequent LiBr cleavage, the resulting carbene(oid) **5** can insert into the tertiary C–H bond.

No allene could be detected by IR and ^{1}H-NMR spectroscopic examination of the crude mixture formed in the reaction of **4a**. The two oxygen atoms in **5** would therefore also appear to prevent a competing cyclopropylidene-allene rearrangement at $-75\,^{\circ}C$[9b,11]. On the other hand, reaction of **4a** at room temperature leads to formation of an allene as well as **6**. **4c** and **4d** could be formed by protonation and methylation of **4b**, respectively[7]. The hydrogenation[12] of **6** (10% Pd on activated charcoal, CH_3OH, 5 bar, 25 °C) affords 3- and 4-methyl-1,6-dioxaspiro[4.5]decane **7** and **8**, respectively (1.5:1) and the natural product **1**[5,13] in an overall yield of 80% (**7** + **8** : **1** = 1.75 : 1).

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CAS Registry numbers:
1, 180-84-7; **2**, 110-87-2; **3**, 4203-49-0; **4a** (isomer 1), 95249-81-9; **4a** (isomer 2), 95249-88-0; **4c**, 95249-89-1; **4d**, 95249-90-4; **6**, 95249-91-5; **7**, 95249-92-6; **8**, 87888-51-5; CH_2=$CHCH_2OH$, 107-18-6; Br_2C:, 4371-77-1.

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[6] The structures of the new compounds are confirmed by IR, MS, and ^{1}H-NMR spectra; **6**: ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 6.3 (t, C-4), 14.6 (d, C-5), 20.3 (t, C-10), 25.4 (t, C-9), 25.5 (d, C-3), 31.0 (t, C-11), 61.6 (t, C-8), 68.0 (t, C-2), 105.0 (s, C-6). **4a**, **6**, and **7** + **8** gave correct elemental analyses.
[7] The relatively large amount (ca. 15%) of **4c** could be explained as follows: The bromocyclopropane compounds **4c** can be formed from *both* diastereomeric dibromocarbene adducts **4a**. Two diastereomeric carbenoids are generated in the reaction of diastereomers **4a** with methyllithium. Of these, only **5** appears to undergo the insertion reaction, since the spiroacetal diastereomeric to **6** was not detected[10]. Since this as well as other reactions apparently do not take place in the case of the other diastereomeric carbenoid, **4b** can, e.g., be protonated almost exclusively to **4c** in the aqueous work-up procedure.
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[10] Formation of the spiroacetal diastereomeric to **6**, in which the cyclopropane ring and oxygen atom O-7 are on opposite sides of the molecule, is not observed. This isomer would result from the reaction of the other diastereomer **4a** with methyllithium. The differentiation of these compounds and the structure assignment to the structure **6** is based on the NOESY experiment. The proton on C-4 *endo* to O-1 shows only cross peaks with the protons of the three-membered ring and with the proton H-2 located on the same side of the molecule. On the other hand, a much more distinct nuclear Overhauser effect should be observed for the H-4_{endo}–H-11 interaction in the case of the other isomer, since the distance between these protons is considerably shorter than that between H-4_{endo} and H-2.
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The First Application of 2D-NMR to the Spectral Analysis of a Paramagnetic Complex. Example: Bis[*R*-(+)-*P*,*P*-diethylthiophosphinic acid-*N*-α-methylbenzylamido]nickel(II)

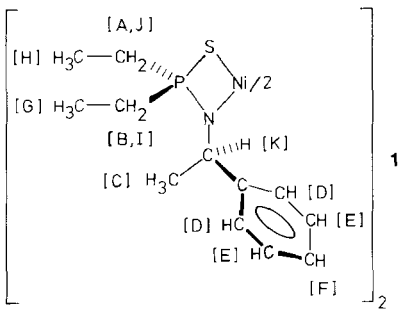
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Paramagnetic transition-metal complexes with short electron spin lattice relaxation times ($< 10^{-11}$ s) can be well characterized by NMR spectroscopy[1]. The assignment of the resonances to individual structural elements, however, is frequently problematic, since as a result of line broadening a fine structure of the signals is usually lacking[2]. Using the nickel complex bis[*R*-(+)-*P*,*P*-diethylthiophosphinic acid-*N*-α-methylbenzylamido]nickel(II) **1** as example, we wish to demonstrate that such problems of assignment can be elegantly solved with the aid of the 2D-NMR technique[3].

1 is obtained according to

$$2\ R\text{-}(+)\text{-}Et_2P(S)NCH(Me)Ph^-Li^+ + NiCl_2 \longrightarrow 2\,LiCl + \mathbf{1}$$

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1

in the form of dark green crystals[4]. The complex, extremely sensitive to hydrolysis, is monomeric in benzene. It is paramagnetic (3.11 B.M., 291 K) and shows the following absorptions in the UV/VIS spectrum (toluene): $\tilde{\nu}(\varepsilon)=6200$ (40), 12270 (40), 17450 (145) cm^{-1} (L mol^{-1} cm^{-1}). **1** therefore contains the pseudotetrahedral chromophore NiN_2S_2[5]. As a result of the paramagnetism the phosphorus resonance in **1** ($\delta=414$, 293 K) shows an extremely strong downfield shift compared to that of the free ligand ($\delta=73$) and that of the analogous diamagnetic zinc complex ($\delta=81$).

The bis-chelate complex **1** has three chirality centers (2C, Ni); hence during its synthesis a mixture of the diastereomers (+, Δ, +) and (+, Λ, +) should be formed. However, only the number of resonances corresponding to one form is observed in the NMR spectra (^{31}P, ^1H), a finding which can be ascribed to rapid Δ-Λ isomerization[6]. As a result of the chirality, both the two ethyl groups on the phosphorus as well as the two methylene protons of each ethyl group behave diastereotopically.

In the 200-MHz ^1H-NMR spectrum of a 0.1 M solution of **1** in [D_6]benzene, eleven characteristic resonances (A—K) are observed (Table 1). They cover the unusually wide range from $\delta=+263.1$ to -9.5.

Table 1. 200-MHz ^1H-NMR data of **1**, $c=0.1$ M in [D_6]benzene, 293 K. Internal standard: benzene.

Resonance	$\delta(^1H)$	Rel. int.	Resonance	$\delta(^1H)$	Rel. int.
A	28.6	1	G	3.6	3
B	24.2	1	H	0.0	3
C	20.5	3	I	−9.0	1
D	19.1	2	J	−9.5	1
E	11.4	2	K	263.1	1
F	6.7	1			

Since the scalar couplings $^nJ_{HH}$ and $^nJ_{PH}$ (n=2—4) are not resolved, conventional methods of NMR spectroscopy cannot be resorted to for the structure interpretation. The coupling relationships not evident in the 1D-NMR experiment, however, are elegantly rendered visible by $^1H,^1H$-correlation spectroscopy (COSY[7]).

The signals A, J, H and B, I, G of the ^1H-homoscalar correlated 2D-NMR spectrum at 200 MHz[8] (Fig. 1) can be assigned by direct inspection to the CH_3—CH_2 groups. A precise stereochemical interpretation of the $\delta(^1H)$ values (Table 1), however, is not possible with the present state of the art, i.e. the notations A and J just as B and I of the resonances of one CH_2 group can be exchanged, as also A, J, H and B, I, G.

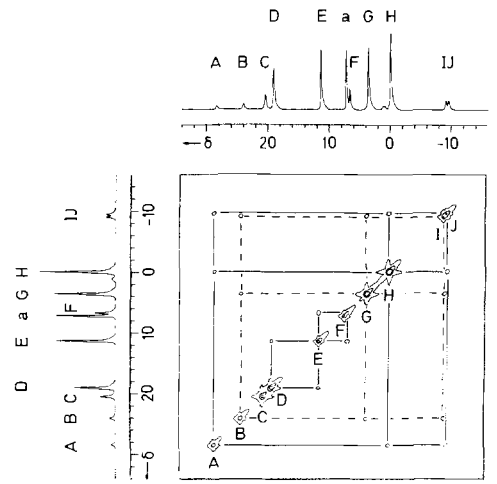


Fig. 1. Homoscalar correlated 2D-^1H-NMR spectrum (COSY 90) of a 0.1 M solution of **1** in [D_6]benzene at 293 K [8]. Size of matrix 512 × 2048, spectral width in F_1 and F_2 10000 Hz, measuring frequency 200.13 MHz, measuring time ca. 16 min, Bruker AM200 spectrometer. The resonance signals of **1** are denoted by capital letters. a: Benzene.

The observed nonequivalence of the methylene protons A, J and B, I with values of $\Delta\delta=38.1$ and 33.2 respectively, is unusually large. Corresponding values of diamagnetic compounds are lower by a factor of about 100[9]. On the basis of their intensities and their coupling behavior, the resonances D, E, F can be unequivocally assigned to the phenyl group: F to the proton in the *para*-position, E to the *meta*- and D to the *ortho*-protons. Resonance C does not couple with any of the other resonances in Figure 1. Therefore, and because of its relative intensity (3 protons) C is assigned to the methyl group on the chiral C-atom. The resonance shifted strongly downfield at $\delta=263.1$ is assigned to the hydrogen atom K, which of all protons is closest to the paramagnetic center.

The signal-structure assignment described here is, to our knowledge, the first example of a successful 2D-NMR correlation of a paramagnetic complex. The 2D-technique also proved to be an efficient method for the interpretation of the structure of the corresponding Ni^{II}-complexes with the achiral ligands $Et_2P(S)NR^-$ (R = Ph, *cyclo*-hex, *t*Bu)[10]. It thus extends the arsenal of suitable methods for the investigation of the structures of paramagnetic coordination compounds. The extremely short relaxation times compared to those of diamagnetic compounds turn out to be exceptionally favorable with regard to the time of measurement[11].

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1, 95248-66-1; *R*-(+)-$Et_2P(S)NCH(Me)Ph^-Li^+$, 95217-04-2; $NiCl_2$, 7718-54-9; *R*-(+)-*P,P*-diethylthiophosphinic acid-*N*-α-methylbenzylamine, 95217-05-3; diethylthiophosphoryl bromide, 3981-46-2; *R*-(+)-α-methylbenzylamine, 3886-69-9; *n*-butyllithium, 109-72-8.

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[3] R. Benn, H. Günther, *Angew. Chem.* 95 (1983) 381; *Angew. Chem. Int. Ed. Engl.* 22 (1983) 390.

[4] Procedure (all operations were carried out under argon in degassed and anhydrous solvents): A solution of 37.7 g (0.16 mol) *R*-(+)-*P,P*-diethylthiophosphinic acid-*N*-α-methylbenzylamide (prepared from diethylthiophosphoryl bromide and *R*-(+)-α-methylbenzylamine in toluene, $\delta(^{31}P) = 73$, m.p. 49.5 °C) in toluene (200 mL) was treated with 100 mL of a 1.55 M solution of *n*-butyllithium in *n*-hexane. The mixture was heated under reflux for 1 h, cooled to room temperature, and treated with 10 g (0.08 mol) anhydrous $NiCl_2$. After further heating for 2 h under reflux LiCl was filtered off, the solvents removed, and the residue crystallized, first from ligroin (100–150 °C)/toluene (3:1) and then from ligroin (100–150 °C). Dark green crystals, m.p. 57–60 °C, yield 19.5 g (46%), $[\alpha]_D^{20} = 183.9$ ($c = 0.68$, toluene).

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[7] COSY = Correlated Spectroscopy: impulse sequence $[D_1 - \pi/2(x) - t_1 - \pi/2(x) - t_2]$. D_1 is the time required for establishment of equilibrium magnetization. t_1 is variable and is determined by number of data and spectral width, while t_2 is the recording time of the normal 1D-NMR spectrum. The data matrix had 512 (t_1) × 2048 (t_2) points. The FID signals were multiplied in both directions by a gaussian function. After the Fourier transformation the resolution in the F_1 and F_2 direction was 9.8 Hz at a spectral width of 10000 Hz in each case.

[8] Resonance K cannot be taken into account in the 2D-NMR experiment since an extension of the range of measurement from 10000 to 60000 Hz leads to too great a loss of digital resolution.

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[11] In the case of the paramagnetic complexes investigated by us D_1 (see COSY impulse sequence) can be set to times $\leq 10^{-3}$ without any loss of information. The measurement of corresponding diamagnetic compounds, on the other hand, requires D_1 times between 1 and 5 s.

BOOK REVIEWS

Modern Synthetic Methods 1983. Vol. 3: Transition Metals in Organic Synthesis. Edited by *R. Scheffold.* Salle + Sauerländer, Frankfurt (for the Federal Republic of Germany, Austria, Switzerland); Wiley, Chichester (for other countries) 1983. 440 pp., paperback, DM 48.00.

The Seminars on Modern Synthetic Methods held in Interlaken are aimed at providing an easy access to important and rapidly developing areas of synthetic organic chemistry. The 1983 Seminar was dedicated to the explosively growing contribution of transition metal chemistry to organic synthesis. The present book restores the remarkably successful conference in a preservable form.

The volume comprises five chapters. The introductory chapter written by *J. K. Stille* (60 pages, 115 references) deals generally with the "Principles of Transition Metal Chemistry", which include the basic structure and bonding in organometallic compounds and fundamental reactions such as oxidative addition, reductive elimination, insertion, nucleophilic addition to coordinated ligands, transmetalation, etc., with emphasis of the relevant mechanisms. The final section describes some representative homogeneous catalytic processes which are achievable by combination of the above simple reactions, typical examples being the Wacker process, Monsanto acetic acid synthesis, transition metal-catalyzed C–C coupling reactions, rhodium-catalyzed olefin hydrogenation, decarbonylation and hydroformylation promoted by rhodium complexes, oxo reactions, and nickel-catalyzed olefin hydrocyanation.

The second chapter by *L. S. Hegedus* is concerned with "Group VIII Transition Metals in Organic Synthesis" (78 pages, 127 references). This is an excellent collection of the classic works in this area and introduces the largely stoichiometric use of nickel, iron, and palladium complexes. This chapter is subdivided, according to the structures of the metal complexes involved, into reactions of carbonylmetal compounds, alkyl complexes, olefin complexes, and π-allyl complexes. Here, particular emphasis is placed on the demonstration of the usefulness of these complexes in natural product synthesis.

The following three chapters deal successively with some specific elements and metal complexes of increasing synthetic importance. *J. F. Normant* et al. present a progress report on "Organocopper and Organomanganese Reagents". Part I of this chapter (33 pages, 63 references) deals mainly with the authors organocopper-mediated stereospecific synthesis of conjugated dienes and enynes. The existing methods for the diene synthesis are also introduced. Part 2 (44 pages, 216 references) is concerned with organomanganese chemistry and outlines the preparation of organomanganese reagents, their reactions with carbonyl and various C=X type functionalities, and application to ketone synthesis. A review entitled "Titanium and Zirconium Derivatives in Organic Synthesis" is then given by *D. Seebach, B. Weidmann,* and *L. Widler* (137 pages, 218 references). These group 4 elements play a significant role as components of the catalysts used in a variety of industrial processes such as Ziegler-Natta polymerization, metathesis, and nitrogen fixation, etc.; however, the present article is restricted to the non-catalytic use of these derivatives. The systematic description is quite impressive. In the laboratory the use of these complexes stems largely from their marked selectivities rather than novel reactivity. The authors deal with the availability and preparation of the reagents and starting materials, with C–C bond-forming processes, and with functionalizations and functional group interconversions. Potential applications in various enantioselective and diastereoselective reactions are also demonstrated. The final chapter (86 pages, 285 references) is devoted to the particularly noteworthy work by *R. Scheffold, G. Rytz,* and *L. Walder* on "Vitamin B_{12} and Related Co-Complexes as Catalysts in Organic Synthesis". It is seen that the cobalt complexes including vitamin B_{12}, though finding few applications in the past, are attracting increasing attention as useful synthetic reagents or catalysts. After a brief introduction, the authors describe cobalt complexes possessing unique structures, and outline their synthesis, properties, and reactions, and application in organic synthesis. The fascinating account on vitamin B_{12}-related chemistry will amuse the readers.

Each article ends with ample literature citations up to 1981 or 1982. This book is characterized by the amount of space alotted to selected experimental procedures, which is extremely helpful to laboratory practitioners.

Organotransition-metal chemistry is now recognized as a major synthetic tool in industrial processes and in the laboratory. To present such an expansively developing area

in a single volume is not an easy task, and, consequently, it has not been the aim of this book to provide a comprehensive coverage of this wide area of chemistry. Rather a valiant efforts has been made at giving an insight into current developments in this field by suitable selection of the authors and subjects, and this concept has, in my opinion, proven successful. This book made a good impression on me; it can be recommended to all advanced students and all experienced chemists in industry and university who are involved in experimental organic chemistry.

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Theoriewandel in der Wissenschaftsgeschichte. Chemie im 18. Jahrhundert. By *E. Ströker*. Vittorio Klostermann, Frankfurt am Main 1982. viii, 324 pp., hardback, DM 78.—, paperback, DM 48.—.

In recent years there have been numerous contacts between the history of science and the theory of science that have proven to be fruitful for both parties: history provides theories on the research methods and the logic of knowledge in the natural sciences with a medium for confirmation and differentiation, the modern theory of science provides historical analyses with categories and perspectives that can shed new light even on well-known sources. Along with other scholars, some of whom were active already in the eighteenth and nineteenth centuries, *Thomas Kuhn* in particular has called attention to the idea of progress in the natural sciences and the conditions that determine such progress. The dynamics of the natural sciences have increasingly come to be seen no longer only in terms of a gain in knowledge; instead, there is a growing awareness of the limitations and the losses involved here. The presuppositions for the development of natural science are ever more often viewed in connection with institutional changes and social history. Forms of such interaction with their varying accentuations according to the time and the specific field involved will prove to become an even more important theme for future studies, whereby the central question will be less concerned with the external than the immanent connections between internal and external dimensions.

The issues provide the background for *Elisabeth Ströker*'s stimulating and important study. In a concrete combination of theory and history, seventeenth and eighteenth century chemistry is presented in view of both the original sources and the scholarly discussion up to the present. This study is prefaced by a consideration of the possible and the already established connections between the theory of the history of science. This book contributes to an expansion in our knowledge both with regard to specific points as well as more general areas. One-sided deductions and approaches relying on explanations from a single cause are refuted. *Ströker* correctly indicates the danger of projecting later views into the past, for instance *Stahl*'s achievements into the phlogiston theory. The primary emphasis is consistently placed on professional and institutional backgrounds as well as on the scientists' intellectual orientations, furthermore, on the scientific mileau and its effect upon the development of a theory. *Ströker* shows that it is not at all possible—or, at least, that it is only in a relative sense possible—to speak of schools and paradigms in eighteenth century chemistry; the idea of traditions turns out to be much more accurate. The development of practical and technical fields possesses a dynamics of its own and can by no means be made primarily dependent upon the controversies regarding phlogiston chemistry. Future investigations will have to clarify the relationship between technology and the natural sciences further. In addition to these direct interconnections, there must have also been social and intellectual conditions which affected technology and the natural sciences.

This study discusses the reception and transformation of the phlogiston theory in detail and the genesis of pneumatic chemistry. The all-too-common exclusive orientation of historical presentations on oxygen is shown to be one-sided. Empirical observations led to modifications, changing theoretical and philosophical opinions also had their consequences. One might add that the phlogiston chemists' interest in the phenomenon of attraction demonstrates that this position in chemistry has a significance for the future which has been ignored by the "progressive" adherents of the oxidation theory. Professor *Ströker* points out new sources and, above all, illustrates new aspects of matters with which we are already familiar. She emphasizes connections which have been neglected in the usual histories of chemistry. *Kuhn*'s model is confronted with historical developments and structures that indicate the need for this model to be relativized and made more precise; the idea of rational argumentation and the augmentation of our knowledge as essential factors in progress is qualified and the concept of a scientific community is rendered questionable as well. *Ströker* advocates neither a univocal preference nor a univocal condemnation of any particular widespead dynamic approach. To the historian of science, this will appear as an advantage; for the theorist of science this means that he will have to continue his search for models that are further differentiated and better integrated.

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Ambident Anions. By *O. A. Reutov, I. P. Beletskaya,* and *A. L. Kurts*. Plenum Publishing Corporation, New York 1983. xiii, 338 pp, bound, $ 59.50.

An introduction to the problems of the reactivity of ambident anions is followed by the most important chapter in this book, 127 pages on enolates and phenolates. The remaining five chapters on nitrites, anions of nitro compounds, cyanides, anions of heterocyclics and on other ambident anions are considerably shorter.

The Russian text was translated into English by *J. P. Michael* and was then photoprinted directly from the manuscript. This process has given rise to defects, which make the book difficult to read. On the one hand, the typeface is wearisomely uniform; on the other hand, the numerous and important tables are poorly arranged and explained. This is a very great pity in a book containing the systematic presentation of extensive experimental series. Many tables do not indicate the total yields of the alkylization and acylization reactions and it is only by addition to 100% that it is possible to guess whether the yields reported refer to the relative or absolute amount of C- or O-product. The book is made more difficult to read by the fact that only a few typed formulas are provided; the very few obvious typing errors constitute a positive feature.

The book contains almost a thousand references, chiefly

of results of the reaction of ambident anions with electrophiles. Attempts to interpret and classify the data are primarily made according to the HSAB principle of *Pearson*; the more up-to-date concepts of frontier orbital and charge interaction are largely ignored. There is a lengthy discussion of the influence of the solvent on the structure and reactivity of the salts.

All in all the book is an extensive summary of experimental results from West *and* East. The references close with 17 citations from 1977 and two from 1978. The index (25 pages) is very good and comprehensive.

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Moleküle und Molekülanhäufungen. Eine Einführung in die physikalische Chemie. By *H.-D. Försterling* and *H. Kuhn*. Springer-Verlag, Berlin 1983. xvi, 369 pp., bound, DM 49.00.

This book provides an introduction to physical chemistry that differs in concept from most other introductions. Instead of the usual arrangement based on the practical requirements of traditional university courses, the present book is arranged so that in logical order quantum theory and statistical thermodynamics are presented before classical thermodynamics and the macroscopic description of chemical systems.

Consequently, the first part of the book opens after a short review of the experimental evidence for the quantum structure of matter with a brief and very clear introduction of the basic concepts of the quantum theory. These concepts are then extended to atoms and more complex molecules. This part which provides the basic knowledge for an understanding of the theory of chemical bonding is written so that a good and well-prepared chemistry student can master the material after the first typical undergraduate courses in physics and mathematics. It is certainly desirable to provide chemistry students as early as possible with the basic guides to the nature of chemical bonding, since both the organic and inorganic undergraduate courses make successful use of simple qualitative theoretical models for explaining structure and reactivity of molecules.

The second part of the book goes beyond the properties of individual atoms and molecules. After a clear and detailed discussion of the intermolecular forces, the kinetic theory of gases and the Boltzmann distribution law the concepts of energy, heat, work and entropy are introduced. This provides the basis for the final section which is concerned with the energetics and kinetics of chemical reactions. The book ends with a special section which considers the limitations of the concepts of physical chemistry and also discusses the evolution problem of life from the point of view of physical chemical processes.

This book which is replete with excellent explanatory diagrams and tables is highly recommended, both for its clarity and its readability. It should be of interest not only for chemistry students as a supplementary physical chemistry textbook, but also for research workers in chemistry who would like to renew their knowledge of the basic principles of physical chemistry from a different point of view.

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Environmental Carcinogens: Polycyclic Aromatic Hydrocarbons. By *G. Grimmer*. CRC Press, Boca Raton, FL, USA 1983. 261 pp, bound, $ 81.50.

This book has been written by a total of 13 authors, led by *G. Grimmer* who is an internationally acknowledged authority on the analysis of polycyclic aromatic hydrocarbons (PAH), and covers, in eight chapters, the present state of knowledge concerning PAHs as environmental carcinogens. It largely consists of an updated English translation of "Luftqualitätskriterien für ausgewählte polyzyklische aromatische Kohlenwasserstoffe" (Umweltbundesamt, Berlin 1979).

Following a foreword by *H. von Lersner* and a short introduction by *D. Schmähl* the first chapter (*G. Grimmer* and *J. Misfeld* provides an overview of the strategy for the identification of PAHs as environmental carcinogens. The second chapter, from the pen of the editor alone, consists of, alongside a detailed introduction to the nomenclature, an explanation of the mechanistic aspects of the formation of PAHs during incomplete combustion processes and gives insight into the complicated area of PAH analysis. The following techniques are discussed: 1. extraction of PAHs from environmental samples such as fats, oils, foodstuffs, soot and water, 2. enrichment techniques such as liquid-liquid distribution and chromatography on solid phases, and 3. separation processes, in particular qualitative and quantitative determination by GC, TLC and HPLC. The third chapter *(G. Grimmer)* is devoted to the occurrence of PAHs in the environment. After a detailed presentation of the PAH profile as a function of the production processes (household fires, powered vehicles, cigarette smoke) the reader is provided with detailed, synoptical information concerning the contamination of air, soil, crude oil, sewage sludge and smoked foodstuffs by PAHs. After describing their uptake and distribution (*F. Pott* and *G. Oberdörster*) the fourth chapter covers their metabolism (*G. Grimmer* and *J. Jacob*). Not only the most important classes of metabolites such as phenols, arene oxides, catechols, dihydrodiols and dihydrodiol epoxides—which are thought today to be the actual carcinogens—but also the xenobiotic metabolizing enzymes (monoxygenases, epoxide hydrolases, glutathione transferases, sulfotransferases and UDP-glucuronosyltransferases) are discussed. The fifth and longest chapter (*D. Schmähl* et al.) deals with test systems for investigating the biological activity of PAHs. The short-term tests (Ames test, cell transformation tests and sebaceous gland atrophy test) which have some bearing on the carcinogenic activity of PAHs as well as the long-term tests in animal models (classified in terms of type of application) are discussed in a well arranged review. This is followed by the sixth chapter *(J. Misfeld)* in which in general introduction to the problems of epidemological investigations is followed by a critical review of studies devoted to the topic "lung cancer and air pollution" with particular reference to PAHs. The seventh chapter *(D. Schmähl)* contains a detailed discussion of the question of the transfer of experimental results from short and long-term tests to man. The last chapter *(S. Dobbertin)* contains a "quintessence" of all that has gone before from the standpoint of the discussion of emission limits for PAHs.

The index greatly facilitates the search for information in this interdisciplinary area. Each chapter is equipped with a list of references. However the literature is only covered in detail up to 1979 with the occasional reference from 1980/81. If a second edition is contemplated not only is the correction of several printing errors recommended—e.g. in Chapter 8 the atmospheric concentrations of ben-

zo[a]pyrene are quoted in ng/cm^3 instead of ng/m^3—but also the correction of the figure on p. 149 and the reference to Fig. 47 on p. 138. There is no doubt that this book fills a gap and will be a regular source of reference both for the toxicologist as well as for the scientist who is concerned with polycyclic aromatic hydrocarbons. The large quantities of information concerning various aspects of toxicology presented in this excellently compiled book justify the above average price.

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der Universität Mainz (FRG)

New Books

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High-Resolution X-ray Crystallography— An Experimental Method for the Description of Chemical Bonds

By Klaus Angermund, Karl Heinz Claus, Richard Goddard, and Carl Krüger*

Dedicated to Professor Günther Wilke on the occasion of his 60th birthday

By increasing the accuracy of an X-ray analysis, results are obtained which allow one to go beyond the location of hydrogen atoms and say something about the distribution of electrons in molecules. Using several examples from organic and organometallic chemistry, the methods, problems, and results of this approach are described.

1. Introduction

The spatial arrangement of the electron density in molecules provides a direct route to an understanding of the chemical bond. In the past few years, therefore, there have been numerous theoretical[2] and experimental[3] studies that have endeavored to determine the changes in electron density that result from redistribution of the valence electrons during formation of chemical bonds.[1] Since the standard diffraction techniques used for X-ray structure determination depend on the interaction of X-rays with the electrons of atoms in a crystal lattice,[4] the diffraction patterns obtained are directly related to the distribution of electrons in the crystal and thus to the electron density distribution in the molecules.

This article describes how the electron density distribution in molecules can be observed by increasing the resolution[5] of the X-ray structure determination.[6–9] Using examples from organic and organometallic chemistry, the feasibility and limitations of this relatively new analytical method will be discussed, with particular attention being given to a critical evaluation of such analyses.

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2. Methodological Aspects of High-Resolution X-ray Structure Determination

The total electron density obtained in a carefully performed X-ray structure determination is rather difficult to interpret because it is dominated by the core electrons, as is shown for a substituted anthracene[10] in Figure 1. The total electron density nevertheless contains complete information about the nature of the bonding in the molecule. In order to present this information in a more useful and visible form the concept of electron deformation density (EDD) has been introduced.[11] The EDD represents the change in the electron density that results from the deformation of the spherical charge distribution around free atoms when chemical bonds are formed. Since it is the electrons in the valence shells that are mainly redistributed during the deformation, it is they that contribute most to the EDD. The spherically symmetrical electron density distribution for a free atom can be accurately calculated by theoretical methods, and is subsequently used to calculate the scattering factors used in the standard X-ray structure determination.[12] The sum of all the electron densities of the spherical atoms placed at bonding distances from one another is known as the promolecule density,[13] and the molecule so formed the promolecule.

Figure 2 shows the promolecule density distribution in 9-*tert*-butylanthracene. The difference between the experi-

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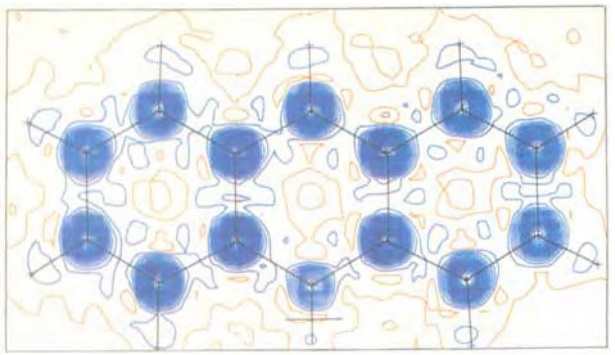


Fig. 1. Total electron density in 9-*tert*-butylanthracene **1**. In this figure as in all the following, blue lines indicate positive EDD and red negative EDD. The zero contour is yellow.

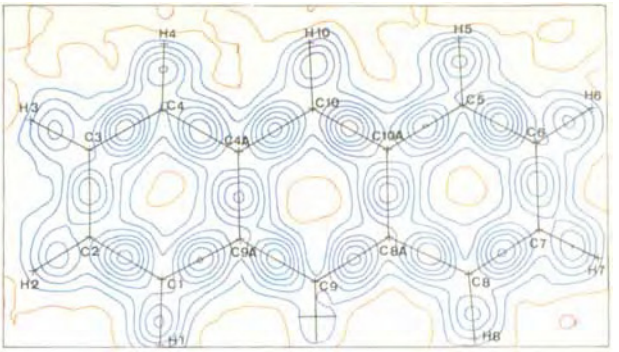


Fig. 3. Deformation density in **1**. Contour lines at 0.1 e/Å^3.

mentally determined or theoretically calculated total electron density, which describes the equilibrium state, and the promolecule density, which corresponds to a hypothetical distribution of electrons, is the EDD. A positive deformation density at a position in a molecule means that there is an increase in electron density over and above the sum of the electron densities of the free, spherically symmetrical atoms. Conversely, a negative deformation density represents a reduction in the corresponding electron density.

Figure 3 shows the deformation density in 9-*tert*-butylanthracene. A positive EDD is found between all bonded atoms. The results of numerous experimental and theoretical studies on a variety of compounds have shown that, depending on the type of atom and bond, not only positive but also negative deformation densities can be observed between atoms bonded to one another.

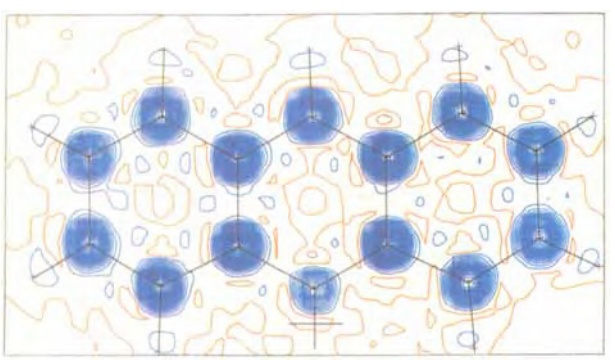


Fig. 2. Promolecule density in **1**.

The fact that a positive EDD is not observed between some types of atoms,[14] particularly those of electronegative elements, does not necessarily imply that there is no bond between these atoms, but rather reflects the difference in the valence configuration between the bonded and the free atom. This can be qualitatively explained by a simple model. When elements such as carbon, nitrogen, oxygen, or fluorine come together and form bonds, their valence configurations change. In the ensuing process electron density can be thought of as being transferred from atomic orbitals to hybrid orbitals situated further away from the atomic nucleus. Table 1 gives the approximate electronic configurations of several elements in their free and orientated (bonded) states. The configurations of the orientated atoms will depend on the type of bonding, and those given in Table 1 serve only as examples.

For the electronegative elements (N, O, F), the transition from spherically symmetric free atoms to bonded atoms also results in the formation of lone pairs. These processes are reflected in the EDD. The EDD in the bonding and lone pair regions can be derived by subtracting the population of a p-orbital in the free atom from that of the corresponding orbital in the orientated atom (see Table 1). According to Table 1, the C–C bond has a positive deformation density, whereas the EDD decreases continuously for N–N, O–O, and F–F. A comparison of the results from such a model with the experimentally determined or theoretically calculated EDD shows that in general it is possible not only to obtain the correct sign of the EDD but also a rough estimate of its value. Conversely, starting from the

Table 1. Simple method for estimating the EDD in the bonding and lone pair regions of molecules containing main group elements. The electron configuration of the orientated atoms were taken from the following molecules or groups: C, ethane; N, hydrazine; O, hydrogen peroxide; F, molecular fluorine; P, PN; S, CS.

Element	Electronic configuration		Difference (B–A) in		Ref.
	Free atom (A)	Orientated atom (B) in molecule	Bond region	Lone pair region	
C	$1s^2 2s^2 p_x^{2/3} p_y^{2/3} p_z^{2/3}$	$1s^2 2(sp^3)^1 (sp^3)^1 (sp^3)^1 (sp^3)^1$	+1/3	–	[15, 1b]
N	$1s^2 2s^2 p_x^1 p_y^1 p_z^1$	$1s^2 2(sp^3)^1 (sp^3)^1 (sp^3)^1 (sp^3)^2$	0	+1	[16]
O	$1s^2 2s^2 p_x^{4/3} p_y^{4/3} p_z^{4/3}$	$1s^2 2(sp^3)^1 (sp^3)^1 (sp^3)^2 (sp^3)^2$	−1/3	+2/3	[17, 14a]
F	$1s^2 2s^2 p_x^{5/3} p_y^{5/3} p_z^{5/3}$	$1s^2 2s^2 p_x^1 p_y^2 p_z^2$	−2/3	+1/3	[18]
P	$1s^2 2s^2 p^6 3s^2 p_x^1 p_y^1 p_z^1$	$1s^2 2s^2 p^6 3s^2 p_x^1 p_y^1 p_z^1$	0	0	[19]
S	$1s^2 2s^2 p^6 3s^2 p_x^{4/3} p_y^{4/3} p_z^{4/3}$	$1s^2 2s^2 p^6 3s^2 p_x^1 p_y^1 p_z^2$	−1/3	+2/3	[19]

EDD it is possible to obtain information about the electronic configuration of the constituent atoms.

In heteronuclear bonds (e.g., C–F) the more electronegative element contributes most to the total electron density and thus appears to determine the EDD. This explains, for example, why bonds involving nitrogen atoms have only slightly positive deformation densities while those involving fluorine have negative values.

Calculated deformation densities for species containing elements from the third row of the periodic table (e.g., PN or CS)[19] show that their bonds have smaller electron deformation densities than the corresponding bonds between lighter elements of the same group. These EDDs can be understood in terms of the small amount of hybridization of the heavier elements in the bonded state.[20]

Further predictions or interpretation of the spatial arrangement of the EDD, particularly in polar bonds and in the region close to transition metals, require consideration of additional effects, such as electronegativity and orbital symmetry. Accordingly, comparison of the magnitude of the EDD in bonds between different elements is not possible and the conclusions drawn from such comparisons may be wrong. It is just as meaningless to compare the EDD of a C–F bond with that of a C–C bond as it is to compare their bond lengths. However, if these aspects are taken into consideration, then a detailed analysis of the experimentally determined EDD provides a good description of the nature of the bonding in a molecule in a low-energy state in the crystal lattice; on the other hand, an interpretation of the theoretically calculated EDD affords a description of the nature of the bonding in the free molecule.

3. Experimental Aspects of High-Resolution X-ray Structure Determination

During the course of every X-ray structure determination, a structural model, consisting of spherically symmetrical non-interacting atoms, is optimized so as to give the best fit between the observed diffracted intensities and the intensities calculated for the model. The total electron density is then calculated by assigning phases, determined from the model, to the measured structure amplitudes. The difference between the observed electron density and the electron density for the model obtained in this way is known as the residual electron density. In favorable circumstances, its spatial distribution allows one to draw conclusions about the electron density distribution in the molecules.[21]

The atomic positions obtained during the refinement process are, however, influenced by the bonding electrons. This effect is particularly pronounced for light atoms, and is clearly illustrated by a comparison of the average C–H bond distances obtained from X-ray diffraction (0.95 Å) with those determined by neutron diffraction (1.08 Å). A more exact determination of the positions of atoms is possible using one of two experimental techniques. In the first method, the exact positions of the atoms are determined by neutron diffraction. This method requires considerable experimental effort and much larger crystals than are needed for the X-ray analysis. Since an additional X-ray structure determination is necessary in order to obtain information about the electron density distribution, problems arise from the difficulty of assimilating the two sets of results, which are necessarily obtained under slightly different experimental conditions. In the second method, the atomic positions are determined using only the X-ray diffraction data by taking advantage of the difference in the scattering ability of the core and valence electrons. A disadvantage of this method is that, in contrast to the neutron diffraction experiment, the determination of the positions of the lighter atoms is more inaccurate than that of the heavy atoms. The first technique[22] has come to be known as the X–N method;[23–27] the second technique is referred to as the X–X method.[28] At the present time the EDD determination of compounds that crystallize in acentric space groups is only possible with extreme difficulty, regardless of which method is used.[29]

The object of a high-resolution study is therefore not to obtain as small a residual electron density distribution as possible but rather to locate accurately all the atoms and to optimize all experimental parameters. Thus, the normal criteria for the estimation of the accuracy of an X-ray structure determination, such as the standard deviations of the atomic and geometrical parameters, are not sufficient for judging the accuracy of an EDD determination; instead, a comparison with theoretical calculations or with structure determinations of chemically similar compounds is necessary.

The experimental and computational effort required for a high-resolution study to allow such a comparison is much greater than that for a standard X-ray structure determination. Symmetry equivalent reflections need to be measured under different experimental conditions in order to eliminate instrumental errors and detect possible double reflections. Since thermal motion of the atoms can lead to a smearing of the observable features in the EDD, as low a measuring temperature as possible is necessary. A temperature of 100 K,[30,31] obtained by cooling the sample with a stream of cold nitrogen gas, has proved to be suitable for the experiments described here. It is essential that this temperature be maintained within a small range (± 0.5 K) over several weeks and that the crystal be kept free of ice.[31] In favorable cases, an effect similar to that of lowering the temperature is achieved when the molecules are held firmly in the crystal lattice by strong intermolecular interactions, such as hydrogen bonds. In such cases, quite acceptable deformation densities have been obtained even at room temperature.[32] A further restriction is that the crystal must be of excellent quality, and its morphology good. In order to correct for absorption effects it is necessary not only to index all the enclosing faces but also to measure them. If it proves necessary to study the substance in a capillary under an inert gas, then an additional correction for the absorption by the glass is essential.[33] Recommendations for experimental precautions have been made by the "Committee on Criteria for Publication of Charge Density Studies."[34] From the above, it is clear that the determination of deformation densities cannot be considered a routine procedure at present.

4. Determination of Deformation Density

4.1. EDDs of Organic Compounds

Several of the experimental difficulties in EDD determinations (see Section 3) are considerably reduced when heavy elements are absent. Organic compounds are thus particularly suited for studying developments in the method, and it was for this reason that the Oxalic Acid Project was initiated.[35] Subsequently, we undertook a comparative study[10] of 9-*tert*-butylanthracene **1**[36] and its valence isomer, 9-*tert*-butyl-9,10[Dewar]anthracene **2**.[37] X-ray structure determinations under standard conditions had shown that there was no molecular disorder in the crystals and that the hydrogen atoms could be unequivocally located. Both these factors are among the most important criteria for determining the crystal quality. If these conditions are not fulfilled, then a satisfactory EDD determination is rendered considerably more difficult.

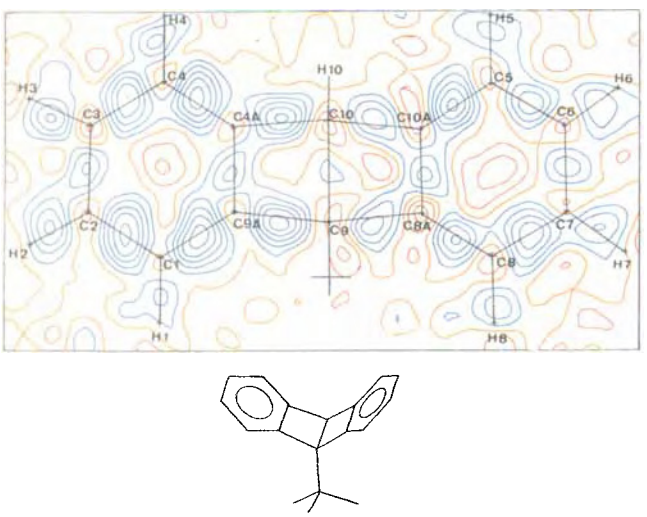


Fig. 4. Deformation density in **2**. Contour lines at 0.1 e/Å^3.

Figure 4 shows the deformation density of **2** in a similar orientation to the EDD of **1** (Fig. 3, Section 2). In **1** there is, as expected, a build up of electron density between all bonded atoms, and the EDD maxima lie on axes drawn between the atomic nuclei. A quantitative analysis (Fig. 5) shows that the observed EDD is directly proportional to bond parameters obtained by semiempirical methods, such as the bond order (calculated by HMO techniques for the idealized unsubstituted anthracene)[38] and the overlap

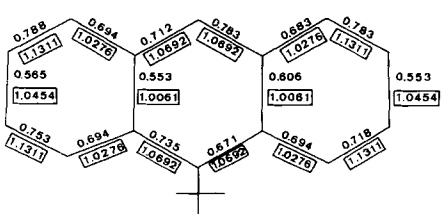


Fig. 5. Comparison of the experimentally determined EDD in the C–C bonds (e/Å^3) with overlap populations (boxes) calculated for idealized **1** by extended Hückel methods.

population (calculated by extended Hückel methods for the idealized 9-*tert*-butylanthracene).[39] Deviations from exact proportionality are only observed in the central ring of the anthracene framework. This is not planar, as was assumed in the calculations, but has a fold angle of 166.2°. The distortion can be attributed to steric interaction resulting from the large substituent at the 9-position.

In contrast to **1**, bent bonds are observed in the entire central bicyclic system of the corresponding Dewar isomer **2**. Electron density maxima are not found along the lines joining the atomic nuclei of bonded atoms, but are shifted about 0.2 Å outward.[21,40] In addition, the locations of the peak maxima in bonds involving the carbon atom at the 9-position are significantly displaced in the direction of the bridging group. This mirrors the effect that is observed in bonds between atoms with different electronegativities. The Dewar bond (C9–C10 1.623(2) Å) is also strongly bent, as can be seen in sections through the bond (Fig. 6). The bond length and the EDD suggest that this is the weakest bond in the molecule. Moreover, as can be seen in Figure 6 left, there is an additional interaction between the Dewar bond and the bonds at C9–C11 and C10–H10. The dihedral angle between the two four-membered rings along the C9–C10 bond is 113°.

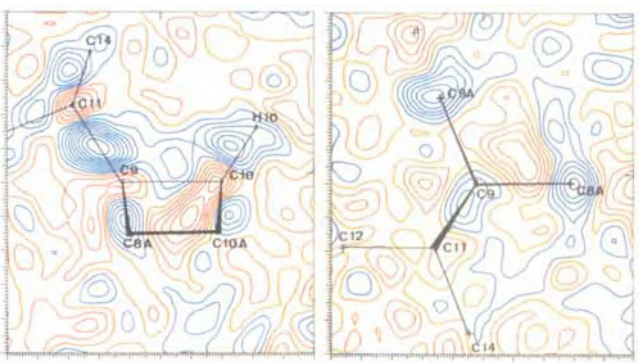


Fig. 6. Left: longitudinal section through the Dewar bond C9–C10 in **2**. Contour lines at 0.05 e/Å^3. The atoms C9, C10, C11, and H10 lie in the plane of the paper. Right: cross section through the Dewar bond. The plane cuts the C9–C10 bond at its midpoint. Contour lines at 0.05 e/Å^3.

The deformation densities given in Fig. 6 can be reproduced by ab initio calculations[41] on the model compound 1-methyl-1,4[Dewar]benzene. The corresponding sections are given in Figure 7. Very accurate ab initio calculations are necessary in order to reproduce the experimentally observed EDD. Comparison of various calculations[42] have shown that it is essential to use a large set of basis functions of at least double-ζ quality. At the present, therefore, ab initio calculations are possible for only a relatively restricted range of compounds.[2]

Nevertheless, it has been found very worthwhile to compare experimental with theoretical results to determine the effects of intermolecular interactions on the EDD of molecules in a crystal lattice since these are not usually taken into account in the ab initio calculations. The analysis of 1,2,3-triazine **3**[43,44] serves to illustrate the influence of intermolecular interactions in the crystal lattice on the EDD of the molecule. Figure 8 shows the experimentally deter-

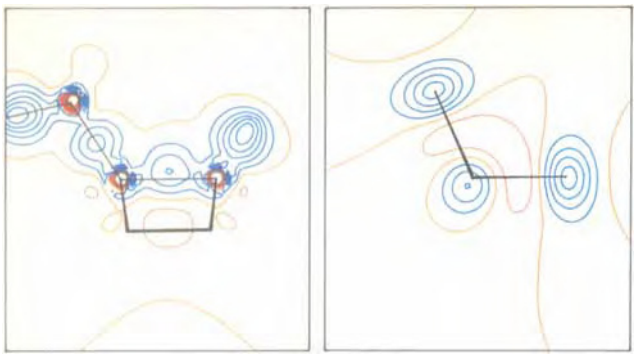


Fig. 7. Left: longitudinal section through the Dewar bond in 1-methyl-1,4[Dewar]benzene. The orientation corresponds to that in Figure 6 left. Ab initio SCF calculation with a double-ζ basis set. Contour lines at 0.1 e/Å^3. Right: cross section through the Dewar bond in 1-methyl-1,4[Dewar]benzene. The orientation corresponds to that in Figure 6 right. Ab initio SCF calculation with a double-ζ basis set. Contour lines at 0.1 e/Å^3.

mined and the theoretically calculated[45] deformation density of triazine. The theoretical deformation densities, shown in Figure 8 middle and right, have a mirror plane of symmetry passing through C2 and N2. This symmetry is also reflected in the observed bond distances (Fig. 9). According to crystallographic criteria, however, the environment of the molecule in the crystal lattice is asymmetric; this is also clearly seen in the experimentally determined deformation density (Fig. 8 left). It is immediately apparent that, in contrast to Figure 8 right, the EDDs in the C1–H1 and C3–H3 bonds differ, and the lone-pair electrons at N1 and N3 have different EDDs and spatial distributions.

An analysis of the packing of the molecules in the crystal shows that, as in 1,3,5-triazine,[46] the molecules stack in parallel layers containing triazine molecules bonded to one another by relatively long C–H···N hydrogen bonds. These layers are held together by both C–H···N hydrogen bonds and π-π bonding interactions[47] (Fig. 10). The atoms involved in these intermolecular interactions are those whose deformation density shows the greatest deviations from the theoretical density calculated for the free molecule.

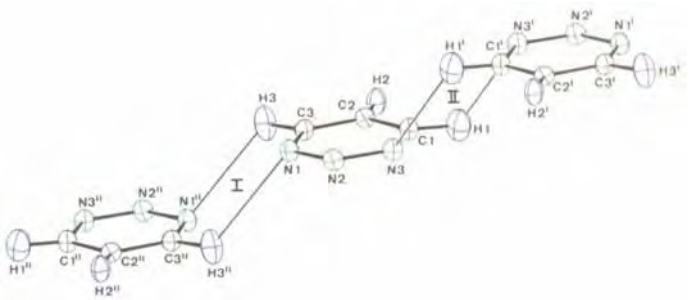


Fig. 10. Interaction between individual layers in crystalline **3**. **I** and **II** indicate the two crystallographically independent but chemically equivalent C–H···N hydrogen bonds. Each layer is represented by one triazine molecule.

Figure 11 shows the deformation density in the intermolecular regions where these interactions occur. The lone-pair electrons of N1 and N3 are clearly directed towards H3″ and H1′ on neighboring molecules. The observation of these weak interactions lies at the present experimental

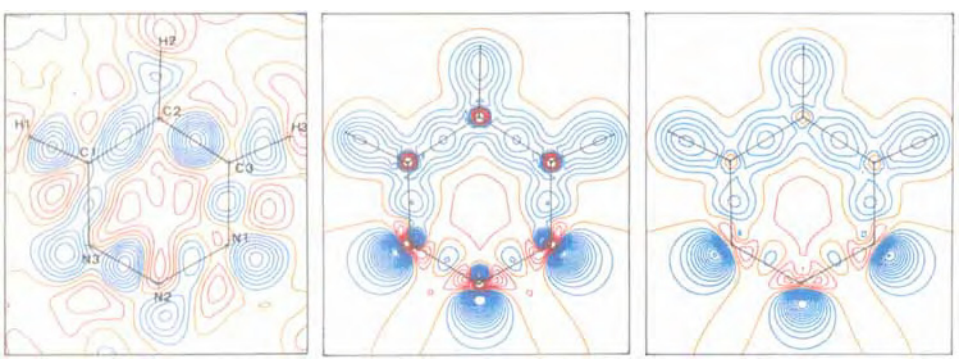


Fig. 8. EDD in **3** (mean plane through the N and C atoms). Contour lines at 0.1 e/Å^3. Left: experimentally determined EDD. Middle: theoretical static EDD (no thermal motion). Ab initio SCF calculation with a double-ζ basis set. Right: theoretical dynamic EDD (thermally smeared). Ab initio SCF calculation with double-ζ basis set.

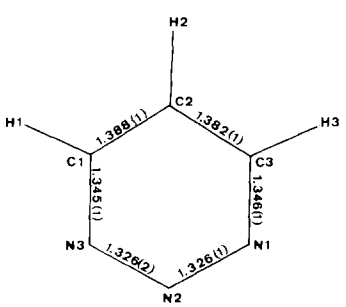


Fig. 9. Bond distances in **3** ([Å], standard deviations in parentheses).

limit of the technique. In this case, it is possible to estimate the experimental error. The two intermolecular interactions occur in regions that are crystallographically independent but chemically equivalent (Fig. 11). Since it is unlikely that experimental inaccuracies will manifest themselves in a similar manner in different regions of the unit cell, the agreement between the two deformation densities gives a measure of their accuracy.

The two-dimensional sections are rather unsuitable for the study and display of what are in general three-dimensional intermolecular interactions and of their effect on the

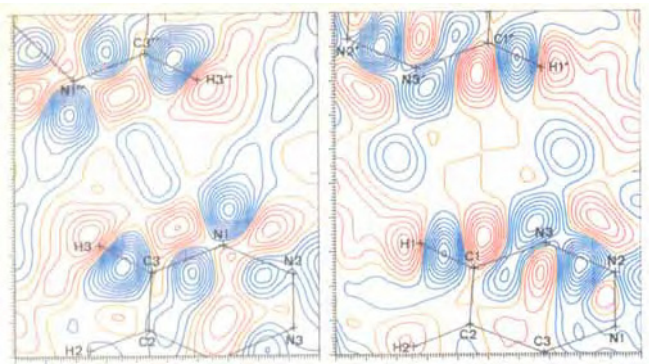


Fig. 11. The intermolecular EDD in crystalline **3** corresponding to Figure 10. Left: **I**: plane through N1, H3, N1'', H3''. Right: **II**: plane through N3, H1, N3', H1'.

intramolecular EDD. The influence of packing effects on the intramolecular EDD can be particularly well represented by a three-dimensional representation[48] (Fig. 12 left and middle), especially since the novel technique used here enables several EDD distributions to be shown simultaneously (Fig. 12 right). As shown in Fig. 12 right, the differences in the EDD in the lone pair regions are particularly large where the hydrogen bonds are formed.

The effect observed here is in disagreement with theoretical calculations on other systems, which predict the probability of observing intermolecular interactions to be quite small.[2a,49,50] Further experiments are, however, necessary in order to clarify this situation. In studies on organometallic compounds, we have already obtained evidence of the influence of packing effects on the EDD of the molecules in a crystal lattice. It was found that in substituted metal carbonyl complexes, the lone pairs on the oxygen atoms of the carbonyl groups are polarized in the direction of the neighboring molecules.[51] The differences between experiment and theory indicate that particular attention needs to be paid to intermolecular interactions when interpreting the results of a high-resolution study, even in those cases where such interactions cannot be inferred from the results of a normal X-ray structure determination.

4.2. EDDs of Organometallic Compounds

In the study of organometallic compounds, numerous additional experimental problems arise. When a heavy atom is present, the lighter atoms make only a small contribution to the total scattering of the molecule. This is one of the reasons for the increased difficulty in locating the light atoms using the X–X method. In addition, as the size of the heavy atom increases, physical effects such as absorption, anomalous dispersion, and thermal diffuse scattering of the X-rays become more important, and the measured intensities must be corrected for these. Insufficiently corrected data give poor EDD distributions with little or no information content.

In order to reduce errors to an absolute minimum, we restricted our studies at first to organometallic compounds containing metals from the fourth period (3d elements). Based on experience gained during studies on the organic compounds described above, and on oxalic acid **4** (Oxalic Acid Project)[35] an optimization of the necessary corrections was made for μ-octatetraenylbis[(η^5-cyclopentadienyl)chromium] **5**. In this study, data sets from four crystals of different sizes, grown from different solvents, were used. From the analyses, we obtained four EDD distributions, which differed only slightly in their absolute values (the number of contour lines) but which were otherwise equivalent.[55] It was shown that, in spite of the different corrections in each case, the spatial distribution of the EDD in organometallic compounds could be sufficiently well determined to allow interpretation.

The technique of measuring several crystals used here requires considerably more experimental and computational effort than is needed for organic molecules. We therefore developed a strategy that allowed us to estimate the accuracy of a single measurement. For molecules containing many electrons, a comparison of the results with those from ab initio calculations, as was the case with the organic compounds described in Section 4.1, is not always possible because of the considerable computation involved for such molecules. The following three criteria have, however, proved useful for estimating the accuracy of a single EDD determination:

1) Different transition metals with similar electronic configurations should show similar EDD distributions.

2) This should also be valid for chemically similar molecular fragments in different organometallic compounds, thus introducing the concept of the internal standard. A necessary condition is that the EDD distribution of the fragment be known from a previous study. The validity of

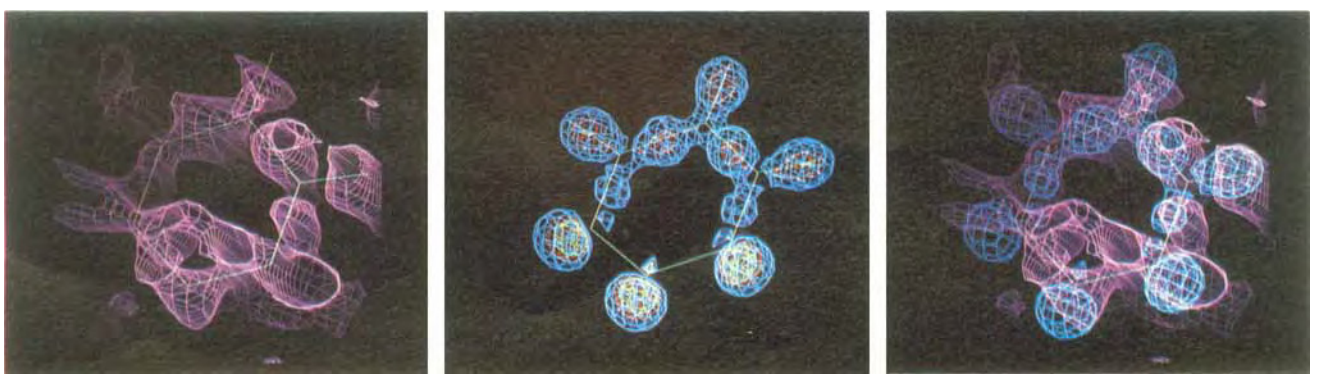
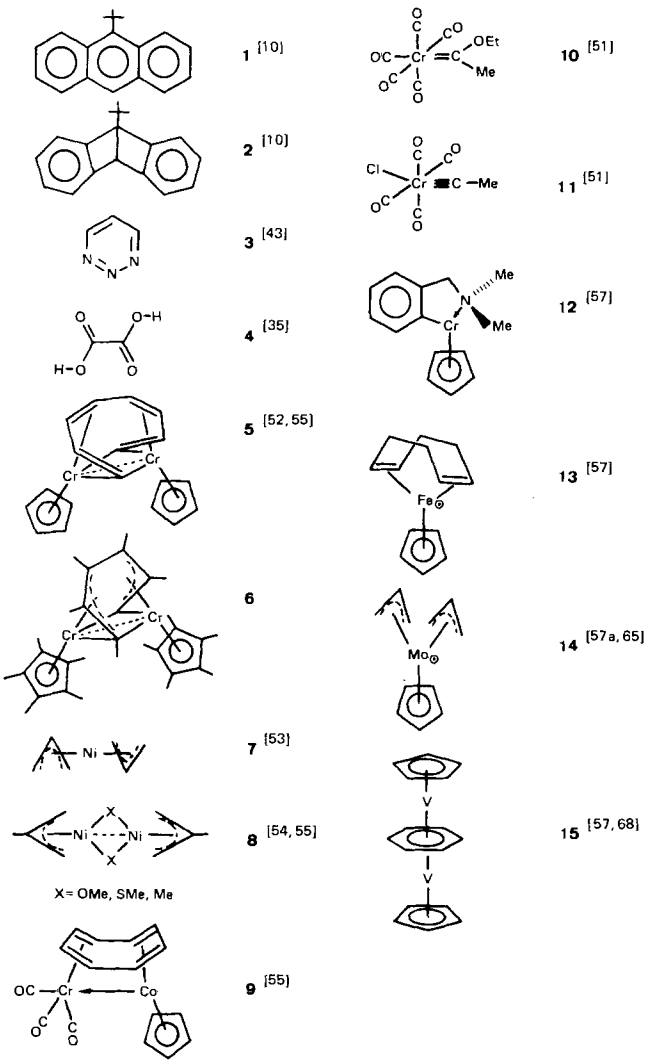


Fig. 12. Spatial representation of the electron deformation density in **3**. Contour surfaces at 0.2 e/Å^3. Left: experimentally determined EDD. Middle: theoretical EDD, calculated as for Figure 8 middle. Right: superposition of experimentally determined and theoretically calculated EDDs.

this assumption may be tested by comparing the EDDs obtained for the molecular fragment from different studies.

3) The EDDs of chemically equivalent but crystallographically independent parts of a molecule may also be compared. In such a case, the presence of a non-crystallographic symmetry allows an estimation of the experimental errors, even when comparable molecular fragments from other studies are not available (cf. intermolecular EDD in 1,2,3-triazine, Section 4.1).

These criteria are considered when we select a compound for study.



Besides EDD determinations on mononuclear organometallic complexes (e.g., **7**), several binuclear organometallic complexes (e.g., **8** and **9**) were studied in order to shed some light on the EDD distribution in metal-metal bonds. The compounds **5**[55] and **6**[56] also belong to this series. In the binuclear complex **5** there are four EDD maxima arranged in a plane about each of the symmetry-independent chromium atoms, 0.7–0.8 Å from the metals. Approximately perpendicular to the maxima and at about the same distance from the metal are two minima, one on each side of the plane. Each metal is thus surrounded by an approximate octahedron of lobes with the minima lying almost along the Cr–Cr axis (Fig. 13).

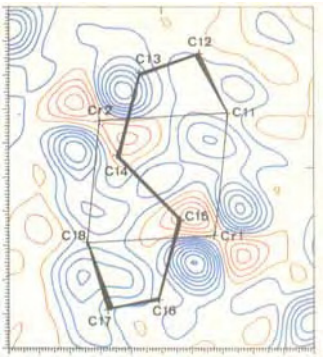


Fig. 13. Experimentally determined EDD in the plane of the metal-metal bond in **5**. Cr1, Cr2, C11, and C18 lie in the plane. Contour lines at 0.1 e/Å^3.

In complex **6** we found a planar arrangement of four EDD minima around each symmetry-equivalent chromium atom and two maxima perpendicular to these (Fig. 14), exactly opposite to that observed in compound **5**. The fact that the EDD distributions in the two chemically equivalent but crystallographically independent halves of **5** are similar (Fig. 13) and that the EDD distribution in the cyclopentadienyl ring in **6** is comparable to that observed in **5** and other compounds, supports the existence of EDD minima along the Cr–Cr axis. Further interpretation, particularly with regard to the bonding, requires additional experimental and theoretical studies on chemically similar compounds.

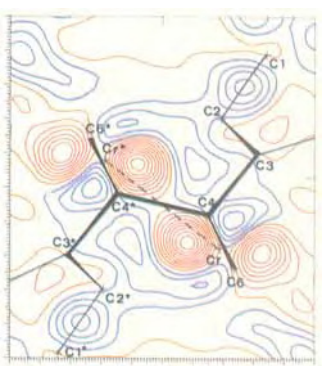


Fig. 14. Experimentally determined EDD in the plane of the metal-metal bond in **6**. Cr, Cr*, C2, and C2* lie in the plane. Contour lines at 0.1 e/Å^3.

We have also studied transition-metal complexes in which the metals are present in unusual electronic configurations (e.g., **8** and **9**) or in which an exact description of the nature of the bonding in novel ligands is required (e.g., **10** and **11**).

Compound **12**,[58] which was studied because of its unusual chemistry, belongs to the first group. In this case, an ab initio study is available for comparison.[59] The molecular structure is shown in Figure 15, which also gives several interatomic distances. The EDD distribution in a plane passing through the metallacycle is shown in Figure 16. The experimental and theoretical methods give essentially the same results. The agreement can be improved when thermal motion is taken into account in the theoretical cal-

culations (Fig. 16 right). Both the experimental and theoretical EDD distributions show an octahedral arrangement of maxima around the chromium atom, which lie 0.5–0.8 Å from the metal. The Cr atom is bonded to the ligand via a $Cr-C_{sp^2}$ bond and the aromatic π system appears to be delocalized over the chromium atom and the nitrogen

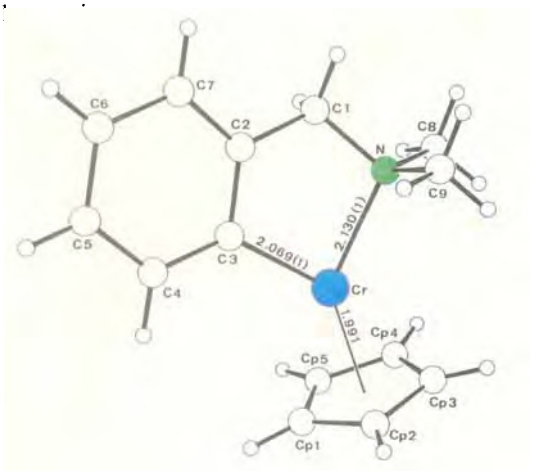


Fig. 15. Crystal structure of **12** (distances [Å]).

Application of several additional techniques allows further information to be obtained from the measured diffraction data. A direct integration of the electron density about the chromium atom[60] gave its charge as +0.3, and refinement of the valence shell populations[61] (Cr: $3d^4 4s^2$, N: $2s^2 2p^3$, and O: $2s^2 2p^4$) for a fixed total charge of zero on the molecule gave +0.43(3). These results are in accord with the theoretical calculations. Figure 17 shows a section of the EDD through two bonds in the aromatic system of the six-membered ring. Elongation of the electron deformation density of the C–C bonds in a direction perpendicular to the plane of the arene is clearly visible and is due to the π system. Although this is the first example where this has been observed in an organometallic compound, such distorted EDD distributions are already known from corresponding studies of organic compounds.[1a,62]

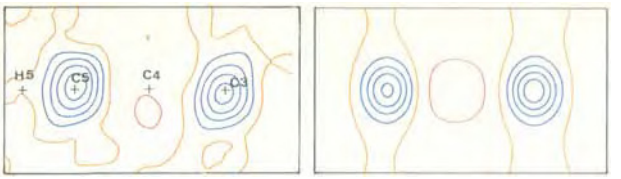


Fig. 17. Section through the benzene ring in **12**. Plane cuts the bonds C5–C6 and C2–C3 at their midpoints. Contour lines at 0.1 e/Å³. Left: experimentally determined EDD. Right: theoretical static EDD, calculated as for Figure 8 middle.

The effectiveness of the technique for clarifying the nature of the bonding in organometallic compounds will be illustrated with three further examples. It will thereby become clear that the high-resolution technique allows more than the usual interpretation of bond distances and angles.

In the two isoelectronic, paramagnetic 17e complexes 1,4-cyclooctadienyl-η^5-cyclopentadienyliron **13**[63] (Fig. 18) and bis(η^3-allyl)-η^5-cyclopentadienylmolybdenum **14**[64]

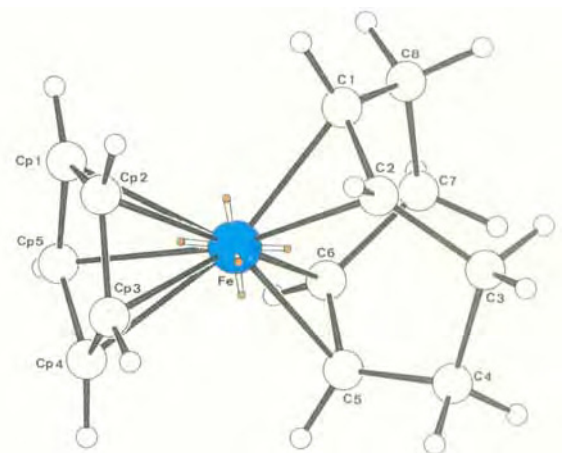


Fig. 18. Molecular structure of **13**, showing the EDD maxima around the iron atom.

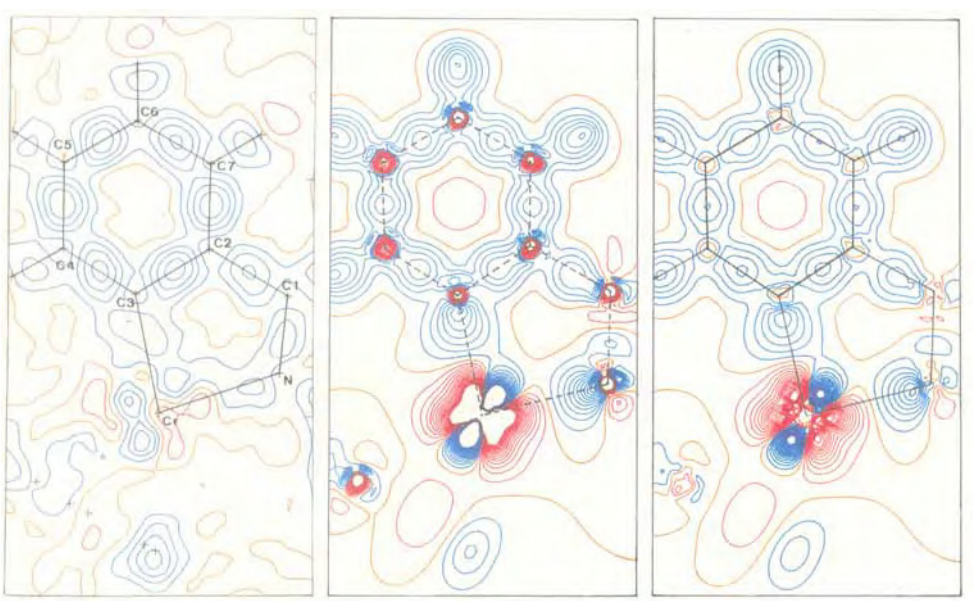


Fig. 16. EDD in the plane of the metallacycle in **12**. Contour lines at 0.1 e/Å³. Left: experimentally determined EDD. Middle: theoretical static EDD, calculated as for Figure 8 middle. Right: theoretical dynamic EDD, calculated as for Figure 8 right.

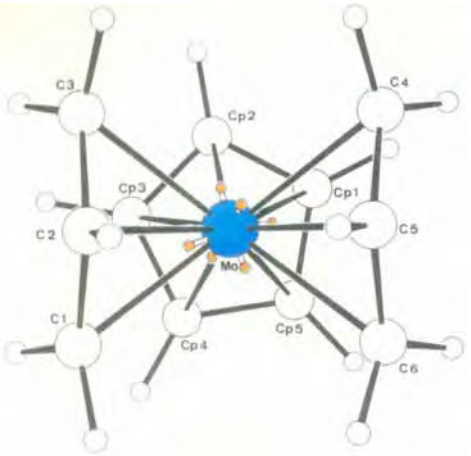


Fig. 19. Molecular structure of **14** (isoelectronic with **13**), showing the EDD maxima around the molybdenum atom.

(Fig. 19), there is also an octahedral distribution of EDD maxima around each metal atom (see Fig. 20 and 21). In both compounds one maximum is directed towards the cyclopentadienyl ring, and another, on the opposite side of the metal, is directed between the ligands. Whereas in **13** there is no interaction of this lobe with the ligands, in **14** there is a steric interaction with the *meso* hydrogen atom on the allyl group, which results in a distortion of the octahedral distribution of the EDD around the metal. As a consequence of the retention of linearity of EDD maxima on opposite sides of the metal, an asymmetry in the cyclopentadienyl ring is induced, which manifests itself in different bond lengths in the five-membered ring. The C–C bonds nearest to the EDD maximum have a higher EDD and are shorter than the other C–C bonds in the ring. The sterically determined asymmetric distortion of the EDD on the transition metal thus provides a possible explanation for the observed differences in the C–C bond distances, which have not yet been satisfactorily explained.

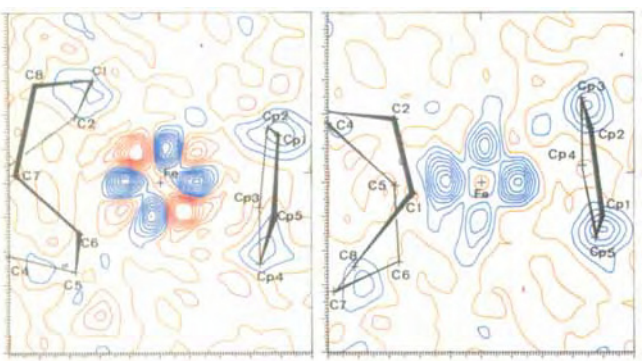


Fig. 20. Sections through the EDD maxima around the iron atom in **13**. Contour lines at 0.1 e/Å^3. Left: plane through the iron atom and the olefinic double bonds of the cyclooctadiene ligand. Right: plane perpendicular to that on the left.



Fig. 21. Section through the EDD maxima around the molybdenum atom in **14**.

The spatial arrangement of the four remaining equatorial EDD maxima in the two complexes is such that when viewed from the direction of the five-membered ring one peak eclipses one of the metal-carbon bonds to the cyclopentadienyl ligand, while the remaining three are directed between the ligands. The X-ray structure determination of the lithium adduct of **13**[66] (Fig. 22) shows that the least sterically hindered maximum is the preferred site of electrophilic attack; the position of lithium corresponds exactly to that of this EDD maximum. Thus it appears possible to determine positions of chemical attack in molecules by studying their electron deformation densities.

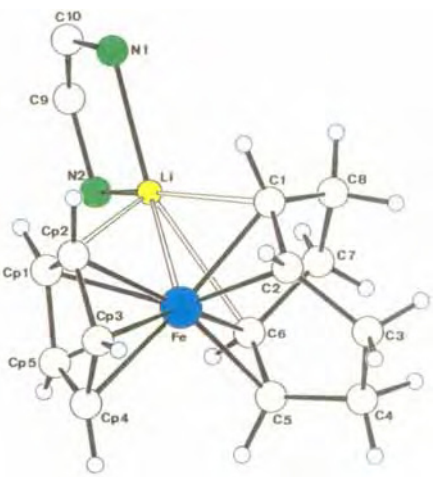


Fig. 22. Molecular structure of the 18e lithium adduct of **13**.

The stereochemical influence of the EDD distribution around transition metals provides a possible explanation for the nature of the bonding in the novel triple-decker complex **15**[66] (Fig. 23). The compound has 26 electrons in the valence shell and therefore does not obey the stability rules for triple-decker complexes put forward by *R. Hoffmann* et al.[69] According to these rules, triple-decker complexes with 30 and 34 valence electrons should be particularly stable. Closer inspection of the EDD in **15** (Fig. 24), whose structure is characterized by a center of symmetry in the central benzene ring, provides a possible explanation for the nature of the bonding in this type of compound.

As in complexes **13** and **14**, the metal atom in **15** is surrounded by an octahedral distribution of EDD maxima. The geometry of the central part of the molecule (V–V* distance 3.400(1) Å; V–C(benzene) average distance 2.236(5) Å) is such that two EDD maxima come close to one another across the center of the benzene ring. The observed distortion of the octahedra around the vanadium atoms can be explained in terms of repulsion of the two

adjacent EDD maxima since they approach one another to within 2.10 Å. The consequences of such a rearrangement of the lobes around the metal on the total bonding system are extensive. The central benzene ring can no longer be considered as a 6-electron ligand, but rather must be viewed as two 3-electron ligands due to the induced asymmetry. The result is particularly noticeable in the EDD in

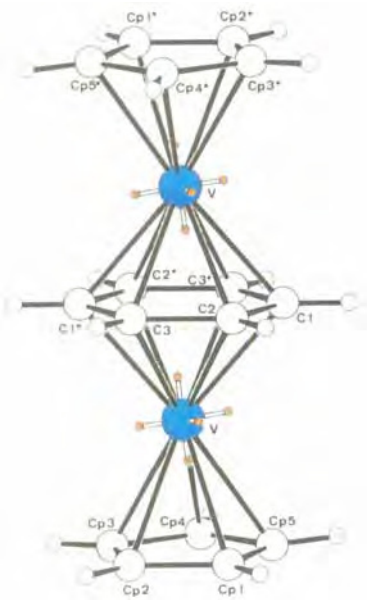


Fig. 23. Molecular structure of the triple-decker complex **15**, showing the EDD maxima around the vanadium atoms.

the plane of the six-membered ring (Fig. 24 right). A change in the bond lengths corresponding to such a distortion can only be observed in the bonds V–C1 (2.227(1) Å) and V*–C1 (2.243(1) Å). As in **13** and **14**, the reorientation of the octahedral EDD distribution in **15** results in an induced asymmetry in the cyclopentadienyl rings. Such an induced asymmetry in the bonding of the five-membered ring could possibly be the reason why the commonly observed disorder of the cyclopentadienyl ligands in sandwich complexes is not observed in this compound. The nature of the bonding in the triple-decker complex **15** can be simply explained, therefore, in terms of a separation of the π-system of the benzene ring into two three-electron units, with the assumption of 13e vanadium atoms.

5. Conclusion

The examples from organic and organometallic chemistry described here show that the experimental determination of the electron deformation density in molecules provides the chemist with a laborious, but none the less powerful technique for studying chemical compounds. This technique, together with the study of reaction paths[71] by the statistical evaluation of structural data from databases,[70] are two of the recent developments in the field of structure determination which are likely to lead to further interesting discoveries.

Many of the results described in this article result from a successful collaboration with numerous colleagues who have provided us with suitable samples. We extend our thanks to them. We are particularly indebted to the director of our institute, Prof. Dr. G. Wilke, for the continuous and generous support of our work. We also thank the Deutsche Forschungsgemeinschaft and the Max-Planck-Gesellschaft for financial support and grants.

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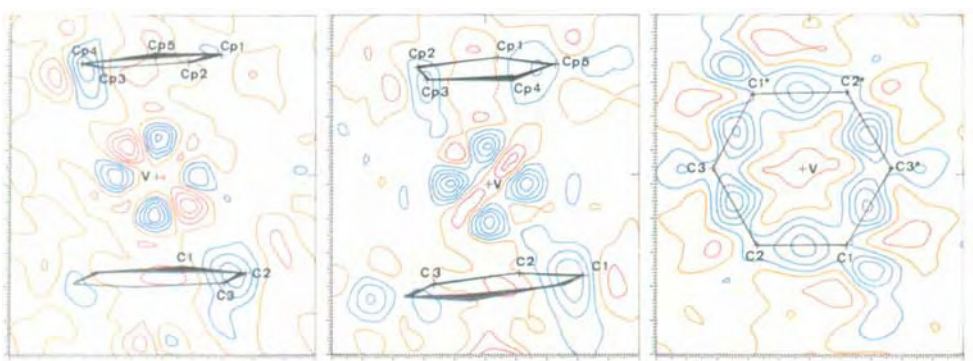


Fig. 24. Experimentally determined EDD in **15**. Contour lines at 0.1 e/Å^3. Left and middle: sections through the EDD maxima around the vanadium atom. Right: EDD in the plane of the central benzene ring.

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[36] **1**: $C_{18}H_{18}$, $P2_1/c$, $a = 11.137(1)$, $b = 6.8927(8)$, $c = 17.792(1)$ Å, $\beta = 107.681(5)°$, $T = 100$ K, $Z = 4$, $\rho_{calcd.} = 1.20$ g/cm^3, $\mu(Mo_{K\alpha}) = 0.63$ cm^{-1}. Enraf-Nonius CAD4 diffractometer; 42375 measured reflections, averaged to 6805 ($R_{av.} = 0.022$), of which 4587 were observed ($I \geq 2\sigma(I)$): $R = 0.040$, $R_w = 0.049$ ($w = 1/\sigma^2(F_0)$) for 326 parameters. CSD 51238 [72].
[37] **2**: $C_{18}H_{18}$, $P2_1/c$, $a = 6.080(1)$, $b = 17.210(5)$, $c = 13.221(2)$ Å, $\beta = 104.69(1)°$, $T = 100$ K, $Z = 4$, $\rho_{calcd.} = 1.16$ g/cm^3, $\mu(Mo_{K\alpha}) = 0.61$ cm^{-1}. Enraf-Nonius CAD4 diffractometer; 25312 measured reflections, averaged to 6263 ($R_{av.} = 0.025$), of which 3816 were observed ($I \geq 2\sigma(I)$): $R = 0.043$, $R_w = 0.038$ ($w = 1/\sigma^2(F_0)$) for 326 parameters. CSD 51238 [72].
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[44] **3**: $C_3H_3N_3$, $P\bar{1}$, $a = 5.7688(4)$, $b = 6.8732(6)$, $c = 5.6725(4)$ Å, $\alpha = 110.080(6)$, $\beta = 113.947(5)$, $\gamma = 95.302(6)°$, $T = 100$ K, $Z = 2$, $\rho_{calcd.} = 1.45$ g/cm^3, $\mu(Mo_{K\alpha}) = 0.96$ cm^{-1}. Enraf-Nonius CAD4 diffractometer; 9046 measured reflections, averaged to 2269 ($R_{av} = 0.027$), of which 2061 were observed ($I \geq 2\sigma(I)$): $R = 0.040$, $R_w = 0.054$ ($w = 1/\sigma^2(F_0)$) for 82 parameters. CSD 51238 [72].
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[55] R. Goddard and C. Krüger in [1a].
[56] **6**: $C_{32}H_{48}Cr_2$, C2/c, $a = 14.569(3)$, $b = 10.720(2)$, $c = 18.333(1)$ Å, $\beta = 102.693(7)°$, $T = 100$ K, $Z = 4$, $\rho_{calcd} = 1.28$ g/cm^3, $\mu(Mo_{K\alpha}) = 7.76$ cm^{-1}. Enraf-Nonius CAD4 diffractometer; 22542 measured reflections, averaged to 7189 of which 5085 were observed ($I \geq 2\sigma(I)$): $R = 0.033$, $R_w = 0.035$ ($w = 1/\sigma^2(F_0)$) for 250 parameters. CSD 51238 [72].
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[58] **12**: $C_{14}H_{17}NCr$, $P2_1/n$, $a = 6.211(1)$, $b = 12.837(2)$, $c = 16.023(1)$ Å, $\beta = 99.113(9)°$, $T = 100$ K, $Z = 4$, $\rho_{calcd} = 1.32$ g/cm^3, $\mu(Mo_{K\alpha}) = 8.60$ cm^{-1}. Enraf-Nonius CAD4 diffractometer; 13494 measured reflections, averaged to 6593 ($R_{av} = 0.023$), of which 5155 were observed ($I \geq 2\sigma(I)$): $R = 0.027$, $R_w = 0.034$ ($w = 1/\sigma^2(F_0)$) for 213 parameters. CSD 51238 [72].
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[63] **13**: $C_{13}H_{17}Fe$, $P2_1/a$, $a = 11.269(1)$, $b = 7.3863(6)$, $c = 12.7368(5)$ Å, $\beta = 103.051(5)°$, $T = 100$ K, $Z = 4$, $\rho_{calcd} = 1.47$ g/cm^3, $\mu(MO_{K\alpha}) = 14.1$ cm^{-1}. Enraf-Nonius CAD4 diffractometer; 18637 measured reflections, averaged to 10687 ($R_{av} = 0.015$), of which 6845 were observed ($I \geq 2\sigma(I)$): $R = 0.027$, $R_w = 0.030$ ($w = 1/\sigma^2(F_0)$) for 195 parameters. CSD 51238 [72].
[64] **14**: $C_{11}H_{15}Mo$, $P2_1/a$, $a = 11.078(1)$, $b = 7.371(1)$, $c = 12.390(1)$ Å, $\beta = 102.376(9)°$, $T = 100$ K, $Z = 4$, $\rho_{calcd} = 1.63$ g/cm^3, $\mu(MO_{K\alpha}) = 12.4$ cm^{-1}. Enraf-Nonius CAD4 diffractometer; 27178 measured reflections, averaged to 6845 ($R_{av} = 0.038$), of which 5397 were observed ($I \geq 2\sigma(I)$): $R = 0.021$, $R_w = 0.024$ ($w = 1/\sigma^2(F_0)$) for 198 parameters. CSD 51238 [72].
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[67] **15**: $C_{16}H_{16}V_2$, $P2_1/n$, $a = 6.0648(7)$, $b = 7.9125(9)$, $c = 13.134(9)$ Å, $\beta = 98.134(9)°$, $T = 100$ K, $Z = 2$, $\rho_{calcd} = 1.62$ g/cm^3, $\mu(Mo_{K\alpha}) = 14.0$ cm^{-1}. Enraf-Nonius CAD4 diffractometer; 21884 measured reflections, averaged to 3304 ($R_{av.} = 0.016$), of which 2915 were observed ($I \geq 2\sigma(I)$): $R = 0.019$, $R_w = 0.026$ ($w = 1/\sigma^2(F_0)$) for 154 parameters. CSD 51238 [72].
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Organocobalt Compounds in the Synthesis of Pyridines—An Example of Structure-Effectivity Relationships in Homogeneous Catalysis**

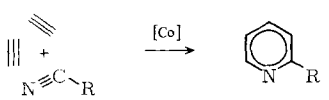
By Helmut Bönnemann*

Dedicated to Professor Günther Wilke on the occasion of his 60th birthday

The cocyclization of alkynes with cyano compounds using organocobalt catalysts of the type [YCoL] has evolved into a versatile and technically useful method for synthesizing pyridine and its derivatives. An important advance came with the realization that the organo group Y remains attached to the cobalt throughout the catalytic cycle. This opened up the possibility of optimizing the catalyst by varying the controlling ligand Y.

1. Introduction

Pyridine and its derivatives are technically important fine-chemicals. Their isolation from coal tar is decreasing, whereas their manufacture by synthetic methods has increased rapidly since 1950: in 1958, ca. 3700 t of pyridine and its derivatives were produced in the USA; by 1978, the yearly production had reached 14000 t, and, in 1980, it was already in excess of 16000 t. In the coming years the annual growth is expected to be 4%.[1] Aside from the parent compound most importance attaches to 2-methyl-, 2-ethyl-, 2-vinyl- and 2-amino-pyridine, all of which can be prepared selectively and in one step from acetylene and the appropriate cyano compound using soluble organocobalt catalysts [Eq. (1)].

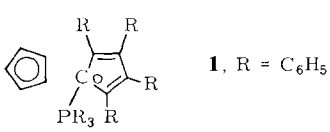


(1)

R = H, CH_3, $HC{=}CH_2$, NH_2

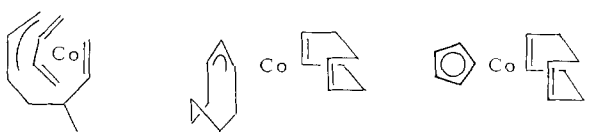
[Co] = soluble cobalt catalyst

As long ago as 1876, *Sir William Ramsay*[2] obtained small amounts of pyridine on passing acetylene and hydrogen cyanide through a red-hot tube. In 1973, *Yamazaki* and *Wakatsuki*[3] first reported the homogeneous catalytic cycloaddition of alkynes and nitriles using the phosphane-stabilized cobalt(III) complex **1**.



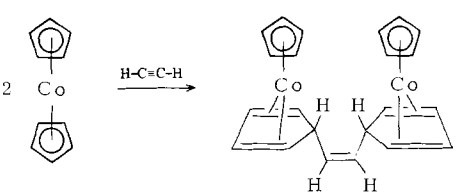
1, R = C_6H_5

At the same time we[4] observed the catalyzed cocyclization [Eq. (1)] on cobalt catalysts prepared in situ, as well as on easily accessible organocobalt-diolefin complexes of the type **2**, **3**, and **4**.



2 **3** **4**

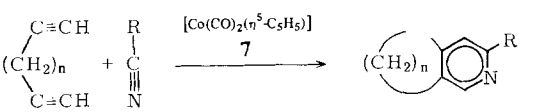
The Japanese authors later turned to cobaltocene **5**,[5,6] since the phosphane complex **1** proved to be unsuitable for practical purposes. *Hardt* (Lonza AG) developed various procedures for preparing pyridine derivatives with **5** as the catalyst.[7] An elegant model reaction by *Yamazaki* and *Wakatsuki*[5] showed that cobaltocene can be regarded as the precursor for the actual catalyst complex **6**: prior to the catalysis, **5** is converted by alkyne into an η^5-diene complex [Eq. (2)].



5 **6**

(2)

Vollhardt et al.[8,9] incorporated α,ω-diynes and nitriles in cobalt-mediated [2+2+2]-cycloadditions [Eq. (3)].



n = 3,4,5; R = alkyl, aryl, etc.

8

(3)

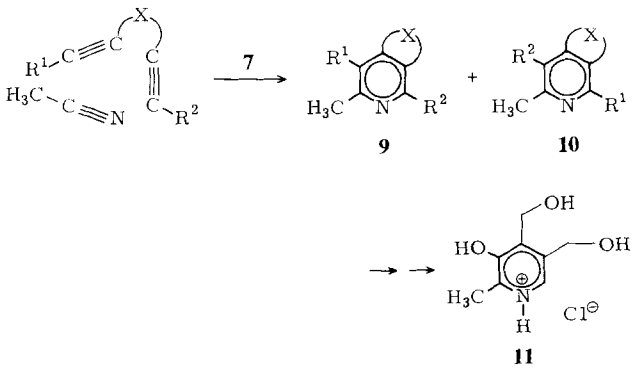
Using this variant of the cobalt-catalyzed cycloaddition, *Schleich* et al.[10] opened up a new route to pyridoxine (Vitamin B_6) as hydrochloride **11** (Scheme 1).

In our experience, substituents in the alkyne and in the cyano component can be widely varied, so that we have been able to develop the basic reaction [Eq. (1)] into a general synthetic method for preparing mono- to penta-substituted derivatives (for preparative results see [11,12]).

We concentrated on the development of highly reactive organocobalt(I) complexes of the type [YCoL], in particular for the homogeneous catalytic synthesis of 2-alkylpyr-

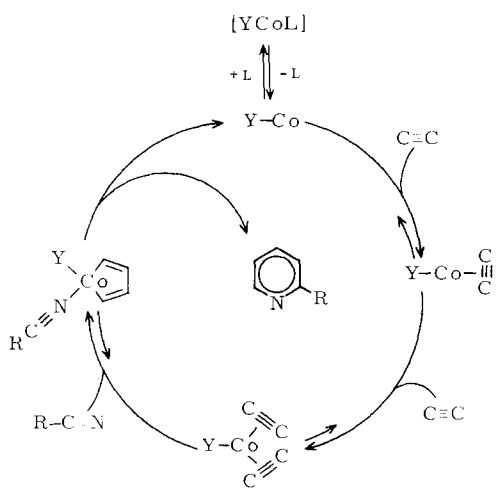
[*] Prof. Dr. H. Bönnemann
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[**] Based on the work of *Helmut Bönnemann, Werner Brijoux, Rainer Brinkmann, Willi Meurers, Michael Radermacher, and Stephan Wendel.* The author thanks his co-workers for their important contributions to this work.



Scheme 1. Synthesis of substituted pyridines. X = O; $R^1 = R^2 = (CH_3)_3Si$; $R^1 = C_2H_5OCO$, $R^2 = (CH_3)_3Si$: ratio **9** : **10** = 16 : 1. Pyridoxine hydrochloride **11** is obtainable by secondary reactions.

idines and 2-vinylpyridine according to equation (1). Since the actual catalytic cycle occurs at a core-complex of the type [YCo], it is possible to change the properties of the catalyst by varying the organyl ligand Y.[13, 14] As shown in Scheme 2, a large number of catalyst complexes having a wide variety of Y and neutral ligands have been synthesized. The catalytic properties of these complexes were tested under standardized conditions. At first, the role of the neutral ligand was thoroughly investigated; in the subsequent catalyst-screening, the catalytic turnover number (TON) of the "controlling ligand" Y was determined.



Scheme 2. Synthesis of substituted pyridines with complexes of type [YCoL]. Y is the controlling ligand, L is the neutral ligand.

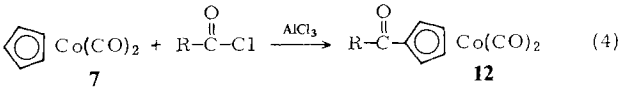
The final step involves optimization of the reaction conditions for the synthesis of 2-alkyl- and 2-vinylpyridine.

2. Synthesis of Complexes of the Type [YCoL]

In order to obtain as broad an insight as possible into the control function of the group Y attached to cobalt, we prepared cobalt complexes having mono- and multiply-substituted η^5-cyclopentadienyl, η^5-indenyl groups as well as boron-containing cyclopentadienyl and η-cyclooctenyl groups. Ethylene, various diolefins, aromatic hydrocarbons, carbon monoxide, and phosphorus-containing compounds served as the neutral ligands.

2.1. Y = η^5-Cyclopentadienyl Derivative

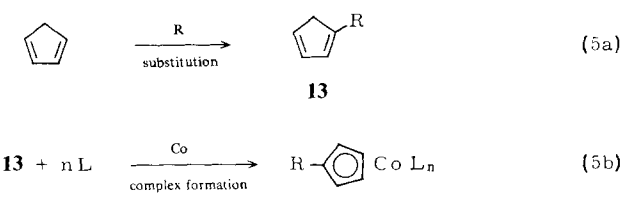
In contrast to ferrocene and similar compounds,[15] in the case of (η^5-cyclopentadienyl)Co^I half-sandwhich complexes only a few examples of ring substitution reactions are known. Thus, the acetyl- and benzoyl-derivatives **12**[16] are obtained on Friedel-Crafts acylation of the complex **7** [Eq. (4)].



(4)

R = CH_3, C_6H_5

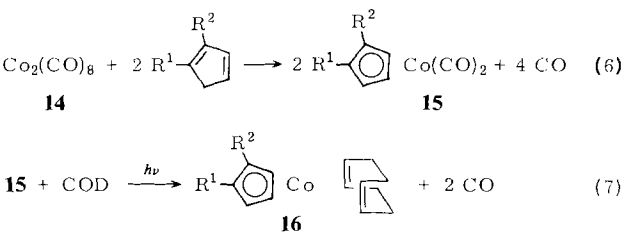
For a general entry to (R–C_5H_4)Co complexes, it is first necessary to prepare appropriately substituted cyclopentadiene derivatives **13** and then in a second reaction step to complex these and the neutral ligand to cobalt [Eq. (5a), (5b)].



(5a)

(5b)

A classic method for the complexation step (5b) involves the reaction of $Co_2(CO)_8$ **14** with monomeric cyclopentadiene derivatives, which leads to the corresponding dicarbonyl complex **15** in 70–90% yield[17, 18] [Eq. (6)].



(6)

(7)

COD = 1,5-cyclooctadiene

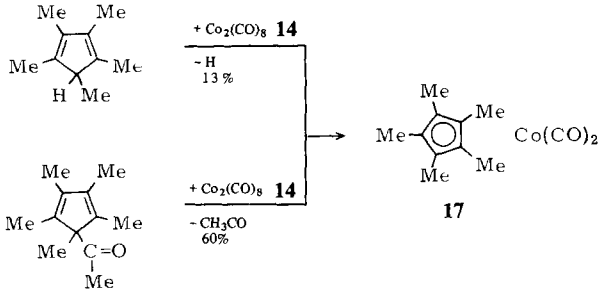
R^1 = H; R^2 = H, CH_3, $(CH_3)_3Si$, C_6H_5

$R^1 = R^2 = (CH_3)_3Si$

The carbonyl groups can be cleaved either thermally or photochemically at room temperature. In the presence of 1,5-cyclooctadiene (COD), diolefin complexes **16** (type **4**) are obtained in high yields [Eq. (7)].

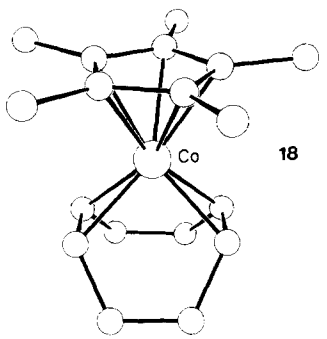
The two-step carbonyl method [Eq. (6), (7), and (8)] proved to be a very versatile catalyst synthesis on a laboratory scale.[19] The complex **17** can be prepared from either 1,2,3,4,5-pentamethylcyclopentadiene[18, 20] or methyl 1,2,3,4,5-pentamethylcyclopentadienyl ketone[21] according to equation (6). The subsequent transformation of **17** into the diolefin complex **18** is achieved in high yield by irradiation in the presence of COD[22] [Eq. (8)].

In order to stabilize the thermally unstable cyclopentadiene derivatives **13** as salts and then to react these to give the corresponding cobalt complexes under mild conditions, we adopted the approach developed by *Rausch* et



(8)

17 + COD $\xrightarrow[78\%]{h\nu}$ [(Me$_5$C$_5$)Co(cod)] **18**



18

al.[23] **14** reacts with an equimolar amount of iodine at 25 °C in tetrahydrofuran (THF) to give the intermediate **19**, which is allowed to react further with cyclopentadienide salts to yield derivatives of type **15** [Eq. (9)].

$$Co_2(CO)_8 + I_2 \xrightarrow{THF,\ 25\,^\circ C} 2\ "ICo(CO)_n" + (8-2n)CO$$

14 **19**

$$\mathbf{19} + M^{\oplus}C_5H_4R^{\ominus} \longrightarrow R\text{-}C_5H_4Co(CO)_2 + (n-2)CO + MI \quad (9)$$

15

M = Li, Na, K, Tl
R = Cl, Br, I, $(C_6H_5)_3C$

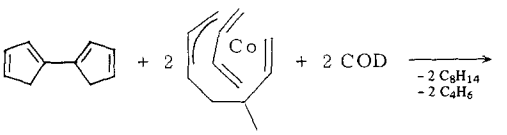
Table 1. Synthesis of [(η^5-RC$_5$H$_4$)Co] complexes [see Eq. (9) and (7)].

R	[(RC$_5$H$_4$)Co(CO)$_2$] Type **15**		[(RC$_5$H$_4$)Co(cod)] Type **16**	
	Yield [%]	Ref.	Yield [%]	Ref.
Cl	54	[23]	90	[19]
Br	57	[23]	**52** 67	[19]
I	12	[23]	86	[19]
HCO	36	[23]	80	[24]
CH$_3$CO	45	[23, 25]	**53** 64	[14, 24]
CH$_3$CHOH	86	[23]	87	[24]
H$_2$C=C(CH$_3$)	26	[23, 27]	92	[24]
C$_2$H$_5$CO	21	[24]	91	[24]
CH$_3$OCO	42	[18, 23]	95	[24]
HOOC	73	[23]	79	[24]
ClCO	70	[23]	[a]	[24]
C$_6$H$_5$NHCO	62	[23]	90	[24]
(H$_5$C$_5$)FeC$_5$H$_4$–CO	5	[23]	54	[24]
[b]	16	[19, 23, 26]	**20** 87	[19]
(C$_6$H$_5$)$_3$C	24	[19]	79	[19]
[c]	42	[19]	62	[19]
(C$_6$H$_5$)$_2$P [d]	4	[19]	52	[19]
(C$_6$H$_5$)$_2$P(S)	10	[19]	[e]	

[a] Decomposition on irradiation. [b] Fulvalene derivative, cf. **20**. [c] (C$_6$H$_5$)$_4$C$_5$H instead of RC$_5$H$_4$. [d] "Monocarbonyl dimer" bridged via P, having the formula [(Ph$_2$PC$_5$H$_4$)Co(CO)]$_2$. [e] Not investigated.

The carbonyl complexes **15** were converted into the corresponding COD-complexes as shown in equation (7). The [YCoL] complexes which were prepared using the Rausch method are listed in Table 1.

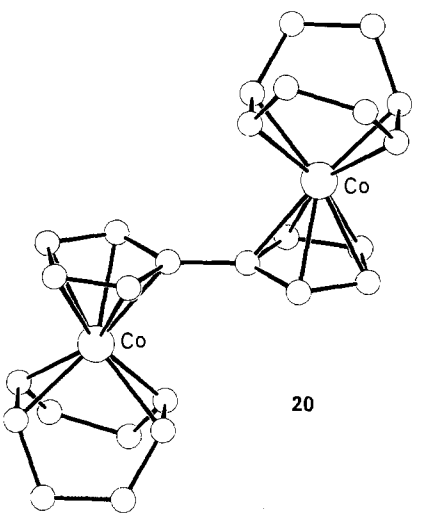
We obtained the binuclear cyclooctadiene(fulvalenediyl)cobalt complex **20** in high yield and avoiding carbonyl intermediates by protolytic substitution of **2** with dihydrofulvalene [Eq. (10)].



(10)

2

[(cod)Co(C$_5$H$_4$–C$_5$H$_4$)Co(cod)] **20**



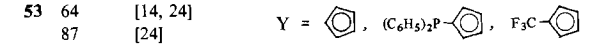
20

Using an analogous method to that developed by *Rausch* via "ICo(CO)$_n$" **19**, we devised a new synthetic route to [YCo(cod)] complexes. This approach is based on the reaction of halotris(triorganophosphane)cobalt(I) complexes with cyclopentadienide salts and subsequent displacement of both triorganylphosphane ligands with COD[19] [Eq. (11)].

$$[XCo(PR_3)_3] + LiY \longrightarrow [YCo(PR_3)_2] + LiX + PR_3$$

$$[YCo(PR_3)_2] + COD \xrightarrow{50\text{–}100\,^\circ C} YCo\text{(}C_8H_{12}\text{)} + 2\ PR_3 \quad (11)$$

R = OC_3H_7, C_6H_5; X = Cl, Br

Y = 

In our search for a one-step synthesis of diolefin-complexes we developed the approach shown in Scheme 3.

In this direct reduction salts of di- and trivalent cobalt are allowed to react with various reducing agents in the presence of the substituted cyclopentadiene RC$_5$H$_5$ and the neutral ligand L to give half-sandwich complexes. Thus, Co(acac)$_3$ reacts in the presence of cyclopentadiene and COD with Al(C$_2$H$_5$)$_3$ to give **4** in 77% yield.[28] Elementary magnesium is better suited as the reducing agent in a technical direct synthesis of the catalyst complex according to Scheme 3. The magnesium is both economical

$$CoX_n + m\,Red \longrightarrow [Co] + Red_mX_n$$

Cobalt salt — Reducing agent — "Naked" cobalt

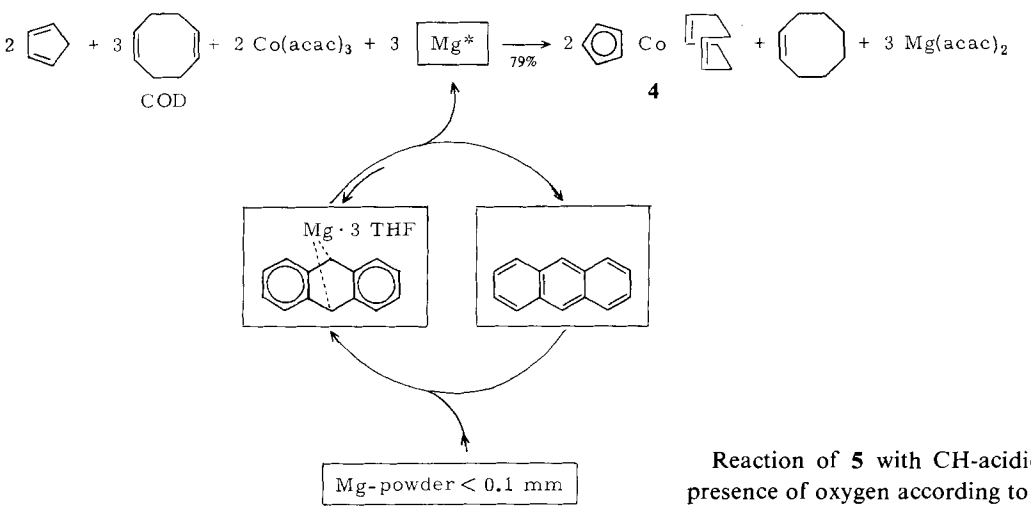
$$[Co] + RC_5H_5 + L \longrightarrow [(\eta^5\text{-}RC_5H_4)CoL]$$

Catalyst complex

L = diolefin, e.g. COD, norbornadiene, RC_5H_5, cyclohexadiene
X = Cl, Br, I, OC_2H_5, acac
n, m = 2, 3
Red = $Al(C_2H_5)_3$, $Al(C_4H_9)_3$, Na, K, Mg, Ca

Scheme 3. Synthesis of catalyst complexes with "naked" cobalt.

and easy to handle. The effectiveness of the reductant is however dependant on its active surface area: if magnesium is employed in Scheme 3 without any special precautions, then the catalyst complex is obtained in only ca. 10% yield due to only partial reduction of the cobalt salt. A substantial improvement was achieved when it was found that the addition of 3–6 mol-% of anthracene to the magnesium powder acts as a phase transfer catalyst to dissolve the magnesium. This "organic soluble" magnesium (Mg*) is quasi-atomic and is therefore able to totally reduce transition metal salts[29] (Scheme 4).



Scheme 4. Preparation of anthracene-activated magnesium (Mg*).

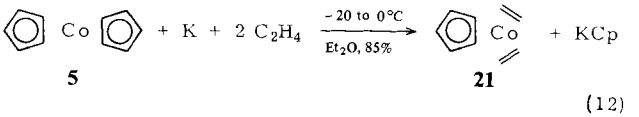
Table 2. Direct synthesis of $[(\eta^5\text{-}RC_5H_4)Co(\eta^4\text{-diolefin})]$ complexes using anthracene-activated magnesium (in analogy to Scheme 4). Numerical values: mmol.

R	Diolefin	$Co(acac)_3$	Mg	Anthracene	RC_5H_5	Diolefin	Yield [%]	Ref.
H	Cyclopentadiene **50**	100	300	6.2	800	—	63	[30]
H	1,3-Cyclohexadiene	100	300	6.2	100	200	53	[31]
H	cod **4**	100	300	6.2	111	250	79	[29, 30]
CH_3	5-Methyl-1,3-cyclopentadiene [a]	100	300	6.2	400	—	62	[31]
CH_3	cod **51**	100	300	6.2	110	250	71	[29, 30]
*t*Bu	cod	50	150	3.1	57	125	42	[29, 30]
C_6H_5	cod	100	300	6.2	90	250	1	[29, 30]
Me_3Si	cod	100	300	6.2	110	250	70	[29, 30]
Me_3Ge	cod	5	15	0.3	5.5	11	30	[19]

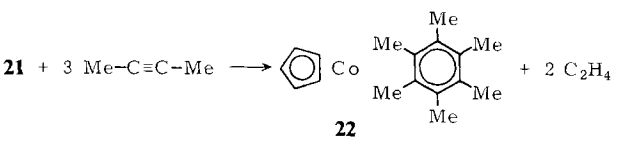
[a] Starting from 1-methyl-1,3-cyclopentadiene.

The resulting "naked cobalt" is stabilized by complexation with olefins. The direct reduction of cobalt salts with anthracene-activated magnesium in THF in the presence of cyclopentadiene or its derivatives and diolefin neutral ligands, in particular COD, represents the currently most economical route to $[(\eta^5\text{-}RC_5H_4)Co(\eta^4\text{-diolefin})]$ complexes (Table 2).

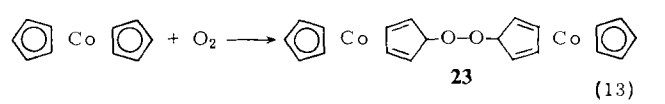
Two routes to give $[(\eta^5\text{-}C_5H_5)CoL]$ systems by varying the neutral ligand L involve transformations of cobaltocene **5**. The displacement of one cyclopentadienyl moiety from **5** with potassium in the presence of ethylene, as described by *Jonas* et al., smoothly yields the bis(ethylene)complex **21**, which reacts with 2-butyne to give the 20-electron system **22**[32] [Eq. (12)].



(12)



Reaction of **5** with CH-acidic organic reagents in the presence of oxygen according to the method developed by *Kojima* and *Hagihara* et al.[33] leads to $[(\eta^5\text{-}C_5H_5)Co]$-complexes which contain substituted η^4-cyclopentadiene groups as stabilizing neutral ligands [Eq. (13)].



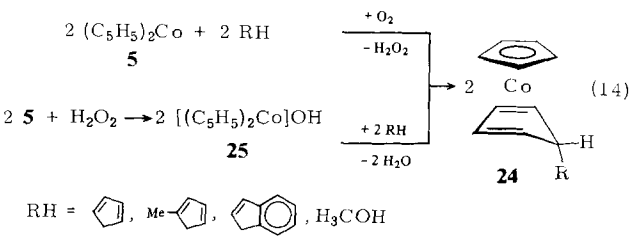
(13)



RH = H_5C_6–C≡CH, H_3C–CO–CH_3, H_3C–CN, H_3C–CH_2–CN, $HCCl_3$
(56%, 70%, 87%, 51%, 97%)

The reaction proceeds via the peroxy bridged complex **23**. In the presence of CH-acidic compounds, the peroxy bridge is cleaved with liberation of H_2O_2 and formation of the η^4-R–C_5H_4 complex **24**. With the intention of convert-

ing cobaltocene **5** into active catalyst complexes of type **24** using simple reagents, we extended the experiments of the Japanese authors[33] to reactions of **5** with cyclopentadiene, methylcyclopentadiene, indene, and methanol in the presence of oxygen [Eq. (14)]. In this way the transformation of an η^5-cyclopentadienyl group into an η^4-cyclopentadiene system having *exo*-substituents was achieved in all cases (yields 30–60%).[19,34]



(14)

The same result was obtained by reaction of **5** with H_2O in the presence of CH-acidic compounds.[19] The intermediate cobaltocenium hydroxide **25** is as basic as the alkali-metal hydroxides[35] and abstracts the proton from the acidic reagent RH to give water. The anion $R^{\ominus}$ undergoes nucleophilic addition to the cobaltocenium ion, and the formation of **24** is accompanied by a change in color from yellow to red.

2.2. Y = Annelated η^5-Cyclopentadienyl Derivative

The η^5-indenyl complex **26** (Fig. 1) was first prepared (in 50% yield) by *Samson* by protolytic substitution of **2** with indene (cf. [36]). The reduction of $Co(acac)_3$ with anthracene-activated magnesium in the presence of indene and COD in an analogous manner to Scheme 4 affords **26** in good yield.[37,38]

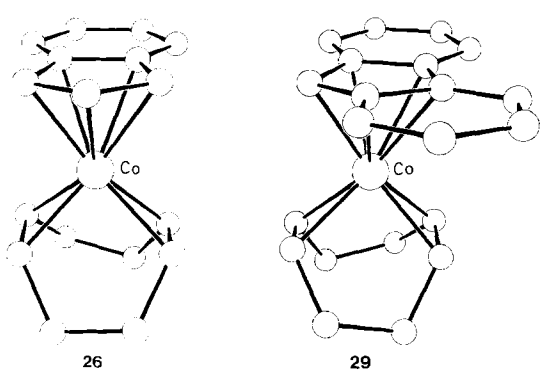
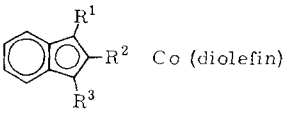


Fig. 1. Structure of η^4-cyclooctadiene(η^5-indenyl)cobalt **26** [38] and η^4-cyclooctadiene(η^5-fluorenyl)cobalt **29** [40] in the crystal.

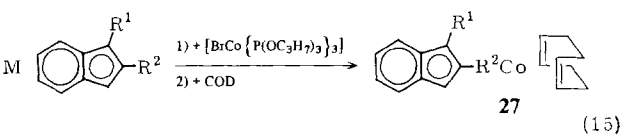
Analogues of **26** having substituted indenyl groups are readily prepared from indene derivatives, diolefins and cobalt salts by direct reduction with anthracene-activated magnesium (cf. Table 3).

Limitations to the direct synthesis are encounted when certain groups on the indene (e.g. amino- and halo-substituents) react with the activated magnesium. In these cases the indirect approach involving reaction of indenide salts with halotris(phosphite)cobalt(I) complexes and subsequent exchange of the phosphite with COD[24] must be resorted to [Eq. (15)].

Table 3. Synthesis of [(η^5-R^1,R^2,$R^3C_9H_4$)Co(η^4-diolefin)] complexes using anthracene-activated magnesium (in analogy to Scheme 4). C_9H_7 = indenyl. The complexes with 1-monosubstituted indenyl moiety were prepared from 1-substituted indene. Exception: $R^1 = C_6H_5$ from 3-phenylindene. Numerical values: mmol.



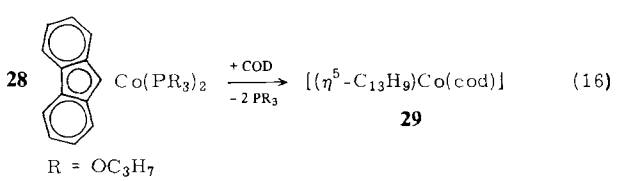
R^1	R^2	R^3	Diolefin	$Co(acac)_3$	Mg	Anthracene	Indene	Diolefin	Yield [%]	Ref.
H	H	H	Norbornadiene	100	300	6.2	250	250	31	[37]
H	H	H	cod **26**	100	300	6.2	250	250	85	[37]
CH_3	H	H	cod	100	300	6.2	107	253	48	[37]
CH_3	H	CH_3	cod	40	120	2.5	40	100	20	[24]
C_2H_5	H	H	cod	100	300	6.2	111	248	55	[24]
*t*Bu	H	H	cod	74	225	4.6	81	185	11	[24]
Me_3Si	H	H	cod	100	300	6.2	115	250	51	[37]
C_6H_5	H	H	cod	50	150	3.1	61	125	26	[24]
H	NMe_2	H	cod	50	150	3.1	55	125	1	[24]



(15)

M = Li, Na, K R^1 = Cl; R^2 = H (9%)
R^1 = H; R^2 = $N(CH_3)_2$ (11%)

The η^5-fluorenyl complex **29** is obtained in almost quantitative yield on reaction of the bis(phosphite) complex[39] **28** with excess COD at 100 °C [Eq. (16)]. The bonding in **29** has been confirmed by X-ray structure analysis[40] (Fig. 1).



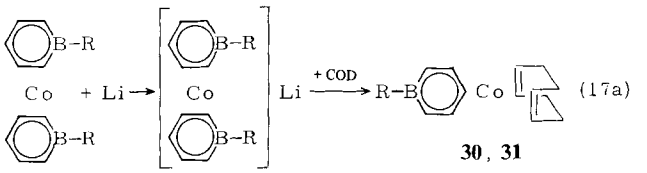
(16)

2.3. Y = Boron-Containing Ligand

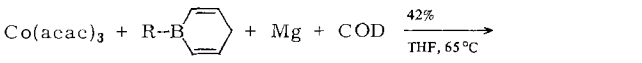
η^6-Borininato ligands were first used as Cp-analogous 6π-electron ligands for cobalt by *Herberich* et al. in 1972[41]. Using bis(η^6-borininato)cobalt as starting material, the diamagnetic COD-complexes **30** and **31** were prepared according to equation (17a).

In an alternative approach we prepared **30** in ca. 40% yield from 1-phenyl-1,4-dihydroborabenzene,[42] COD and $Co(acac)_3$ by direct reduction with soluble Mg*[13] [Eq. (17b)].

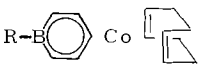
Siebert et al.[43] have described the preparation of numerous transition metal complexes having η^5-dihydro-1,3-diborolyl ligands. The preparation of the complex **33** was



(17a)

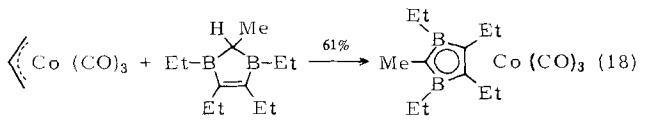


(17b)



30, R = C_6H_5; **31**, R = C_2H_5

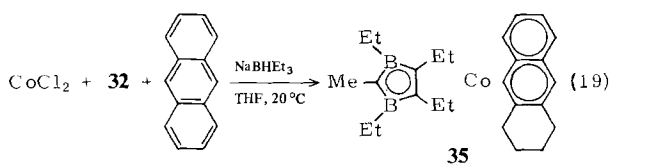
achieved by *Siebert* and *Bochmann* by reaction of the dihydrodiborole[44] **32** with $Co_2(CO)_8$ **14**.[45] Better yields were obtained by protolytic substitution of **34** with **32**[46] [Eq. (18)].



(18)

34 **32** **33**

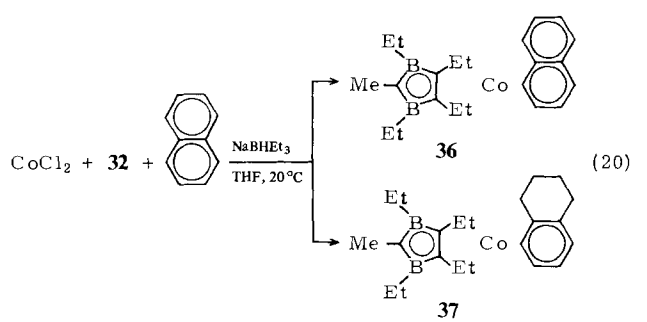
We obtained the crystalline, red, carbonyl-free complex **35** by reduction of $CoCl_2$ with $NaBH(C_2H_5)_3$ in the presence of the ligand **32** and anthracene[47] [Eq. (19)].



(19)

35

The structure of **35** was deduced from the ^{13}C-NMR data. An analogous reaction using naphthalene as the stabilizing ligand gave a mixture of **36** and **37** in the ratio 20:80[47] [Eq. (20)]. **36** and **37** are deep-red crystalline compounds; their structures could be unequivocally determined by ^{13}C-NMR spectroscopy. If the indene system is



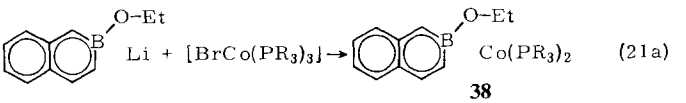
(20)

36

37

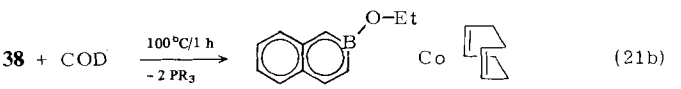
extended by introduction of a boranediyl group, then formally "boranaphthalenes" result.[48] In collaboration with *Paetzold* and *Finke*[49] we were able to bind such a system to cobalt by the routes shown in equation (21a) and (21b).

Reaction according to equation (21a) furnishes the phosphite-stabilized complex **38**. This intermediate is converted into the diolefin complex **39** [Eq. (21b)], which, after chromatography, separated as dark red crystals. **39** was completely characterized by its NMR and mass spectra.



(21a)

38



(21b)

R = OC_3H_7 **39**

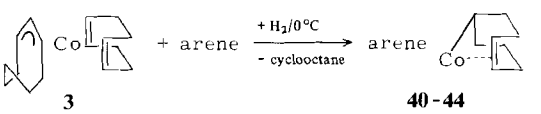
2.4. Y = η^3-Cyclooctenyl

Besides the CpCo-analogous complexes discussed above, one can also use η^3-allyl-Co^I complexes in the pyridine synthesis [Eq. (1)]. In this case, the catalysis cycle occurs at an η^3-allylcobalt core-complex with 12 outer electrons[12-14] (Fig. 2).



Fig. 2. η^3-Allylcobalt core-complex.

We were able to prepare the long known[50] catalyst complex **3** in 70% yield from $Co(acac)_3$ and COD by direct reduction with $Al(C_2H_5)_3$.[14] A convenient synthesis of **3** based on cobaltocene has recently been developed by *Jonas* et al.[51] When **3** is allowed to react with hydrogen in the presence of arenes, the allylic C_8-ring is eliminated as cyclooctane and one obtains a new class of crystalline [Co(η^6-arene)(η^1,η^2-cyclooctenyl)] complexes such as **40**–**44** [Eq. (22)][52].



(22)

3 **40-44**

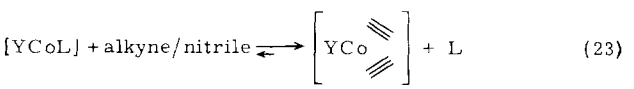
	Arene	Yield [%]
40	Benzene	62
41	Mesitylene	41
42	Hexamethylbenzene	12
43	Aniline	76
44	Anisole	69

Using ^{13}C-NMR spectroscopy it can be shown that the eight-membered ring in the new 18-electron complexes **40**–**44** is not bonded to cobalt as an allyl-system, but as an η^1,η^2-system.

3. The Role of the Neutral Ligand L

As shown in Scheme 2, the initial step in the cobalt-catalyzed pyridine synthesis is the displacement of the neutral ligand L from [YCoL]-complexes by alkyne/nitrile. From complex-chemical[53] and kinetic[54,55] findings it is evident

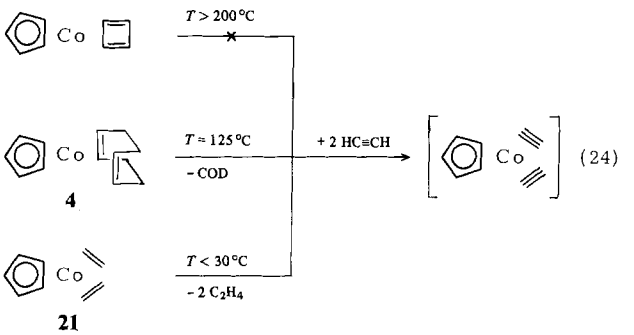
that the coordination sites of the core-complexes [YCo] are occupied by two alkyne molecules to give **45**.



(23)

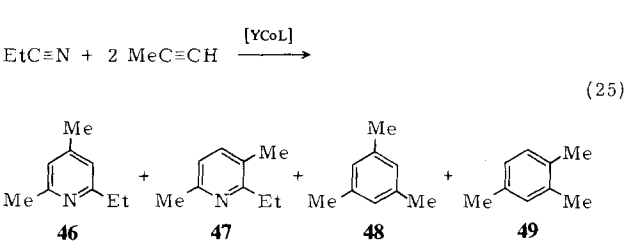
45

As can be deduced from equation (23), L merely functions as a "place-reserver" which stabilizes the catalytic central unit [YCo] as isolable complexes. The liberation of the propagating species **45** depends on the complexing ability of the neutral ligand. The nature of L is therefore of prime importance for the "starting behavior" of the various [YCoL]-complexes in the pyridine synthesis [Eq. (24)].



(24)

Ethylene is already displaced from the cobalt of **21** at room temperature in the presence of the substrates,[32d] whereas cyclobutadiene and its derivatives cannot be displaced from the central metal, either thermally or photochemically.[9] The chelating COD-ligand is a compromise between the weakly stabilizing neutral ligand and the "blocking" systems, since, as evidenced by GC, it can be displaced in a temperature range of practical importance (110—130 °C). The major influence of the various ligands on the initial step of the catalysis [Eq. (23)], and, therefore, on the "starting behavior" of the various [YCoL]-complexes in the catalyzed pyridine synthesis, was investigated using a test reaction [Eq. (25)]. In this study certain con-



(25)

centration ratios were adopted and a continuous flow apparatus (Fig. 3)[14, 54, 55] was used[19] (catalyst: 4.3 mmol/L; propyne: 262 g/L = 6.6 mol/L; propiononitrile: 213 g/L = 3.9 mol/L; toluene: 345 g/L).

The temperature of the reactor was slowly increased from 25 to a maximum of 180 °C and the propyne conversions on the various catalysts were determined on-line. The temperature range in which the first propyne-conversion could be measured indicated the "start" of the catalysis.

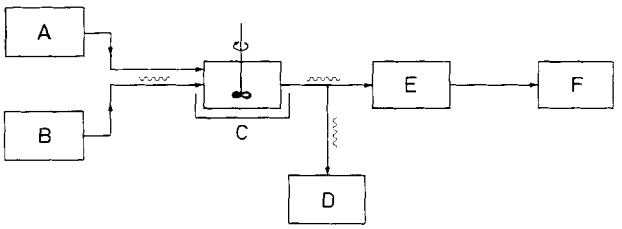


Fig. 3. Continuous flow apparatus for the optimization of homogeneous catalytic processes. A: catalyst solution, B: starting compounds, C: thermostated reactor, D: trap, E: gas-chromatograph, F: data evaluation.

Thereafter, the temperature-dependence of the propyne-conversion was monitored and the temperatures at which each [YCoL]-system continually gave 65% propyne conversion in the test reaction [Eq. (25)] were determined. Figure 4 shows five such conversion/temperature curves.

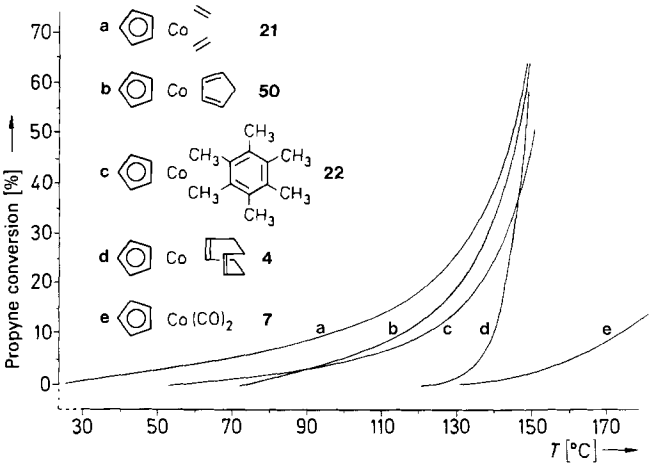
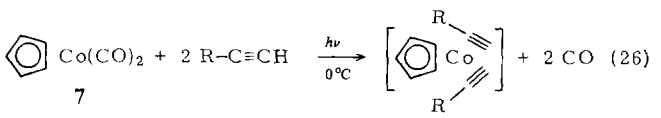


Fig. 4. Propyne conversion and reaction temperature for various [η^5-C_5H_5)CoL]-complexes as catalysts.

As can be seen in Figure 4, the "start behavior" of the individual (C_5H_5)Co compounds is clearly dependent on the complexing ability of the neutral ligands: the ethylene complex **21** already liberates the propagating (C_5H_5)Co-species at room temperature (curve a); the hexamethylbenzene complex **22** causes the first propyne-conversion at 50—60 °C (curve c); the η^4-cyclopentadiene- and COD-complexes **50** and **4**, respectively, first cause propyne-conversion at 75—85 °C and 120—125 °C, respectively (curves b and d). The conversion/temperature curves a—d of the (C_5H_5)Co-catalysts **21**, **50**, **22**, and **4** have the same characteristics: the influence of the neutral ligand on the liberation of the "active species" **45** [Eq. (23)] is noticeable in the temperature range in which 0—25% propyne-conversion takes place. Even the bis(ethylene)-complex **21** only achieves 25% propyne-conversion at ca. 120 °C. Above 120 °C the conversion/temperature curves a—d become more similar. In this temperature range the neutral ligands have been almost completely displaced, so that the propyne-conversion, which is now independent of the neutral ligand, depends on the catalytic activity of the (C_5H_5)Co-unit. At 150 °C, the catalyst complexes **21**, **50**, **22**, and **4** continually convert 65% of the propyne pumped in. With the dicarbonyl complex **7**, the catalytic propyne conver-

sion only starts above 130°C, and even at 150°C only 5% conversion occurs. It can be seen from the conversion/temperature curve e that thermal cleavage of the carbonyl ligands is incomplete even at 150°C. If the carbonyl groups are displaced photolytically[56] from the $(C_5H_5)Co$-unit as shown in equation (26), then the catalytically active species can be generated even below 0°C. The temperature/conversion behavior of **7** then closely corresponds to curve a.



If low reaction temperatures have to be used in the pyridine-synthesis because of thermally labile starting compounds, then the bis(ethylene)-complex **21** or the photolytic elimination of the carbonyl groups in the dicarbonyl complex **7** should be chosen. The reaction rates, however, are slow at room temperature, so that long reaction times or high catalyst concentrations are required. Using the test reaction (25) the individual [YCoL]-complexes can be characterized by the following parameters:

1) *Starting temperature*
(temperature-interval in which the first propyne-conversion is detected)
2) *Reaction temperature*
(required for 65% propyne conversion)
3) *Regioselectivity*
(molar ratio **46** to **47** or **48** to **49**)

Table 4 summarizes the results obtained for some [YCoL]-complexes.[19]

Table 4. Data for [YCoL] complexes in the test reaction (25). Apparatus, see Figure 3; for conditions see text.

Catalyst Y	L	Starting temperature [°C]	T [°C] [a]	**46** / **47**	**48** / **49**
C_5H_5	2 CH_2=CH_2 **21**	<30	148	1.60	2.59
C_5H_5	Me_6C_6 **22**	55–65	150	1.72	2.58
C_5H_5	5-Methyl- [57] 1,3-cyclopentadiene	70–80	148	1.66	2.60
C_5H_5	2-Pyron [58]	65–75	149	1.66	2.65
C_5H_5	C_8H_6 **50**	75–85	148	1.70	2.70
C_5H_5	3-(2,4-Cyclopentadienyl)indene	90–95	147	1.62	2.63
C_5H_5	5-Methoxy-1,3-cyclopentadiene	115–120	149	1.70	2.64
C_5H_5	cod **4**	120–125	147	1.71	2.65
MeC_5H_4	cod **51**	120–125	165	2.02	2.06
Indenyl	cod **26**	95–100	127	1.48	2.64

[a] Reaction temperature for 65% propyne conversion.

Depending on the stabilizing effect of the ligand L in the $[(C_5H_5)Co(diolefin)]$ series the "starting temperature" varies between 30 and 125°C. In the η^4-cyclopentadienyl ligands, substituents with +I effect promote the displacement of ligand, whereas substituents with −I effect hinder the displacement, so that the "starting temperature" is increased. Inspection of Table 4 also shows that all $[(C_5H_5)Co(diolefin)]$-complexes convert 65% of the propyne in the continuous flow system under comparable conditions. After complete displacement of the neutral ligands, all the $(C_5H_5)Co$ systems have the same catalytic activity. Changes in the Y-ligands do however have a major influence on the "starting temperature" and the reaction temperature required for 65% conversion. This is evident on comparing the COD complexes **4**, **51**, and **26**.

The regioselectivity, which, within experimental error, is the same for all the $(C_5H_5)Co$-catalysts, changes immediately when the Y-ligand is varied.

In Figure 4 it can be seen that replacement of olefinic ligands L by stronger complexing carbonyl groups hinders the liberation of the propagating species **45**. The blocking of the $(C_5H_5)Co$-moiety by strongly coordinating ligands even at 150°C is reflected by the propyne conversions listed in Table 5.

Table 5. Starting temperature and propyne-conversion at 150°C using $[(C_5H_5)CoL]$-systems.

Catalyst	Starting temperature [°C]	Propyne conversion [%]
$[(C_5H_5)Co(cod)]$ **4**	120–125	65
$[(C_5H_5)Co(CO)_2]$ **7**	130–140	5
$[(C_5H_5)Co(PPh_3)_2]$ [53]	80– 85	16
$[(C_5H_5)Co(C_5H_5)]$ **5**	105–115	20

A change of the Y-ligand at the cobalt while keeping the same neutral ligand has a major effect on the "starting behavior" and the activity in the pyridine synthesis (cf. Fig. 5).

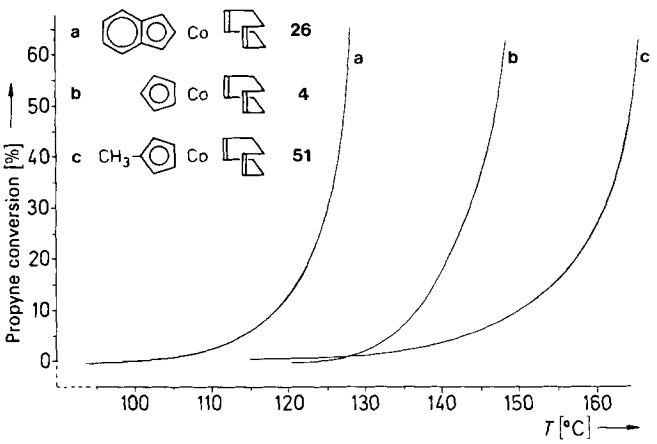


Fig. 5. Propyne conversion and reaction temperature for various [YCo(cod)]-complexes as catalysts.

Replacement of an η^5-cyclopentadienyl by an η^5-indenyl group as Y-ligand at the cobalt lowers the "starting temperature" by 25°C. This indicates that Y has an influence on the dissociation of L according to equation (23). A comparison of the conversion/temperature curves in Figure 5 shows that, after dissociation of the neutral ligand from [YCo(cod)], separate curves a–c result at higher temperatures. Whereas a uniformly effective YCo-system is generated after dissociation of the neutral ligands L from the $[(C_5H_5)CoL]$-complexes (as seen from the trend toward

congruence of the curves at 150°C and 65% conversion in Fig. 4), the results given in Figure 5 for various [YCo(cod)]-complexes show that the Y-ligand has a major influence on the "starting behavior" and on the activity of the catalyst. As can be seen in Table 4, the selectivity of the cobalt catalyst is also effected by Y. Comparison of the results obtained with methylcyclopentadiene as the neutral ligand L and as ligand Y clearly illustrates the roles played by these types of ligands. The result obtained with [(η^5-C_5H_5)Co(η^4-MeC_5H_4)] is no different from that obtained with other [(η^5-C_5H_5)CoL]-systems (Table 4) as far as the reaction temperature for 65% propyne conversion and the product distribution is concerned. If, however, the methyl group is introduced into the cyclopentadienyl part of the catalyst, which remains attached to the metal as the Y-ligand in the whole catalysis cycle, and therefore effects its reactivity, then the substituent effect is reflected in the activity and selectivity of the catalyst.

The role of the neutral ligand in [YCoL]-systems consists therefore in stabilizing the propagating central unit [YCo] by complexation and in effecting the "starting behavior" by liberating the active species at various temperatures. If the species **45** has been formed [Eq. (23)], the liberated neutral ligand has no further influence on the activity and selectivity in the catalytic cycle. In order to develop a catalyst which is reactive and selective one must therefore vary the ligand Y.

4. The Controlling Function of the Ligand Y

4.1. Catalyst-Screening Using Test Reaction (25)

In order to compare various [YCo]-systems, we investigated a series of [YCo(cod)]-complexes in the test reaction (25) under identical conditions in the continuous flow apparatus (Fig. 3).[24] Differences in the product distributions are due to the influence of Y, as all experiments were carried out under stationary conditions and hence kinetic effects or influence of the neutral ligand can be ruled out. The reaction temperature T required for 65% propyne conversion in the continuous system is a measure of the activity of the [YCo]-moiety. The lower the required temperature, the more reactive is the particular [YCo]-system. The molar ratio of pyridine- to benzene-derivatives gives the chemoselectivity and the ratio of the pyridine isomers **46** to **47** characterizes the regioselectivity.[13,14] Table 6 summarizes the results obtained.

Inspection of Table 6 reveals that the three above-mentioned parameters are strongly controlled by the ligand Y.

Table 6. Reaction temperature T (for 65% propyne conversion), chemo- and regioselectivity, and ^{59}Co-NMR shift of [YCo(cod)] catalysts in dependence of Y. For conditions see Eq. (25); ΔT and δ_{rel}, see text. $\delta(^{59}Co)$ of $K_3Co(CN)_6 = 0$.

	Y	T [°C]	ΔT [°C]	Chemoselectivity $\frac{46+47}{48+49}$	Regioselectivity $\frac{46}{47}$	**46** [%]	**47** [%]	$\delta(^{59}Co)$	δ_{rel}
	Y = η^5-Cyclopentadienyl derivatives								
①	$(CH_3)_5C_5$ **18**	220	+73	1.9	3.51	77.8	22.2	−1413	−237
	C_6H_5–NH–CO–C_5H_4	>200	>+53	1.7	2.19	68.7	31.3	[b]	
	HOOC–C_5H_4	185	+38	1.6	1.98	66.4	33.6	[b]	
②	Bicyclo[3.3.0]octadienyl **54**	180	+33	1.5	2.50	71.4	28.6	−1261	− 85
③	CH_3–C_5H_4	162	+15	1.9	2.02	66.9	33.1	−1227	− 51
④	CH_3–CHOH–C_5H_4	182	+35	1.6	1.73	63.4	36.6	−1212	− 36
⑤	Cl–C_5H_4	170	+23	1.4	1.79	64.2	35.8	−1199	− 23
⑥	C_5H_5	147	0	1.8	1.71	63.1	36.9	−1176	0
⑦	*t*Bu–C_5H_4	152	+ 5	2.3	1.77	63.9	36.1	−1166	+ 10
⑧	Me_3Si–C_5H_4	144	− 3	3.4	1.67	62.5	37.5	−1149	+ 27
⑨	H_2C=C(CH_3)–C_5H_4	185	+ 38	2.0	1.74	63.5	36.5	−1127	+ 49
⑩	C_6H_5–C_5H_4	140	− 7	1.9	1.73	63.4	36.6	−1088	+ 88
	1,2-(Me_3Si)$_2$–C_5H_3	138	− 9	6.2	2.25	69.2	30.8	[b]	
⑪	CH_3CO–C_5H_4 **53**	123	−24	2.4	1.46	59.3	40.7	−1055	+121
	Ph_4–C_5H	124	−23	6.9	2.70	73.0	27.0	[b]	
⑫	C_2H_5CO–C_5H_4	124	−23	2.5	1.42	58.7	41.3	−1051	+125
⑬	CH_3OCO–C_5H_4	125	−22	2.4	1.57	61.1	38.9	−1047	+129
⑭	OHC–C_5H_4	129	−18	1.8	1.43	58.8	41.2	−1033	+143
⑮	C_6H_5CO–C_5H_4	119	−28	2.4	1.22	55.0	45.0	−1001	+175
	Y = η^5-Indenyl derivatives								
	2-(CH_3)$_2$N–C_9H_6	175	+49	0.9	3.65	78.5	21.5	[b]	
⑯	1,3-(CH_3)$_2$$C_9H_5$	165	+39	2.3	2.56	71.9	28.1	−1018	−171
⑰	1-CH_3–C_9H_6	146	+20	2.0	1.94	66.0	34.0	− 931	− 84
⑱	1-C_2H_5–C_9H_6	144	+18	1.9	2.08	67.5	32.5	− 930	− 83
⑲	C_9H_7 **26**	126	0	2.3	1.48	59.7	40.3	− 847	0
⑳	1-*t*Bu–C_9H_6	125	− 1	1.7	3.42	77.4	22.6	− 826	+ 21
	1-C_6H_5–C_9H_6	123	− 3	2.5	1.30	56.5	43.5	[b]	
㉑	1-Me_3Si–C_9H_6	110	−16	2.2	2.31	69.8	30.2	− 688	+159
	Y = η^5-Fluorenyl								
	$C_{13}H_9$ **29**	170 [a]		0.9	2.46	71.1	28.9	− 384	
	Y = η^6-Borininato derivatives								
	1-C_2H_5–C_5H_5B **31**	124		2.6	3.28	76.6	23.4	−1018	
	1-C_6H_5–C_5H_5B **30**	120		2.5	2.52	71.6	28.4	− 975	
	Y = η^3-Cyclooctenyl								
	C_8H_{13}	130 [a]		0.5	2.32	69.9	30.1	− 270	

[a] 15% propyne conversion. [b] No ^{59}Co-NMR spectrum obtained.

The influence of Y on the charge distribution at the cobalt is easily determined from the ^{59}Co-NMR chemical shifts[14,59] (Fig. 6). If one relates the ^{59}Co-NMR-shifts in

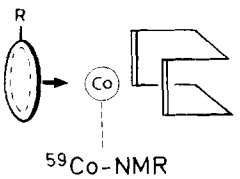


Fig. 6. Determination of ligand effect by ^{59}Co-NMR spectroscopy.

the series of η^5-cyclopentadienyl and η^5-indenyl complexes with the values of the unsubstituted parent compounds ($\delta_{rel}(^{59}Co)=0$), then a correlation between the relative chemical shifts and the electronic character of the ring substituent is found: alkyl groups which act as electron donors cause a larger deshielding of the metal center, whereas phenyl or acetyl groups decrease the deshielding. The influence of the substituents is clearly additive, so that $\delta_{rel}(^{59}Co)$ for $Y=Me_5C_5$ is five times higher than that found for $Y=MeC_5H_4$. In the case of Y = cyclopentadienyl or indenyl one can refer to them as "catalyst families" in which the electronic character of the parent systems can be widely varied by introducing further ring substituents (fine-control). This fine-control of the catalyst properties by additional substituents is mainly due to electronic effects. Thus, for example, in the η^5-C_5H_5 series an additional acetyl group on the ring induces an increase in the catalyst activity in comparison to a 1-hydroxyethyl group, which has nearly the same steric requirements. In the (η^5-cyclopentadienyl)Co-series, the pentamethyl system shows the lowest activity in the test reaction (25), whereas the highest activity at 65% propyne conversion is found for the benzoyl-substituted system (factor 1000 times more reactive than the pentamethyl system). Mesomeric substituent effects influence the activity more than inductive effects, so that replacement of a methyl- by a chloro-substituent only has minor influence on the activity. The regioselectivity is in general inversely proportional to the catalyst activity. Exceptions are found when $Y=1,2\text{-}(Me_3Si)_2C_5H_3$ and Ph_4C_5H. In these cases, both high regioselectivity and activity are found. This is probably due to the accumulation of sterically demanding substituents. Changing from (η^5-cyclopentadienyl)Co to (η^5-indenyl)Co catalysts lowers the reaction temperature required for the same propyne conversion by 20°C. This indicates that the latter complexes are four times more reactive. Additive substituent effects in the ^{59}Co-NMR spectra are also found in these "catalyst families", as can be seen by comparing the δ_{rel}-values for the mono- and dimethyl substituted derivatives. The fine-control of the activity and selectivity by additional indenyl ring substituents is as found in the η^5-cyclopentadienyl series. The results obtained with Y = fluorenyl and η^3-cyclooctenyl in the test reaction (25) listed in Table 6 cannot be directly compared with the other results as only 15% propyne conversion was achieved and an increase in reaction temperature resulted in catalyst decomposition. The substitution of an η^5-cyclopentadienyl by an η^3-cyclooctenyl group attached to cobalt causes a change in the chemoselectivity so that mainly benzene derivatives are formed.[13] With η^6-borininato groups as the controlling ligand Y attached to cobalt highly reactive catalysts with excellent chemo- and regioselectivity are obtained. A comparative study of [YCo(cod)] systems in a continuous flow system therefore allows a differentiation of molecular catalyst properties.

4.2. Correlation of the Control with ^{59}Co-NMR Data[14,24]

If one compares the change in the catalyst properties caused by ring substituents in the cyclopentadienyl- and indenylcobalt series with the relative chemical shifts $\delta_{rel}(^{59}Co)$ given in Table 6, then parallel trends become evident, especially between the activity and the signal position in the ^{59}Co-NMR spectrum. Furthermore, the increase in activity found on going from Y = cyclopentadienyl to Y = indenyl is reflected in a downfield shift. Y = η^6-borininato lies between the two "families" as far as activity and ^{59}Co-NMR shift are concerned. A relationship between the regioselectivity and the relative chemical shift $\delta_{rel}(^{59}Co)$ is also found: the more negative the $\delta_{rel}(^{59}Co)$ value the greater the control of ligand Y in favor of the symmetrically substituted pyridine derivatives **46**. If one plots the $\delta_{rel}(^{59}Co)$ values against the reaction temperature T which is needed for 65% propyne conversion in the continuous flow system for the [(C_5H_5)Co(cod)] family, then an almost linear correlation is found for the 15 members of this "catalyst family" (Fig. 7).

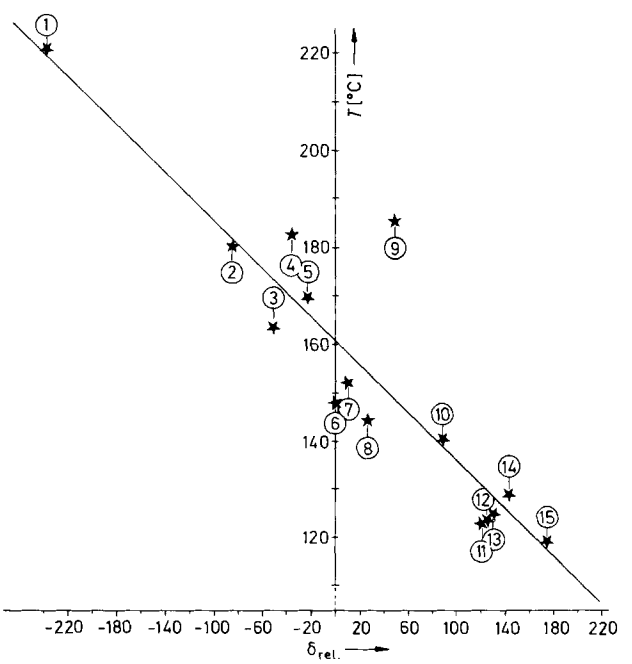


Fig. 7. Catalytic activity of [YCo(cod)]-complexes (Y = cyclopentadienyl derivative) as function of the ^{59}Co-NMR shift (reaction temperatures T in the test reaction (25) under standard conditions; ①—⑮ see Table 6).

Substituted [YCo(cod)]-systems (Y = cyclopentadienyl derivative) which have ^{59}Co resonances which are shifted to higher field ($\delta_{rel}(^{59}Co)$ is negative) are less active than [(C_5H_5)Co(cod)], whereas derivatives having downfield shifts ($\delta_{rel}(^{59}Co)$ is positive) show enhanced activity. The

linear relationship between the reaction temperature T and $\delta_{rel}(^{59}Co)$ in this catalyst family can also be expressed by the regressional equation (27).

$$T\,[°C] = 160.6 - 0.25 \cdot \delta_{rel}(^{59}Co) \quad (27)$$

significance level 95%, Fisher test;
correlation coefficient $r = 0.91$

[YCo(cod)]-complexes (Y = cyclopentadienyl derivative) with large positive $\delta_{rel}(^{59}Co)$ values are therefore particularly active. A similar quasi-linear correlation between regioselectivity and ^{59}Co-NMR shift is found in this series. The pentamethyl derivative preferentially forms the symmetrically substituted isomer **46**, whereas the benzoyl-substituted catalyst produces most of the asymmetric isomer **47**. Both catalysts are found at the extremities of the $\delta_{rel}(^{59}Co)$ shift scale. The linear relationship found between regioselectivity and ^{59}Co-NMR shift in this series can also be described by regressional equations (28a) and (28b).

$$\mathbf{46}\ [\%] = 64.93 - 0.05 \cdot \delta_{rel}(^{59}Co) \quad (28a)$$

$$\mathbf{47}\ [\%] = 35.07 + 0.05 \cdot \delta_{rel}(^{59}Co) \quad (28b)$$

significance level 95%, Fisher test;
correlation coefficient $r = 0.95$

This correlation is shown graphically in Figure 8.

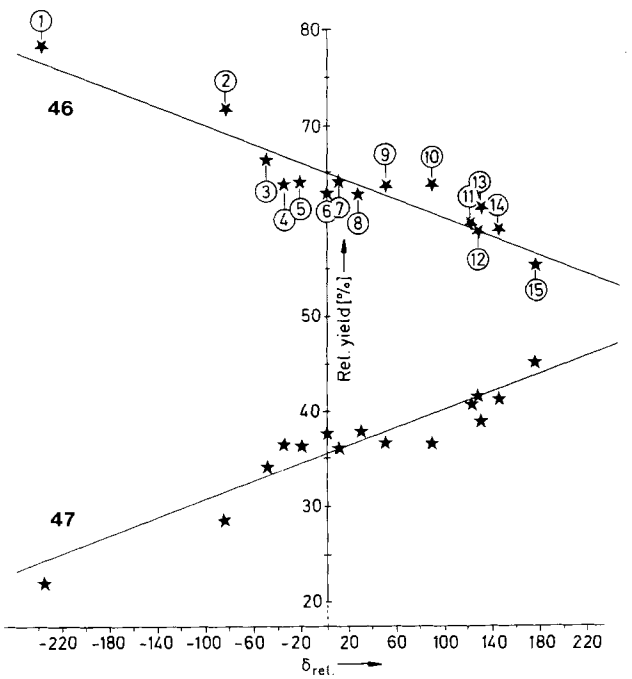


Fig. 8. Regioselectivity of [YCo(cod)]-complexes (Y = cyclopentadienyl derivative) as a function of the ^{59}Co-NMR shift (relative yield of **46** and **47** in the test reaction (25) under standard conditions; ①—⑮, see Table 6).

A direct relationship between catalytic properties and ^{59}Co-NMR shifts also appears to exist in other [YCo(cod)] catalyst families. In the indenylcobalt series we have ^{59}Co-NMR data for the parent compound and five derivatives thereof. As shown in Figure 9, a linear relationship between catalyst activity and $\delta_{rel}(^{59}Co)$ is also found in this case [cf. regression equation (29)].

$$T\,[°C] = 131.6 - 0.17 \cdot \delta_{rel}(^{59}Co) \quad (29)$$

significance level 95%, Fisher test;
correlation coefficient $r = 0.98$

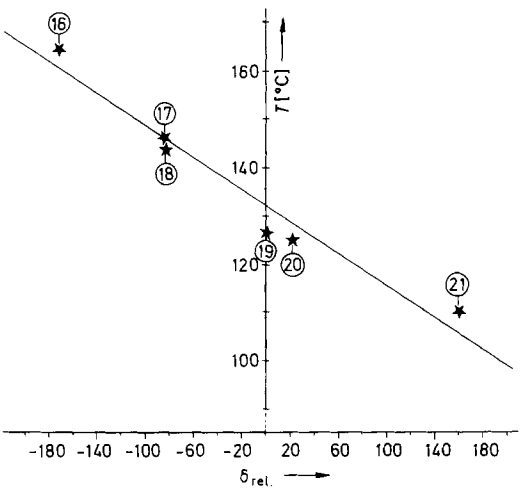


Fig. 9. Catalytic activity of [YCo(cod)]-complexes (Y = indenyl derivative) as a function of the ^{59}Co-NMR shift (reaction temperatures T in the test reaction (25) under standard conditions; ⑯—㉑, see Table 6).

An increasing shielding of the cobalt-cores by alkyl substituents is found in the η^5-cyclopentadienyl or η^5-indenyl systems. Increased electron density at the cobalt core therefore causes a reduction in the catalytic activity. In contrast, electron-withdrawing substituents lower the electron density at the cobalt core, resulting in deshielding and higher catalytic activity.

The empirically found correlations [Eq. (27)—(29)] have hitherto proven valid for the cyclopentadienylcobalt- and indenylcobalt-core complexes. We consider the ^{59}Co-NMR, and transition metal-NMR spectroscopy in general to be a very promising method for efficient catalyst screening because of the wide chemical shift scale and the sensitivity towards substituent effects.

4.3. Relationship between Crystal Structure and the Catalytic Activity

For purposes of comparison, several X-ray structure determinations were carried out in the η^5-cyclopentadienyl and η^5-indenyl series[40]. Some results are shown in Figure 10.

The X-ray structure data shows[40] that the average C—C-distance in the η^5-cyclopentadienyl rings and the average C=C-distance in the complexed COD remain constant. The distance between the Co atom and the center of the cyclopentadienyl ring or between the Co atom and the center of the C=C bond in COD do not vary to any relevant extent. The compounds investigated can, however, be classified into two groups according to the position of the substituents on the η^5-system relative to the arrangement of the C=C bond of the cyclooctadiene (Table 7). In the case of structure type I the substituent on the cyclopentadienyl ring crosses a double bond of the complexed COD, i.e. relative to the cobalt atom it is therefore *transoid* to the second double bond of the complexed COD. In the struc-

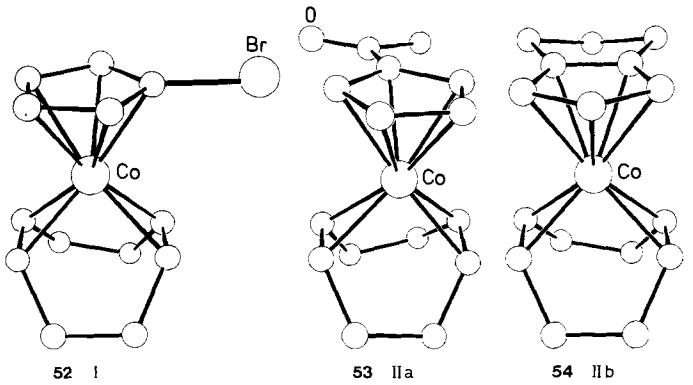


Fig. 10. Structure types of [YCo(cod)] complexes, Y = cyclopentadienyl derivative (see Table 7).

ture type IIa the bond of the substituent on the cyclopentadienyl ring is approximately *parallel* to both double bonds of the complexed COD. Structure type IIb also has a parallel orientation, but contains sterically very demanding substituents. If one correlates the structures with the ^{59}Co-NMR findings, then it becomes evident that substituents

Table 7. Structure types of [YCo(cod)] complexes (cf. Fig. 10).

		
Type I Y	Type IIa Y	Type IIb Y
$Cl-C_5H_4$ $Br-C_5H_4$ **52** $(CH_3)_5C_5$ **18** [a] **20**	$(C_6H_5)_4C_5H$ $(CH_3)_3Si-C_5H_4$ $CH_3CO-C_5H_4$ **53** C_9H_7 **26**	$(C_6H_5)_3C-C_5H_4$ Bicyclo[3.3.0]octadienyl **54**

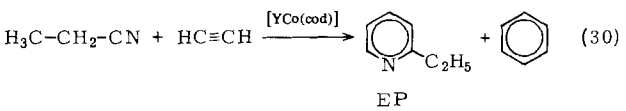
[a] [YCo(cod)] = [(cod)$CoC_5H_4-C_5H_4$Co(cod)].

with strong donor ability (δ_{rel}(^{59}Co) is negative) belong to structure type I. Complexes of this type have a *lower* activity in the catalysis than the unsubstituted ligand Y. Cyclopentadienyl or indenyl derivatives which have a positive δ_{rel}(^{59}Co) value all belong to the structure group IIa. Compounds in this group have electron-withdrawing substituents and are more active than the parent compounds in the catalysis. Sterically demanding donor substituents force a parallel orientation of substituent and COD double bond (structure type IIb). Apart from these exceptions (type IIb), obviously induced by steric effects, correlations are found between structure type I or IIa, sign of the relative ^{59}Co-NMR shifts, and catalytic activity. The linear relationship between ^{59}Co-NMR shift and catalytic activity of the cyclopentadienyl- and indenylcobalt catalysts indicates that a relationship between electron distribution at the cobalt and the activity of various complexes in the catalysis is to be expected. In order to shed light on this, high resolution X-ray structure analyses are currently being carried out involving determination of deformation density by the X–X- and X–N-methods[60] on the complexes **4**, **53**, and **54**.

5. Application: Maximization of the Catalytic Turnover Number TON

5.1. 2-Ethylpyridine

With the intention of achieving maximal catalytic turnover numbers (TON_{Py}) for the industrially interesting synthesis of 2-ethylpyridine [Eq. (30)] we systematically investigated ca. 60 [YCoL]-complexes in a batch reactor.[19]



EP

The catalytic screening in the continuous flow system (see Table 6) enables a characterization of the catalyst properties. For preparative purposes, the alkyne concentration and temperature also have to be optimized for the various catalysts. Since two acetylene molecules are coordinated to the cobalt in the rate determining step,[53,54] the catalytic conversion has to be performed with a high stationary alkyne concentration.

The concentration of acetylene in organic solvents increases overproportionately with increasing pressure.[61] This is particularly the case when nitriles are used as solvents between 5 and 25 bar (Fig. 11).

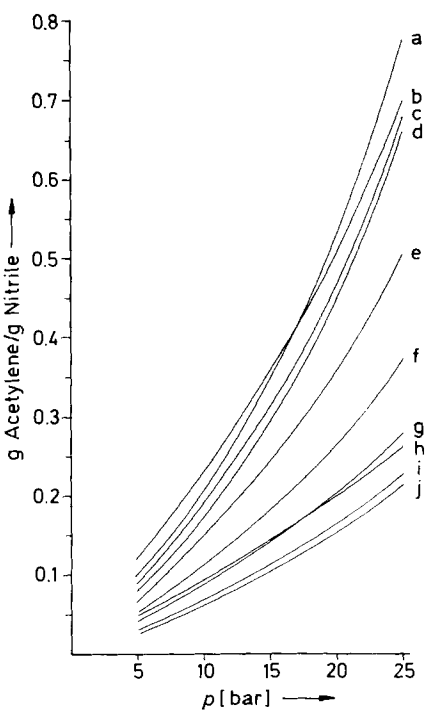


Fig. 11. Solubility of acetylene in nitriles and related compounds at 25 °C as a function of pressure. a: acetonitrile; b: isobutyronitrile; c: propiononitrile; d: acrylonitrile; e: butyl cyanide; f: methyl thiocyanate; g: benzonitrile; h: decyl cyanide; i: undecyl cyanide; j: benzyl cyanide.

The series of optimization experiments was carried out in a batch reactor[62] without inert gas using acetylene pressures of up to 60 bar. The safety precautions mentioned in "Technical Rules Acetylene"[63] were adhered to. The maximal TON values for the 2-ethylpyridine synthesis [Eq.

(30)] for some of the [YCo]-catalysts are given in Table 8. The values vary between 50 and 7000 product forming steps per cobalt, i.e. by a factor of 140. As expected from the catalyst screening involving variation of Y (Table 6), maximal TON values are obtained with such [YCo]-systems having electron-withdrawing groups on the ligand Y. Conversely, alkyl substituents lower the TON values drastically. In a reaction time of 2 h nitrile conversions between 2 and 42% are achieved. Catalysts which achieve propyne conversions in excess of 20% can be regarded as preparatively useful. The 2-ethylpyridine yield (based on nitrile conversion) varies between 15 and maximally 98%. Best chemoselectivity is found for the 1,2-bis(trimethylsilyl)cyclopentadienylcobalt catalyst, which gives ca. 11 moles of 2-ethylpyridine derivatives per mole of benzene. In the series $Y = Me_3E-C_5H_4$ (E = C, Si, Ge) the TON-maximum is found when E = Si. In the series Y = halocyclopentadienyl the best TON was found for the chloro substituent. The η^5-chlorocyclopentadienyl ligand proved to be noticeably more effective in the batch reactor than would be expected from its position in the "activity scale" (Table 6). This result again demonstrates that an optimization of the reaction parameters is vital prior to practical use of the catalysts.

Table 8. Synthesis of 2-ethylpyridine (EP) on [YCo(cod)] and related complexes according to reaction (30). Best values in bold print, poorest values in italics.

Catalyst 0.14 mmol [a]	Acetylene [g] [b]	T [°C] [c]	Nitrile conversion [%]	EP Yield [%]	EP Benzene	TON_{Py} [d]
$(Ph_4C_5H)Co(cod)$	62	110–165	25.7	91.8	7.9	**6946**
$(CH_3OCO-C_5H_4)$-Co(cod)	60	100–160	**41.6**	94.5	6.2	6060
$(CH_3CO-C_5H_4)$-Co(cod) **53**	75	90–160	36.5	93.4	4.9	5267
$(C_6H_5CO-C_5H_4)$-Co(cod)	93	95–185	40.0	**97.7**	4.6	4612
$(Cl-C_5H_4)Co(cod)$	62	115–160	30.5	91.9	6.4	4597
$(C_6H_5NHCO-C_5H_4)Co(cod)$	65	100–180	30.5	88.7	4.4	4140
$(1-Me_3Si-C_9H_6)$-Co(cod)	86	70–142	27.8	91.8	3.3	3735
$(C_5H_5)Co(C_5H_6)$ **50**	75	60–165	24.5	91.3	3.3	3532
$(Me_3Si-C_5H_4)Co$ (cod)	42	130–201	23.0	92.8	7.7	3499
$(Br-C_5H_4)Co$ (cod) **52**	72	110–140	22.9	91.1	5.1	2931
$(C_5H_5)Co(cod)$ **4**	50	130–180	22.5	80.0	5.4	2926
$(C_9H_7)Co(cod)$ **26**	48	100–120	23.5	84.3	6.5	2761
$[1,2-(Me_3Si)_2C_5H_3]$-Co(cod)	48	120–165	17.4	93.5	**10.7**	2611
$(1-CH_3-C_9H_6)$-Co(cod)	53	130–180	20.3	85.6	3.3	2323
$(CH_3CHOH-C_5H_4)Co(cod)$	52	115–200	23.2	89.8	6.7	2214
$(tBu-C_5H_4)Co(cod)$	50	150–180	19.7	83.1	4.5	2065
$(C_5H_5)Co(C_5H_5)$ **5**	45	110–185	16.3	73.4	7.1	2024
$(I-C_5H_4)Co(cod)$	52	105–145	14.6	80.4	6.2	1765
$(CH_3-C_5H_4)$-Co(cod) **51**	43	140–176	18.6	64.9	6.0	1732
$(Me_3Ge-C_5H_4)$-Co(cod)	44	135–181	13.8	83.6	4.3	1653
$(C_5H_5)Co(CO)_2$ **7**	41	125–196	13.3	75.1	5.3	1646
$(1-C_6H_5-C_5H_5B)$-Co(cod) **30**	52	to 122	8.8	91.9	5.7	1604
(Bicyclo[3.3.0]octadienyl)Co(cod) **54**	26	150–202	13.6	67.8	8.1	1527
(Mesitylene)$Co(C_8H_{13})$	54	105–180	12.7	82.2	3.5	1262
(1-Ethoxy-3,4-benzoborinin-ato)Co(cod) **39**	44	135–180	9.0	77.4	2.6	1122
$(Me_2N-C_9H_6)Co(cod)$	54	115–161	9.7	75.5	2.2	872
($MeEt_4$-Dihydrodiborolyl)-Co(tetrahydroanthracene) **35**	59	to 140	6.4	58.9	1.8	668
$(1-Cl-C_9H_6)Co(cod)$	41	110–168	5.6	60.2	4.1	505
$(Ph_2P-C_5H_4)Co(cod)$	39	130–194	6.0	69.8	2.4	493
($MeEt_4$-Dihydrodiborolyl)-$Co(CO)_3$ **33**	26	to 180	7.4	66.3	10.2	460
$(C_5H_5)Co(PPh_3)_2$	35	to 180	6.5	62.0	2.3	417
(Fluorenyl)-Co(cod) **29**	52	to 152	3.6	72.4	*1.4*	344
$(C_8H_{13})Co(cod)$	56	to 130	3.4	26.7	3.1	113
$(Me_5C_5)Co(cod)$ **18**	29	to 185	*1.9*	*15.4*	2.1	*50*

[a] In 150 mL propiononitrile. [b] Acetylene reservoir at 20 °C in 150 mL propiononitrile. [c] Reaction temperature range. [d] Based on 2 h reaction time.

Comparison of the TON values of the [YCoL] complexes having various neutral ligands, verifies that strongly complexing ligands such as triphenylphosphane or CO hinder the liberation of the propagating species. The maximal TON values for these complexes, which are stabilized by more easily displaced ligands, are all of the same order of magnitude.

The maximum amount of acetylene which can be first introduced at room temperature, so that the maximum safety limit of 60 bar is not exceeded at the reaction temperature, is of importance for the preparative success of the cobalt-catalyzed 2-alkylpyridine synthesis [Eq. (30)]. Highly reactive catalysts quickly use up the acetylene reservoir, so that the pressure stabilizes after reaching a maximum between 40 and 60 bar and rapidly sinks at the end of the reaction. When using [YCo]-systems of low reactivity only small amounts of acetylene in the reservoir are used, so as not to exceed the safety limit of 60 bar. The temperature control is also of importance in the 2-alkylpyridine synthesis. A temperature control is used to slowly increase the temperature until the catalysis sets in and the strongly exothermic reaction is then moderated by water cooling. The thermal stabilities of the individual [YCo]-systems vary widely; the trimethylsilylcyclopentadienylcobalt system remains equally active at 200 °C, whereas the indenylcobalt system already decomposes at 140 °C under the catalysis conditions. In order to make full preparative use of the activity, especially for the highly reactive [YCo]-systems, the amount of acetylene and the temperature control have to be carefully optimized. Minor deviations from the optimal combination of the parameters can lead to TON value fluctuations of 1000 for one and the same catalyst.

5.2. 2-Vinylpyridine

The 2-vinylpyridine synthesis [Eq. (31)] must be carried out below 130–140 °C, since acrylonitrile and 2-vinylpyridine undergo thermal polymerization.[64] When using [YCo]-systems which only catalyze this reaction above 130 °C, the reaction must be carried out in dilute benzene or toluene solutions so that the TON values do not exceed ca. 500.

$$H_2C{=}CH{-}CN + 2\ HC{\equiv}CH \xrightarrow{[YCo(cod)]} \underset{VP}{\text{(N, CH=CH}_2\text{)}} + \bigcirc \quad (31)$$

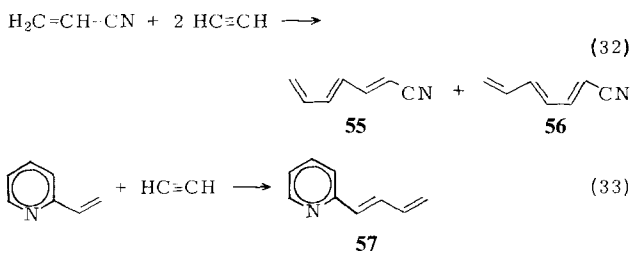
Only very active catalysts can be used for achieving the conversion (31) in pure acrylonitrile. We investigated all the catalysts that were active below 125 °C according to the "activity scale" (Table 6) in a batch reactor for achieving reaction (31). A solution of the catalyst in pure acrylonitrile was saturated with acetylene at ca. 20 bar and then heated to 130 °C. The TON values found in this way after two hours' reaction time are summarized in Table 9.

Table 9. Synthesis of 2-vinylpyridine (VP) on [YCo(cod)] and related complexes according to Eq. (31) in the temperature range up to 130 °C.

Catalyst 0.14 mmol [a]	Acetylene [g] [b]	Nitrile-conversion [%]	VP Yield [%]	VP / Benzene	TON_{Py} [c]
(1-C_6H_5–C_5H_5B)Co(cod) **30**	58	14.2	61.6	6.6	2164
(Ph_4C_5H)Co(cod)	57	15.5	73.7	8.5	1625
(CH_3OCO–C_5H_4)Co(cod)	58	14.9	69.2	5.4	1513
(C_2H_5CO–C_5H_4)Co(cod)	64	15.1	80.4	6.1	1421
(CH_3CO–C_5H_4)Co(cod) **53**	58	12.9	81.1	5.8	1345
(C_6H_5CO–C_5H_4)Co(cod)	67	11.9	78.9	6.0	1286
(1-Me_3Si–C_9H_6)Co(cod)	75	7.1	68.2	5.1	648
(C_9H_7)Co(cod) **26**	63	8.9	38.6	6.0	568
(MeEt$_4$-Dihydrodiborolyl)$Co(CO)_3$ **33**	68	5.4	53.4	4.3	346
(1-Ethoxy-3,4-benzoborininato)Co(cod) **39**	46	3.0	31.8	7.4	265

[a] In 150 mL acrylonitrile. [b] Acetylene reservoir at 20 °C in 150 mL acrylonitrile. [c] Based on 2 h reaction time.

The best results to date were obtained with the η^6-phenylborininato complex **30**. The outstanding position of this catalyst is apparently due to the fact that the catalytic vinylation reactions (32) and (33) are largely suppressed by it. All other catalyst systems named in Table 9 cause the reactions of acrylonitrile and 2-vinylpyridine to give appreciable amounts of **55** and **56** or **57**. These activated olefins can compete with acetylene for cobalt coordination sites and they therefore act as catalyst poisons.



Since indenylcobalt-core complexes are generally more reactive than the cyclopentadienylcobalt systems in the pyridine synthesis, it is to be expected that the introduction of boron into the indenyl system might have a similar positive effect on the catalytic activity in the 2-vinylpyridine synthesis, as was previously found on going from the cyclopentadienyl- to the η^5-borininato ligand.[13] The use of the complex **39** with Y = 3,4-benzoborininato[49], however, only gave relatively low TON values in the 2-vinylpyridine synthesis [Eq. (31)]. Similar results were also found with the 1,3-dihydroborolyl complex **33**. It is possible that the introduction of the boron is compensated by an activity-reducing secondary effect of the alkyl substituents or ethoxy group. This question will first be answered on carrying out the vinylpyridine synthesis [Eq. (31)] using boron-containing control ligands Y having activating substituents.

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Catalytic Synthesis of Organolithium and Organomagnesium Compounds and of Lithium and Magnesium Hydrides—Applications in Organic Synthesis and Hydrogen Storage**

By Borislav Bogdanović*

Dedicated to Professor Günther Wilke on the occasion of his 60th birthday

A recent development in homogeneous catalysis is the discovery of catalysts that are active for the lithiation of 1-alkenes to alkenyllithium compounds and lithium hydride as well as for the hydrogenation of lithium and magnesium under mild conditions. The catalytically prepared magnesium hydride is highly reactive and adds to 1-alkenes to give diorganomagnesium compounds and can also be used in the preparation of, for example, silane and "active" magnesium. The use of metal hydrides in hydrogen storage is discussed: hydrogenation/dehydrogenation experiments show that the catalytically prepared magnesium hydride (which can be doped with a second metal) can be used as a high-temperature hydrogen storage material.

1. Introduction

For decades organolithium and organomagnesium compounds (mainly in the form of Grignard reagents) have been among the most frequently used organometallic reagents for organic synthesis.[1] They are usually prepared by reaction of metallic lithium or magnesium with organic halides.[1–3]

In the following article it is shown that dialkylmagnesium compounds can be prepared catalytically in a manner analogous to the synthesis of trialkylaluminum compounds.[4] An important role in the catalytic activation of lithium is probably played by "poly-lithium complexes" which are formed from lithium and 1,6,6aλ⁴-trithiapentalenes (Section 2), while the catalytic hydrogenation of magnesium involves the activation of the metal through the re-

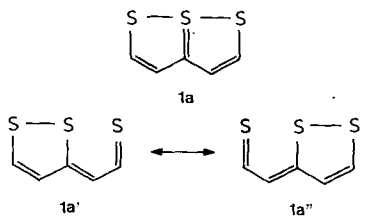
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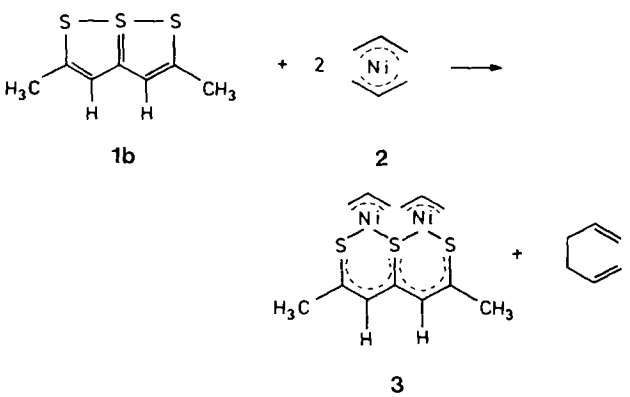
versible formation of "magnesium-anthracene" (Section 4). In both cases the formation of the catalytically active species involves a second metal—in general, a transition metal.

2. Poly-Lithium Complexes from Lithium and Phenyl-Substituted 1,6,6aλ⁴-Trithiapentalenes or Related Compounds[5,6]

The investigation of the reaction of the 1,6,6aλ⁴-trithiapentalenes **1a**[7-9] with lithium originated in the observation that **1b** reacts with bis(η³-allyl)nickel **2** to give the



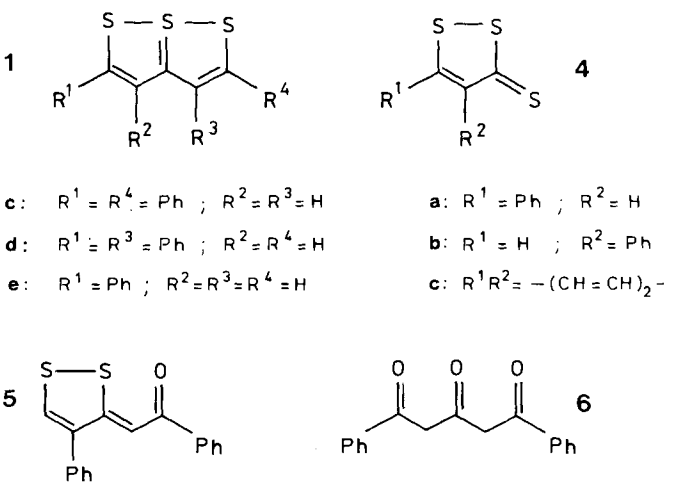
binuclear nickel complex **3**[10] in what can formally be regarded as a redox process.

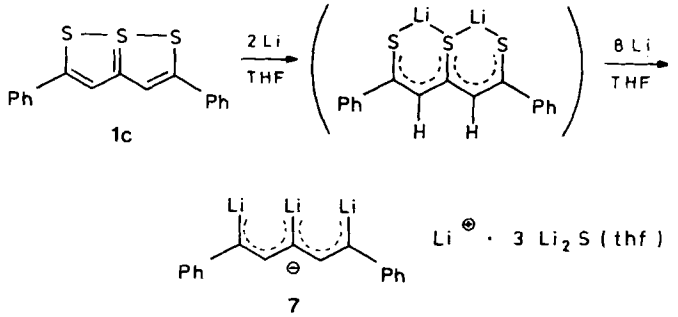


Since the reduction of the trithiapentalenes either with potassium or electrochemically has been reported to proceed only as far as the radical anion,[11,12] we decided to investigate whether they could be reduced to the dianion with excess alkali metal.[13] It was discovered that the phenyl-substituted trithiapentalenes **1c**—**1e** react in tetrahydrofuran (THF) or 2-methyltetrahydrofuran (MeTHF) not with two but with nine or ten mol Li per mol compound to give highly reactive, soluble "poly-lithium" complexes. Similar behavior was observed for 3*H*-1,2-dithiol-3-thiones **4a**—**c** (6—7 Li/compound), 2-(4-phenyl-3*H*-1,2-dithiol-3-ylidene)acetophenone **5** (≈10 Li/compound), and 1,5-diphenyl-1,3,5-pentanetrione **6** (≈8 Li/compound).[5]

The poly-lithium complex **1c**Li_{10}(thf) was suggested to have the constitution **7** on the basis of its reactions with water, methyl iodide, pentacene, and hydrogen.

Thus, the reaction of **1c** with lithium in THF or MeTHF is accompanied by the cleavage of all the C—S and S—S bonds present and their replacement by C—Li and S—Li bonds, whereby the resulting lithium sulfide is complexed to the organolithium compound.[14] The reaction of **1d**,**e**, **4a**—**c**, **5**, and **6** with lithium in THF or MeTHF probably proceeds in an analogous manner. This assumption is supported by the ^{7}Li- and ^{1}H-NMR spectra of the poly-lithium complex formed by treating **1d** with lithium.[5] More detailed information on the structure of these poly-lithium species is not available since all attempts to obtain satisfactory crystals failed. In connection with this work, it did, however, prove possible to obtain the crystal structure of the THF-TMEDA (*N*,*N*,*N*′,*N*′-tetramethylethylenediamine) adduct of benzophenonedilithium.[15]





3. Catalytic Reactions Using Trithiapentalene-MX_n-Lithium and Related Systems

3.1. The Catalytic Lithiation of 1-Alkenes[16,17]

The uncatalyzed reaction of 1-alkenes with lithium leads to 1-alkynyllithium compounds and lithium hydride; (*E*)-1-lithio-1-alkene was identified as a side product.[18]

$$RCH{=}CH_2 + 4\,Li \longrightarrow RC{\equiv}CLi + 3\,LiH$$

R = *n*-alkyl

The reaction of ethylene with lithium in dimethoxymethane or THF in the presence of biphenyl or naphthalene results in a low yield of vinyllithium, 1,4-dilithiobutane, and α,ω-dilithioalkanes.[19] Acidic hydrocarbons, 1-alkynes,[20] triphenylmethane,[21] and cyclopentadiene[22] can be directly metalated with lithium.

THF solutions of the "poly-lithium complexes" (Section 2) have only weak activity for the lithiation of 1-alkenes. The addition of metal halides MX_n leads to an increase in the catalytic activity and also allows the selectivity of the

lithiation to be influenced. Particularly active is the combination of **1c** or **1d** with $ZnCl_2$, $FeCl_3$, or $CuCl_2$ and lithium.[23]

The lithiation of ethylene with **1c**/2$ZnCl_2$/Li as catalyst leads to the formation of vinyllithium in 70—75% yield and is accompanied by the formation of lithium hydride and traces of α,ω-dilithioalkanes.

$$H_2C{=}CH_2 + 2\,Li \xrightarrow[0\,^\circ C,\ 1\,bar]{cat./THF} H_2C{=}CHLi + LiH$$

The vinyllithium can be separated from the precipitated lithium hydride and isolated in crystalline form as $C_2H_3Li \cdot thf$[16] or in a solvent-free form.[24]

The effect of the MX_n components on the activity and selectivity of the **1c**/2MX_n/Li catalysts was investigated in the case of the lithiation of propene. The products of this reaction are lithium hydride and the four isomers **8a**—**d**, the relative amounts of which were determined by silylation with chlorotrimethylsilane followed by gas chromatographic (GC) analysis of the resulting organosilanes (Table 1).

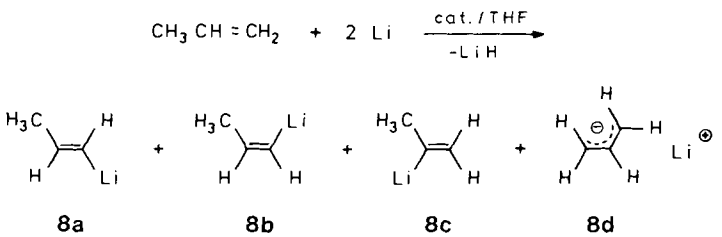
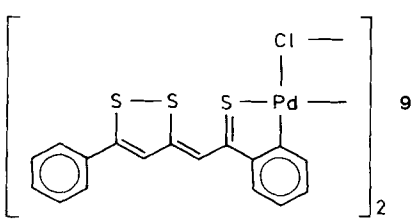


Table 1. The influence of metal salts on the activity and selectivity of catalysts for the lithiation of propene. Catalyst: 1% **1c**; [**1c**] = 0.04 mol/L.

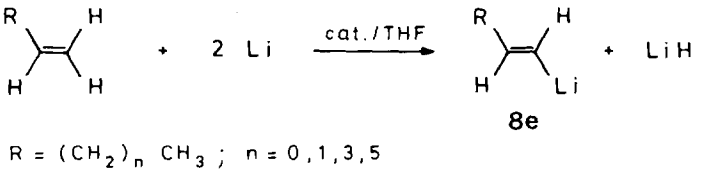
MX_n	mmol C_3H_6 / mmol cat·h	Total yield of C_3H_5Li [%] [a]	Isomer distribution [%] [b]			
			8a	**8b**	**8c**	**8d**
$ZnCl_2$	7–8	75–83	85–90	0.5–1	2–6	8–9
$CdCl_2$	5	47	90	1	2	7
$HgCl_2$	2	40	94	0.7	—	5
$FeCl_3$	5	56	83	2–3	7	7
$CuCl_2$	5	59	68	1	9	22
$PtCl_2$	3	75	37	1	2	60
[c]	1.6	41	13	0.3	1	85

[a] Relative to the initial concentration of Li. [b] GC analysis of the silylated product. [c] Catalyst: **9**.

When **1c**/2$ZnCl_2$/Li is used as catalyst, **8a** is formed with 85—90% selectivity. **8a** could be isolated by recrystallization or in a solvent-free form having 98—99% isomeric purity.[16,24] The amount of allyl lithiation is dependent on the nature of the MX_n component and increases in the order $FeCl_3$, $CuCl_2$, $PtCl_2$. The highest selectivity for **8d** (85%) was obtained using complex **9** which was prepared from **1c** and $PdCl_2$.[25]

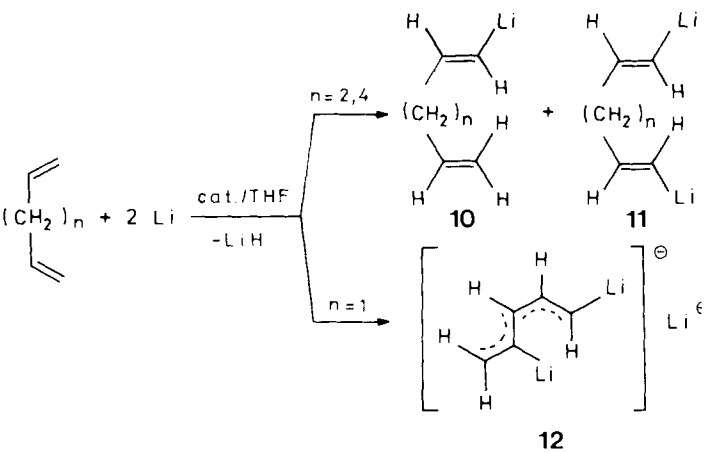


Higher 1-alkenes can be lithiated with 90—97% selectivity to (*E*)-1-lithio-1-alkenes **8e** with the **1c**/2$ZnCl_2$/Li catalyst.



R = $(CH_2)_n CH_3$; n = 0, 1, 3, 5

The lithiation of 1,5-hexadiene or 1,7-octadiene in the presence of **4c**/2$CuCl_2$/Li[23] gave a mixture of (*E*)-1-lithio-α,ω-alkadiene **10** and (*E*,*E*)-α,ω-dilithio-α,ω-alkadiene **11**, whereas reaction of 1,4-pentadiene with the same catalyst afforded the crystalline trilithium compound **12**.[26]



The mechanism of the catalytic lithiation (Scheme 1)[19a] presumably involves the stepwise addition (e.g., via **13**) of two lithium atoms to the C=C bond to give the 1,2-dilithioalkane **14**[27] followed by β-elimination of lithium hydride. Depending on the stereochemical course of the β-elimination from **14**, four isomers can form; e.g., **8a**—**d**, the products obtained from the lithiation of propene.

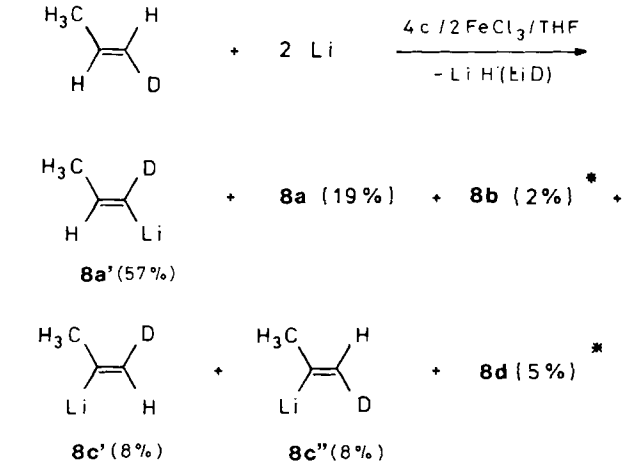
$$RCH{=}CH_2 \xrightarrow{Li} \underset{\mathbf{13}}{RCHCH_2Li} \xrightarrow{Li}$$

$$\underset{\mathbf{14}}{RCHLiCH_2Li} \xrightarrow[-LiH]{R=CH_3} \mathbf{8a-d}$$

Scheme 1.

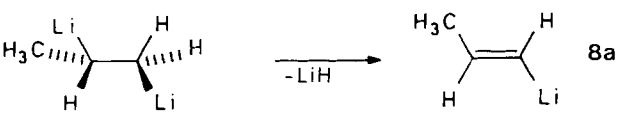
This mechanism is supported by the *E*/*Z*-isomerization observed during the catalytic lithiation of (*E*)-1-deutero-1-propene, which resulted in the isomerization products (*E*)-1-deutero-1-lithio-1-propene **8a**′ and (*Z*)-1-deutero-2-lithio-1-propene **8c**′.[26]

Rotation about the C—C bond is possible in both **14** and its precursors (e.g., **13**). The high *E*-stereoselectivity observed for the catalytic lithiation of propene and other 1-alkenes (the *E*/*Z* ratio of 1-lithio-1-alkenes is 98/2—99/1 or higher) is possibly a result of steric restriction during the



[*] Degree and position of deuteration not determined

β-elimination from **14**. For example, β-elimination following the *syn*-addition of two Li atoms to the C=C bond can be expected to proceed preferentially by a *syn*-mechanism when the large CH_3 (or alkyl) group and Li occupy anticlinal positions.



It is still not fully understood how the MX_n component in the catalyst controls the direction of lithiation of propene to give **8a** or **8d**.

3.2. Catalytic Hydrogenation of Lithium

In 1968 it was reported that sodium can be catalytically hydrogenated under mild conditions using a catalyst prepared from titanium tetraisopropoxide, naphthalene, and sodium.[28] Bis(η^5-cyclopentadienyl)titanium dichloride in THF is also an active catalyst for this reaction.[29]

Lithium can be hydrogenated under mild conditions using trithiapentalene/MX_n/lithium and related systems as catalysts.[6,30] The preferred catalyst consists of a combination of **1c** or **4c** with $FeCl_3$ and lithium in THF and is capable of hydrogenating lithium almost quantitatively at 0° and 1 bar H_2 (Fig. 1). The lithium hydride precipitates from solution in a finely divided, highly reactive form.

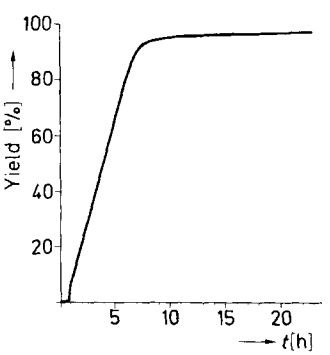


Fig. 1. The hydrogenation of lithium at 0°C; Catalyst: 2 mol-% **4c**, 4 mol-% $FeCl_3$, [**4c**] = 0.041 mol/L: Hydrogen up-take followed with an automatic gas-burette [31].

4. Catalytic Synthesis of Magnesium Hydride[32]

Drastic conditions and long reaction times are needed to prepare magnesium hydride from the elements.[33] Because of the potential significance of the hydrides of magnesium, its alloys, and its intermetallic compounds as reversible hydrogen storage systems,[34] many attempts have been made to increase the rate of hydrogenation by adding a further metal (see Section 8). At the start of our investigations, little was known about the use of homogeneous transition-metal catalysts in this reaction.[35]

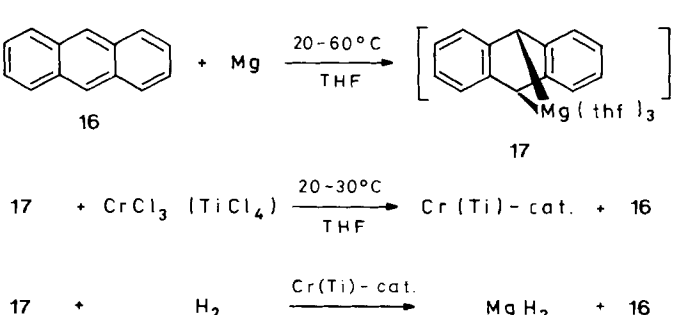
In analogy to the catalytic hydrogenation of lithium (Section 3.2), we initially investigated combinations of trithiapentalene with transition-metal halides as catalysts for the hydrogenation of magnesium. A catalytic reaction was observed upon addition of anthracene to activate the magnesium. According to *Ramsden*,[3] anthracene reacts with magnesium in THF to give insoluble "magnesium-anthracene". The reaction of magnesium and anthracene (or magnesium-anthracene) with, in particular, the halides of chromium, titanium, or iron in THF produces a hydrogenation catalyst that is active under mild conditions. The reaction proceeds slowly at room temperature and normal pressure and faster at 60–65 °C under pressure.[32]

$$Mg + H_2\,(1-80\ \text{bar}) \xrightarrow[20-65\,^\circ C]{\text{Mg-anthracene/MX}_n\text{/THF}} \underset{\mathbf{15}}{MgH_2}$$

$MX_n = CrCl_3$, $TiCl_4$, $FeCl_2$

Magnesium hydride **15** can be routinely prepared by this method and the reaction has been carried out on up to a 15-kg scale. Recent improvements in the catalyst have enabled the time required to be reduced from 12–16 h[32a] to 1–2 h.[36]

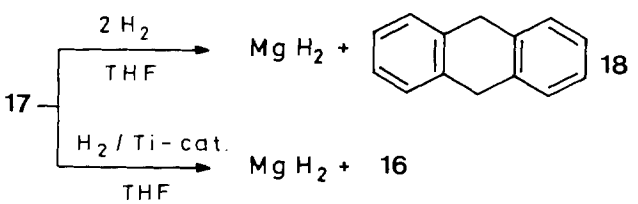
The following reactions have been shown to be involved in the hydrogenation reaction using the Mg-anthracene/$CrCl_3$ or Mg-anthracene/$TiCl_4$ catalyst:[32a] 1) Magnesium reacts with anthracene **16** in THF to give magnesium-anthracene **17**,[37] which is present in a temperature-dependent equilibrium with magnesium and **16**;[37] 2) The catalytically active transition-metal complex is formed by reaction of **17** with $CrCl_3$ or $TiCl_4$ in THF with release of anthracene **16**;[36] 3) **17** is hydrogenated to magnesium hydride in



Scheme 2.

the presence of the soluble chromium or titanium catalyst, **16** being liberated (only traces of 9,10-dihydroanthracene are detected). The first and third equations in Scheme 2 form a catalytic cycle, with **17** as reactive intermediate.

Insight into the role of the transition metal and of **17** in the catalytic hydrogenation of magnesium is afforded by a comparison of the hydrogenation of **17** in the presence and in the absence of a catalytic amount of $TiCl_4$. Hydrogenation of a suspension of **17** in THF at 58°C with hydrogen at 75 bar results in the slow (35 h) absorption of 2 mol H_2/mol **17** with the formation of magnesium hydride and 9,10-dihydroanthracene **18**. If, however, the hydrogenation is carried out under the same conditions in the presence of 1/50 mol $TiCl_4$ per mol **17**, the only reaction observed is the hydrogenation of magnesium at a tenfold faster rate with liberation of anthracene **16**.

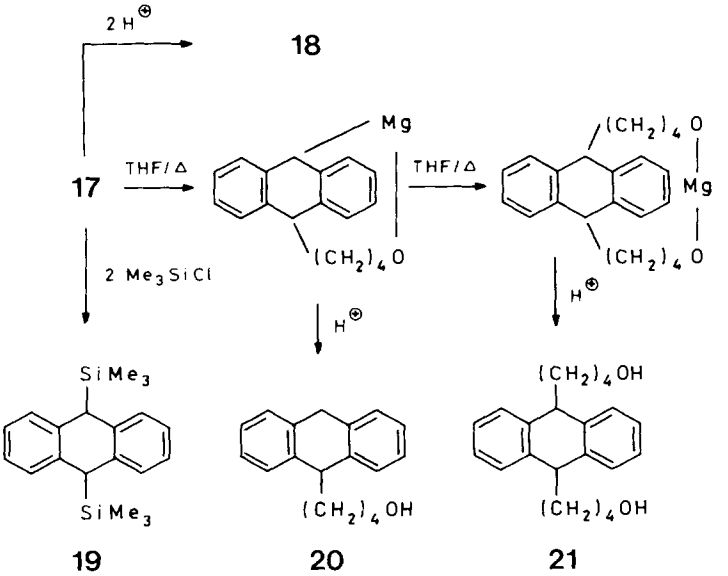


The titanium catalyst is responsible for the formation of MgH_2 and **16** in the hydrogenation of **17**, while the reaction of **16** with magnesium maintains a stationary concentration of **17**.[38] Kinetic measurements show that the rate of formation of **17** in THF at 60°C is proportional to both the anthracene concentration and the Mg surface area.[37] In agreement with this, an increase in the anthracene concentration at 60°C leads to an increase in the rate of hydrogenation of the magnesium.[38]

In view of the importance of **17** for the catalytic hydrogenation of magnesium and for the synthesis of transition-metal complexes using anthracene-activated magnesium as a reducing agent,[39] the compound has been characterized both chemically and by NMR spectroscopy; moreover, the kinetics of its formation have been studied.[37] The ^1H- and ^{13}C-NMR spectra indicate that the magnesium atom in **17** is bonded to carbon atoms 9 and 10 of the anthracene ring. The Mg–C bond can be described as being covalent with a strongly polar character—the hybridization of the C-atoms lying between sp^2 and sp^3.

17 reacts in two ways. It behaves as a diorganomagnesium compound, i.e., as a nucleophile, upon protonolysis[37] and upon hydrogenolysis in the absence of a catalyst, both of which lead to **18**,[38] as well as in the reactions with chlorotrimethylsilane[36] and THF (at 120°C under pressure),[37] which lead to the 9,10-dihydroanthrylene derivatives **19**–**21**.

In contrast, the Mg–C bonds in **17** formally undergo homolytic cleavage in the dissociation reaction to give **16** and magnesium[37] as well as in the catalytic hydrogenation[38] and in reactions in which anthracene-activated magnesium is used as a reducing agent.[39] In these cases, **17** acts as a source of "soluble, atomic magnesium". The anthracene (**16**) that is liberated during reactions of this type can react with further magnesium to give **17** and thus



acts as a phase-transfer catalyst[39,40] to activate large quantities of magnesium.

5. Reactions of Catalytically Prepared Magnesium Hydride

The reactivity of magnesium hydride depends largely upon the method of preparation and upon the nature of any impurities present. Whereas samples prepared from the elements at high temperature and pressure are stable in air and only react slowly with water,[41] the product formed by pyrolysis of diethylmagnesium burns in air and reacts violently with water.[41a,42] The hydrogenation of magnesium in the presence of excess butadiene in THF leads to a reactive magnesium hydride powder having a large specific surface area (100 m^2/g).[43] The magnesium hydride prepared by *Ashby* et al.[44] from diorganomagnesium compounds or Grignard reagents and $LiAlH_4$[45] (or from $MgBr_2$ and NaH)[46] is particularly reactive. This "active" magnesium hydride has been used to prepare magnesium hydride halides,[47] alkoxides,[48] amides,[49] alkyls, and aryls[50] and has also been added to alkenes and alkynes[51] (see Section 5.1) and used to reduce organic compounds.[44]

In contrast to the magnesium hydride prepared from the elements,[33,41] the catalytically prepared sample **15**[32,36] is particularly reactive and is of potential interest as a hydrogen storage material and for the following applications:

- Separation of H_2 from gas mixtures
- Reducing and drying agent
- Preparation of soluble magnesium halide hydrides, of active magnesium, and of elements and their hydrides
- Cleavage of allyl ethers
- Carrier for heterogeneous catalysts
- Addition to 1-alkenes to give diorganomagnesium compounds (hydromagnesation)

Of these the reaction with alkenes (Section 5.1) and the use in hydrogen storage (Section 8) have been investigated in some detail.

For synthetic purposes **15** can be used either as a suspension in THF or as a solid, the highest activity being provided by a freshly prepared suspension. Only the solid is of interest for hydrogen storage. Both solid and suspension are pyrophoric and react violently with water; they should therefore be handled with care. Depending upon the catalyst and the hydrogenation and isolation conditions, the solid contains varying amounts of impurities: THF (1—5%), **16** (0.02—0.1%), **18** (0.02—0.2%),[*] **20** and **21** (together 0.1—0.3%),[*] *n*-butanol (0.3—0.8%),[*][37] $MgCl_2$ (5%), and Cr or Ti (0.1—0.7%). The specific surface area is 70—130 m^2/g. Electron microscopy (Fig. 2) and X-ray diffraction show the solid to consist of agglomerates (0.5 μm) of microcrystals (0.05 μm).[52] The high specific surface area makes **15** a suitable carrier for catalysts.[53]

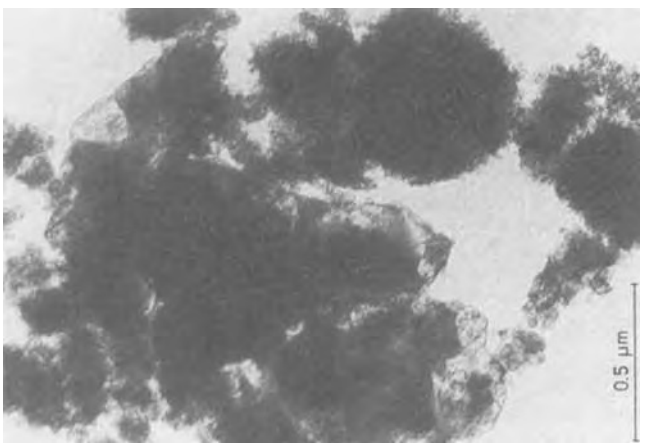


Fig. 2. An electron micrograph of catalytically prepared MgH_2 **15**.

5.1. Catalytic Addition to 1-Alkenes ("Hydromagnesation" of Alkenes)[54]

Although the addition of the hydrides of aluminum,[55] boron,[56] silicon,[57] tin,[58] and zirconium[59] to alkenes and alkynes (hydrometalation) has been intensively studied during the last 25—30 years, little attention had been given prior to our studies to the addition of well-characterized magnesium hydrides to C=C bonds. The uncatalyzed reaction between magnesium hydride, prepared by various methods, and ethylene or other olefins affords a low yield of dialkylmagnesium compounds.[60] Recently, the Cp_2TiCl_2-catalyzed addition of "active" magnesium hydride to 1-alkenes and alkynes has been reported.[51] More attention has been given to the "indirect", titanium-[61] or nickel-catalyzed,[62] addition to alkenes and alkynes of "active" magnesium hydride prepared from Grignard reagents having β-hydrogen atoms.

Dialkylmagnesium compounds have attained industrial importance in the preparation of highly active Ziegler catalysts.[63] At present they are prepared according to the Grignard method via the Schlenck equilibrium[64] or by alkylation of magnesium chloride with organolithium compounds.[64c,65]

Attempts to add **15** to 1-alkenes led to the discovery that the **17**/$TiCl_4$ and to a lesser extent **17**/$CrCl_3$ catalysts, which are used for the hydrogenation of magnesium (see Section 4), also catalyze the addition reaction. The synthesis of diethyl-, dipropyl-, or dibutylmagnesium can, for example, be carried out by preparing **15** in the presence of the **17**/$TiCl_4$ catalyst and then treating it in situ with ethylene, propene, or 1-butene.[66] For instance, ethylene is converted quantitatively into the dialkylmagnesium compound within 2.5 h at 75 °C, and, after 3 h at 80—100 °C, 1-butene has reacted to 85—90%.[67]

$$Mg + H_2 \xrightarrow[THF]{17/TiCl_4} \mathbf{15} \xrightarrow[THF]{2\,CH_2=CHR} Mg(CH_2CH_2R)_2$$
$$R = H,\ CH_3,\ C_2H_5$$

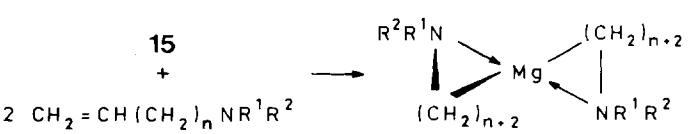
More active catalysts for the addition of **15** to 1-alkenes are obtained by the reaction of **15** with zirconium tetrahalides. In general, **15**, prepared using a Cr catalyst, is combined with the Zr catalyst and then reacted with the 1-alkene to give the dialkylmagnesium compound.

$$Mg + H_2 \xrightarrow[THF]{17/CrCl_3(TiCl_4)} \mathbf{15} \xrightarrow[THF]{ZrCl_4/2\,CH_2=CHR} Mg(CH_2CH_2R)_2$$
$$R = H,\ alkyl$$

The dialkylmagnesium compounds, prepared in THF, can be used directly for synthetic purposes; alternatively, the complexed THF can be removed in a vacuum at elevated temperatures to give, after extraction or crystallization, a hydrocarbon solution or a solid free of catalyst and practically free of THF.[54,67] The preparation of dialkylmagnesium compounds from magnesium hydride and 1-alkenes has several advantages over the usual procedures:[64,65] only about half as much magnesium is needed, only traces of magnesium-containing side products are formed, and, instead of primary alkyl halides, 1-alkenes can be used as starting materials. The reaction of the dialkylmagnesium compounds with electrophiles indicates that the catalytic addition of the hydride to the 1-alkene occurs in a highly regiospecific manner with up to 99.7% $M \rightarrow C_1$ addition. Practically no reaction is observed between MgH_2 and 1,1- or 1,2-dialkylalkenes.

15 can also be added catalytically (Zr-catalyzed) to tertiary allyl- and homoallylamines to give the monomeric compounds **22** and **23**, respectively, which can be distilled in vacuum.

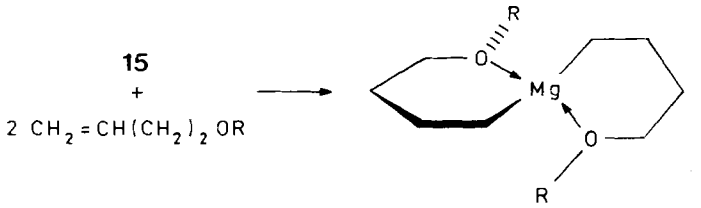
The catalyzed addition of MgH_2 to homoallyl ethers occurs to give the analogous compounds **24**,[68,69] whereas the reaction with allyl ethers leads instead to reductive cleavage of the allyl-O bond.[68,70]



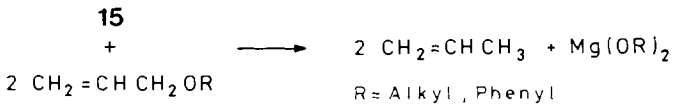
R^1, R^2 = Alkyl **22**: n = 1 **23**: n = 2

[*] After hydrolysis.

The catalyzed addition of **15** to isoprene and styrene has been discussed elsewhere.[71]



24: R = Alkyl



5.2. Reaction with Functionalized Organic Compounds

Relatively little attention has been given to the reaction of **15** with organic compounds having functional groups. Aliphatic and aromatic esters, aldehydes, and ketones afford only low yields of the alcohols upon reduction with **15** since the main reaction is condensation. The reductive cleavage of allyl ethers with **15** has been mentioned above (Section 5.1). *n*-Butyl chloride is reduced to *n*-butane by **15** in boiling THF, whereas magnesium chloride hydride (see Section 6) is the product of the reaction with allyl chloride.

5.3. Synthesis of Hydrides

15 reacts with chlorosilanes and organo-chlorosilanes in THF at room temperature (or slightly above) to give silanes in high yield. This reaction has been used, among others, to prepare SiH_4 (which is used in the synthesis of highly pure silicon)[72–74] in a one-pot synthesis from Mg, H_2, and $SiCl_4$.[75] (Methods for preparing SiH_4 are summarized in [74,76,77]).

The reaction of **15** with alkali-metal alkoxides in ether results in the formation of alkali-metal hydrides and soluble alkali-metal alkoxomagnesates.[78,79] *Nöth*[80] has shown that **15** reacts in THF at room temperature with diborane to give crystalline $Mg(BH_4)_2 \cdot 3\,thf$.

$$\mathbf{15} + n\,MOR \longrightarrow M_{n-2}Mg(OR)_n + 2\,MH$$
$$M = Li, Na, K;\ n = 3-5;\ R = Et, t\text{Bu}, cyclo\text{-}C_6H_{11}$$

6. Magnesium Chloride Hydride

Magnesium chloride hydride **25** is formed in low yield in the reaction of **15** with magnesium chloride in THF.[47] The yield is quantitative if the magnesium is hydrogenated with the **17**/$CrCl_3$ catalyst at 0°C in a saturated solution of $MgCl_2$ in THF (see Section 4).[32b,81] **25** (yield ca. 80%) is also obtained via the reaction of **15** with allyl chloride in THF[68] and is of interest as a soluble reducing agent and in Mg–H addition (hydromagnesation) reactions.

$$Mg + MgCl_2 + H_2 \xrightarrow{cat./THF} \underset{\mathbf{25}}{2\,HMgCl}$$

$$\mathbf{15} + CH_2{=}CHCH_2Cl \longrightarrow \mathbf{25} + CH_2{=}CHCH_3$$

7. Active Magnesium from Catalytically Prepared Magnesium Hydride

Activated forms of magnesium are used in chemical synthesis, particularly for Grignard reactions,[19] as reducing agents,[82] and in the preparation of magnesium-butadiene[83] and related compounds. With activated magnesium, the reactions are frequently more efficient and in some cases new reactions[84] are observed. According to *Rieke*, an active form of magnesium can be prepared by reducing a magnesium halide with an alkali metal (particularly potassium in THF or 1,2-dimethoxyethane),[85,86] if necessary with addition of naphthalene as an electron-transfer reagent.[87,88] Vaporization of magnesium leads to a finely divided form[89] which has also been used in synthesis.[90]

A highly reactive, pyrophoric form of magnesium, Mg*, which can be used in synthesis, can be prepared by dehydrogenation of **15** at 250°C at reduced pressure or above 300°C at normal pressure. This material has a specific surface area of 20–28 m^2/g.

$$\mathbf{15} \rightleftharpoons Mg^* + H_2$$

This method of preparation differs from those discussed above in that no solvent is present and the Mg* is not contaminated by alkali metal or alkali-metal halides.[91] The high reactivity of Mg* towards hydrogen is discussed in Section 8.3.

8. MgH_2/Mg as a Hydrogen Storage System

By way of introduction, the use of hydrogen as an energy source and the problems associated with its storage will first be reviewed.

8.1. Hydrogen as an Energy Source and Hydrogen Storage

Hydrogen is in many respects an ideal secondary energy source and its potential to solve present and future energy problems is the subject of widespread investigation and discussion.[92] Its advantages include the highest energy content per unit weight of all chemical fuels,[93] its versatile applications as a source of energy, and its simple, economical transportation as a gas through pipelines.[94]

The main advantage of hydrogen over coal, oil, or natural gas, taking into consideration air pollution and the threat of climatic changes in the next millenium as a result of a possible increase in the CO_2 content of the atmosphere (the "green house" effect),[97] is its combustion to water.[96]

A number of problems stand in the way of the development of a hydrogen economy, and an increase in the use of hydrogen as a source of energy is expected only towards the end of this century.[95] These problems are associated with both the production of hydrogen using primary energy sources (e.g., the sun or nuclear power) and the introduction of hydrogen as an energy source for industry, transportation, or the home, including the problem of hydrogen storage. The use of hydrogen in many of these areas (particularly transportation) rests upon the availability

of a simple, economic, and safe way to store large quantities of hydrogen in a small volume and with an acceptable weight.

In principle, hydrogen can be stored either in the elemental form, as a gas or a liquid, or in a chemical form. As a chemical form of hydrogen storage, metal hydrides are receiving the most attention.[98] NH_3 is used industrially to store hydrogen[99] and the use of methylcyclohexane has been considered.[100]

8.2. Metal Hydrides as Reversible Hydrogen Storage Systems

The reaction of hydrogen with metals, metal alloys, and intermetallic compounds frequently results in the formation of metal hydrides. Since these reactions are exothermic and reversible, the metal hydrides can release hydrogen if heated.

$$M + n/2\,H_2 \rightleftharpoons MH_n + \text{heat}$$

M = metal, metal alloy, intermetallic compound

In principle, the sequence can be repeated as often as desired and forms the basis for the use of the metal hydride/metal system in both hydrogen storage and heat storage.

Important criteria for the choice of the metal hydride are a high hydrogen content per unit weight and volume, a temperature-dependent hydrogen dissociation pressure, and a satisfactory rate of reaction, as well as the repeatability of the dehydrogenation/hydrogenation process and the effect of impurities in the hydrogen. Moreover, economic factors (raw material and production costs) play a crucial role. Table 2 summarizes data for some metal hydride/metal/H_2 storage systems. The so-called low-temperature storage systems (LaNi- or FeTi-H_2) contain relatively small amounts of hydrogen per unit weight but this is liberated at 20°C. On the other hand, the high-temperature systems (Mg_2Ni- and Mg-H_2) liberate hydrogen only at temperatures above 250°C. The hydrogen density in all these hydrides is higher than that in liquid hydrogen.

Table 2. Characteristics of various metal/metal hydride systems.

	Wt.-% H_2	Decomposition temperature [°C] (P_s = 1 bar)	Energy density [MJ/kg]
TiFe/TiFeH	1.00	− 6	1.2
$TiCr_2$/$TiCr_2H$	1.20	− 20	1.4
TiCo/TiCoH	1.30	130	1.4
$LaNi_5$/$LaNi_5H_6$	1.37	20	1.5
Mg_2Al_3/$Mg_2Al_3H_4$	3.00	230	3.6
Mg_2Ni/Mg_2NiH_4	3.16	250	3.8
Mg/MgH_2	7.66	284	9.0

Magnesium hydride has the highest hydrogen content (7.6%), and hence the highest energy density per unit weight (9 MJ/kg), of all the metal hydrides studied; moreover, magnesium is relatively cheap. Magnesium would therefore seem to be an optimal hydrogen storage material. So far, however, the unfavorable kinetic behavior of the MgH_2/Mg system,[33d-h, 101] as well as the high dissociation temperature, have made its use unattractive. The doping or alloying of magnesium with a second metal (Al,[102] In,[33e] Ce,[103] La,[103c] Fe,[104] and other metals[105]) or the formation of intermetallic compounds (Mg_2Ni,[34b, 102, 103a, 106] Mg_2Cu,[33g, 34a] $LaNi_5$[105a]) results in an improvement in the rate of dehydrogenation/hydrogenation, but a relatively high proportion of the second metal is needed (e.g., 10 wt.-% Ni)[103a, 106] and the storage capacity is less than that of magnesium hydride.[103a]

8.3. Catalytically Prepared Magnesium Hydride as a Hydrogen Storage Material[107]

We have used two methods to investigate the properties of various MgH_2 samples for hydrogen storage: the sample is either taken through one or more dehydrogenation/hydrogenation cycles under normal pressure or it is subjected to a series of cycles under slightly elevated (maximum 15 bar) pressures.

The normal pressure experiments are carried out in the specially constructed thermovolumetric apparatus shown in Fig. 3.[31] The oven with the MgH_2 sample (0.5—1.0 g) in the sample container is heated above the decomposition temperature of MgH_2 at normal pressure (284°C), e.g. to 330°C, and the liberation of hydrogen is followed using an automatic gas-burette. At the same time, the temperature of the sample is recorded. After complete dehydrogenation, the oven temperature is lowered to a value below 284°C (e.g., 230°C) and the absorption of hydrogen by the magnesium is followed in the same way. This procedure can be used to measure empirically the hydrogen content of MgH_2 (or of other metal hydrides) and to study the rate of release and up-take of hydrogen at normal pressure.[31]

The behavior of the various samples of MgH_2 (Fig. 4) depends upon their origin and treatment. The MgH_2 prepared at high temperature[33i] (Fig. 4a) liberates 3.5 wt.-%

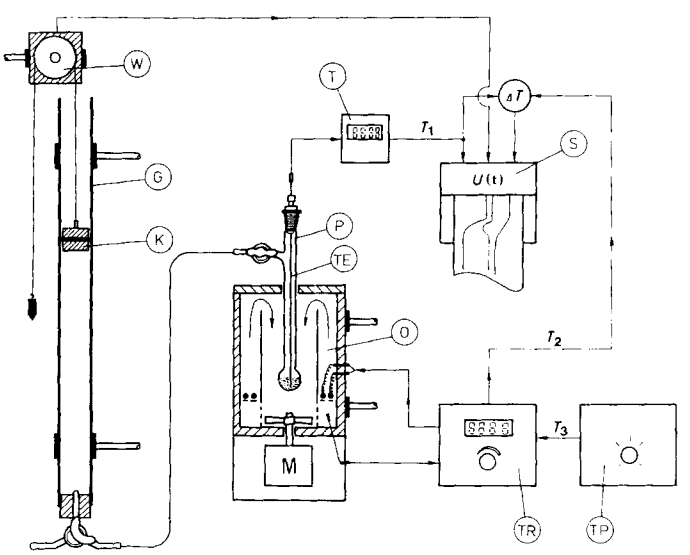


Fig. 3. Thermolysis apparatus used to investigate hydrogen storage materials at normal pressure. G, gas-burette; K, flask; W, displacement/voltage converter, O, electrically heated oven; P, sample container; T, digital thermometer; TE, thermocouple; TP, temperature program; TR, temperature control unit; S, three-channel recorder; T_1, sample temperature; T_2, oven temperature; T_3, programmed temperature.

hydrogen over 6 h at 382 °C; the rehydrogenation at 230 °C leads to the reabsorption of only a small fraction of the hydrogen released. The dehydrogenation of a sample prepared from magnesium alloyed with 10% Ni (Fig. 4b) takes place rapidly at 330 °C with the release of 6.3 wt.-% hydrogen. However, here again only a partial rehydrogenation is observed at 230 °C and normal pressure. A more satisfactory result is obtained for the rehydrogenation of **15** (Fig. 4c) under the same conditions, and still further improvement in the properties can be obtained by doping **15** with traces (0.5—2%) of a second metal using a specially developed procedure (Fig. 4d).[108] Three dehydrogenation/hydrogenation cycles at normal pressure using doped **15** are shown in Fig. 5. To our knowledge, the conditions used are the mildest for the charging of a magnesium-based H_2 storage material.

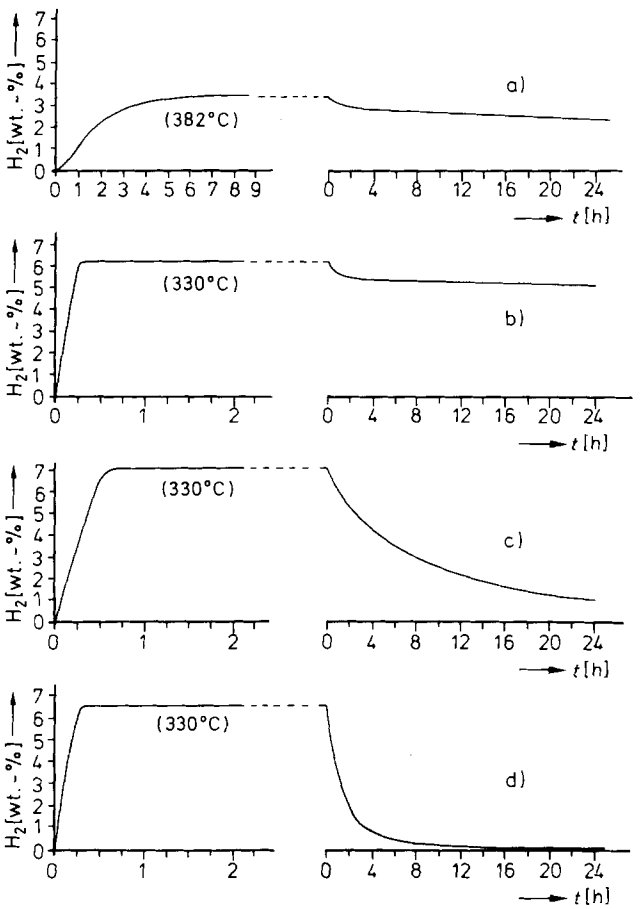


Fig. 4. Storage properties of various MgH_2 samples at normal pressure. a) technical MgH_2; b) hydrogenated $Mg_{90}Ni_{10}$ alloy; c) **15**; d) doped **15**. Left: dehydrogenation at 1 bar, temperature in parentheses; right: rehydrogenation at 1 bar, 230 °C.

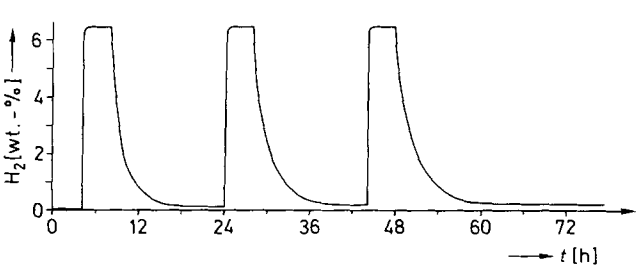


Fig. 5. Three hydrogenation/dehydrogenation cycles carried out on doped **15**.

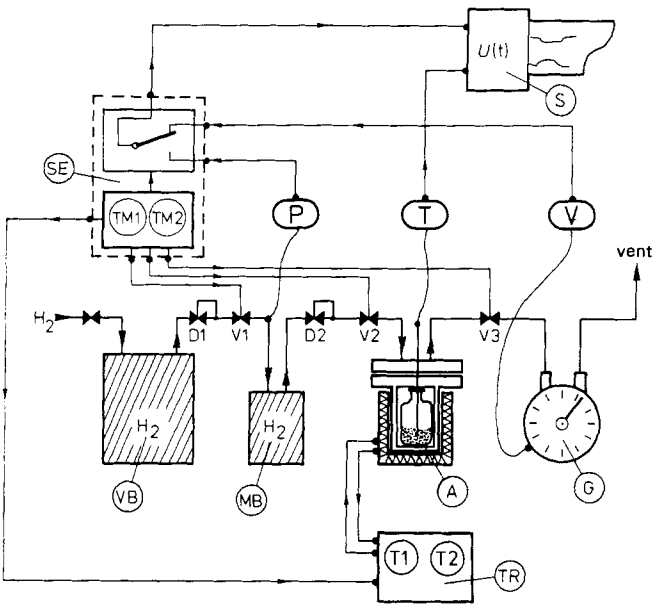


Fig. 6. An automatic apparatus for investigating MgH_2 samples under pressure (schematic drawing). A, autoclave with heater; D_1, D_2, pressure reduction valves; G, gasometer; MB, H_2 cylinder; P, pressure transducer; S, two-channel recorder; SE, electronic control unit; T, digital thermometer; T_1, T_2 temperature sensor for hydrogenation and dehydrogenation; TM1, TM2, timer for hydrogenation and dehydrogenation; TR, temperature control unit; V, gas volume transducer; V_1, V_2, V_3, electronically controlled valves; VB, H_2 source.

The series of cycles at elevated pressures are carried out in a fully automated apparatus (Fig. 6). Samples of **15** or **15** doped with a second metal, **15'**,[108] (or other magnesium hydride or metal hydride samples) are subjected typically to 30—50 dehydrogenation/hydrogenation cycles during which the hydrogenation pressure, temperature, and duration as well as the dehydrogenation temperature and duration can be varied. After 30—50 or more cycles, the kinetics and the storage capacity of the MgH_2/Mg systems **15** and **15'** are unaltered, within the experimental error, even though hydrogen having only 99.9% purity (i.e., not ultra-pure H_2) was used for these experiments. The rates of hydrogenation of **15** and **15'**, however, are very different (Fig. 7). The largest difference is observed for the

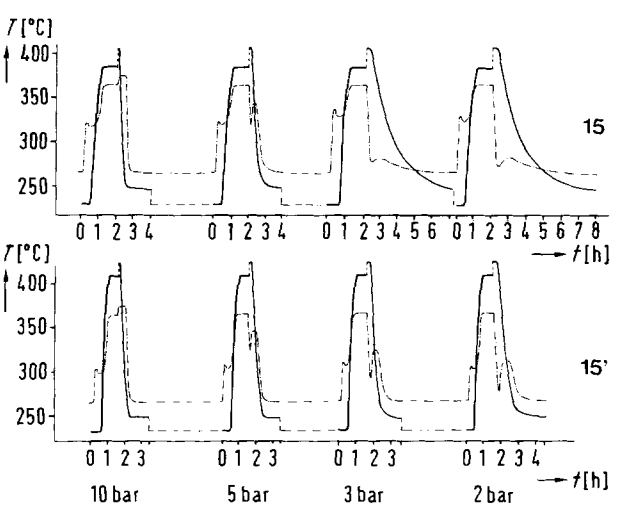


Fig. 7. Comparison of the storage properties of **15** and **15'** at various pressures. ——: H_2 absorption and desorption (arbitrary units); – – – –: temperature curve.

low pressure (2—3 atm of H_2) experiments: the effective hydrogenation time for **15** is three times longer. At higher pressures the difference in rate between the doped and undoped samples becomes less since, as the rate of hydrogenation increases, heat transfer becomes the rate-determining factor.

The results indicate that both **15** and **15′**, which have the highest (7%) known hydrogen storage capacity, might well have potential in hydrogen storage, whereby the mild hydrogenation conditions and the high rate of absorption and desorption of H_2 observed for **15′** could be of practical advantage.

To test the use of **15** as a hydrogen storage material, a number of hydride storage tubes were filled with cylindrical pellets of **15** (Fig. 8). The use of **15** in pellet form increases the hydrogen density per unit volume[109] while at the same time improving the heat conductance and decreasing the pyrophoric nature of the powder.[110] The storage capacity and kinetic behavior of the pellet form of **15** in a 60—70 cycle run at elevated pressure was shown to be similar to that of the powder.



Fig. 8. Pelleted, air-stable Mg/MgH_2 storage material with hydride storage tube (Zentrale Forschung der Daimler-Benz AG).

The applications of this magnesium-based hydrogen storage system range from hydrogen, and therefore energy, storage[98] to hydrogen transport,[111] heat storage,[112] and hydrogen separation and purification.[113]

Our investigations have shown that certain active forms of magnesium, which can be obtained, e.g., by dehydrogenation of **15** or **15′**, can be used to separate and purify hydrogen.[114] These even react with hydrogen at 200—230 °C and a partial pressure of 20—30 mbar and are inert towards methane or its homologues. Thus, hydrogen can be removed, in a one-step process, from mixtures of hydrogen and such gases and can subsequently be recovered by dehydrogenation of the resulting magnesium hydride. Only traces (1—2%) of hydrogen remain in the treated gas. It is of interest that the rate of absorption of hydrogen is hardly affected by traces (up to ca. 1 mol-%) of CO, CO_2, NH_3, or water vapor (saturated at 10 atm). These gases either react irreversibly with the active magnesium (or MgH_2) or are converted into other products (CO is reduced to CH_4). In this way, impurities can be removed from the gas; however, this is accompanied by a decrease in the hydrogen storage capacity. In contrast, the hydrogenation of the $LaNi_5$- or FeTi-H_2 storage systems is markedly inhibited by traces of CO, O_2, or H_2O in the hydrogen.[115] The following features characterize the use of **15** and **15′** in hydrogen storage:

- The initial catalytic hydrogenation of the magnesium can be carried out under mild, energetically favorable conditions.
- The kinetic characteristics can be improved by doping with traces of a second metal.
- **15** and **15′** do not have to be activated,[33h, 105a, 116] i.e., full activity (optimal kinetics and maximal absorption) is reached immediately without the need for a number of preliminary absorption-desorption cycles.
- The "active" magnesium derived from **15** or **15′** takes up hydrogen at a pressure lower than that observed for any previous magnesium-based storage system.
- The rate of hydrogenation is only slightly affected by the presence of impurities in technical hydrogen.

9. Summary and Outlook

The catalytically prepared magnesium hydride has made it possible to combine the high hydrogen-storage capacity of magnesium with a satisfactory rate of up-take and release of hydrogen (even at 1 bar), without having to resort to alloys. The use of soluble organometallic catalysts allows the initial hydrogenation to be carried out under mild conditions and gives a product that has favorable properties for chemical and practical purposes. It is to be hoped that such mild methods will be applied not only to the hydrogenation and activation of magnesium and the alkali metals but also to other areas involving the chemical conversion of metals.

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Oxidation of Organometallic Compounds

By Jack Halpern*

Dedicated to Professor Günther Wilke on the occasion of his 60th birthday

Stable organometallic compounds, notably of the later transition metals (groups VI—VIII), usually are characterized by closed shell electron configurations (typically 18-electron valence shells) which are destabilized by electron addition or removal. One-electron oxidation of such compounds results in the formation of unstable radical ions, whose characteristic reactivity patterns include susceptibility to nucleophilic attack, disproportionation, and metal-carbon bond dissociation. Two-electron oxidation may result in dissociation or oxidation of the organic ligand. In this review studies on the chemical and electrochemical oxidations of metal carbonyls, metal-olefin complexes, and alkyl transition-metal compounds are described. The studies encompass the following themes: (1) The kinetics and thermodynamics of the initial redox steps; (2) The characterization and reactivity patterns of the resulting oxidation products; (3) The synthetic and catalytic applications of organometallic redox processes.

1. Introduction

Whereas electron-transfer and simple redox reactions of inorganic coordination compounds have been extensively studied, and many features of their kinetics and mechanisms are well understood,[1] our knowledge and understanding of the corresponding redox chemistry of organometallic compounds is much less advanced. Indeed, only within the past decade have such redox processes received significant attention and study.

With a few notable exceptions (for example, $[V(CO)_6]$[2] and $[Fe(C_5H_5)_2]^{\oplus}$)[3] stable organometallic compounds, especially of the later transition metals (groups VI to VIII), correspond to closed shell electron configurations (often 18-, sometimes 16-, electron valence shells) which are destabilized by electron addition or removal, generating unstable products that undergo further reactions. Equations (1)—(3) illustrate this distinction (R = alkyl or aryl; Hdmg = dimethylglyoximato(1−); L = H_2O, py, etc.).

$$\underset{18e}{[Fe(CN)_6]^{4\ominus}} \xrightarrow{-e^{\ominus}} \underset{17e}{[Fe(CN)_6]^{3\ominus}} \quad \text{(stable)} \qquad (1)$$

$$\underset{18e}{[Cr(CO)_6]} \xrightarrow{-e^{\ominus}} \underset{17e}{[Cr(CO)_6]^{\oplus}} \quad \text{(unstable)} \qquad (2)$$

$$\underset{18e}{[R{-}Co(Hdmg)_2L]} \xrightarrow{-e^{\ominus}} \underset{17e}{[R{-}Co(Hdmg)_2L]^{\ominus}} \quad \text{(unstable)} \qquad (3)$$

This review is concerned particularly with the chemical and electrochemical oxidation reactions of organo-transition metal compounds, including those containing carbonyl, olefin, and alkyl ligands. The themes to be considered include: (1) the kinetics and mechanisms of the initial redox processes, (2) the characterization of the initial (often unstable and short-lived) organometallic oxidation products and the study of their chemical reactivities, and (3) the roles of oxidation of organometallic compounds in catalytic oxidation and other catalytic processes.

Only insofar as they impinge upon these themes will attention be directed to certain related topics, notably chemical and electrochemical *reductions* of organometallic compounds,[4,5] oxidative-addition and reductive-elimination reactions,[6,7] and redox reactions of non-transition metal organometallic compounds,[8,9] Attention is directed in the cited references to other reviews of some relevant aspects of these topics.

2. Oxidation of Metal Carbonyls

Our interest in this theme had its origin in our early studies on the oxidation of CO in aqueous solution by metal ions such as Hg^{II} and Ag^{I} [Eq. (4) and (5)].[10,11]

$$CO + 2\,Hg^{2\oplus} + H_2O \longrightarrow CO_2 + Hg_2^{2\oplus} + 2\,H^{\oplus} \qquad (4)$$

$$CO + 2[Ag(NH_3)_2]^{\oplus} + 2\,H_2O \longrightarrow CO_3^{2\ominus} + 2\,Ag + 4\,NH_4^{\oplus} \qquad (5)$$

These and subsequently identified oxidations of CO by other metal ions, such as Rh^{III}, Ni^{II}, and Cu^{II}, have been interpreted as proceeding through mechanisms involving hydroxycarbonyl (or metallacarboxylic acid) complexes such as **1** [Eq. (6) and (7)].[12]

$$Hg^{2\ominus} + CO + H_2O \xrightarrow{\text{rate-determining}} [Hg{-}\underset{\underset{\mathbf{1}}{\|}}{\overset{O}{C}}OH]^{\oplus} + H^{\oplus} \xrightarrow{\text{fast}} Hg^0 + CO_2 + 2\,H^{\oplus} \qquad (6)$$

$$Hg^0 + Hg^{2\oplus} \xrightarrow{\text{fast}} Hg_2^{2\ominus} \qquad (7)$$

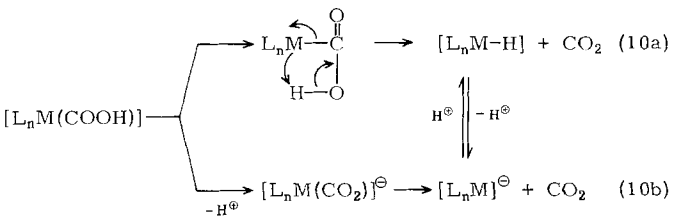
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Pathways analogous to that depicted above for the oxidation of free CO extend also to the oxidation of coordinated CO. Thus, certain metal carbonyl complexes are decomposed by reaction with H_2O (or $OH^{\ominus}$) with the formation of CO_2 (or $CO_3^{2\ominus}$) and a reduced metal carbonyl or a metal hydride [Eq. (8) and (9)].[13,14]

$$[Fe^0(CO)_5] \xrightarrow{OH^{\ominus}} [Fe^0(CO)_4(COOH)]^{\ominus} \xrightarrow{2\,OH^{\ominus}} [Fe^{-II}(CO)_4]^{2\ominus} + H_2O + HCO_3^{\ominus}$$
$$\Updownarrow$$
$$[HFe^0(CO)_4]^{\ominus} + OH^{\ominus} \qquad (8)$$

$$trans\text{-}[Pt^{II}Cl(PEt_3)_2(CO)]^{\oplus} \xrightarrow[-H^{\oplus}]{H_2O} trans\text{-}[Pt^{II}Cl(PEt_3)_2(COOH)] \longrightarrow trans\text{-}[HPt^{II}Cl(PEt_3)_2] + CO_2 \qquad (9)$$

Only recently have several examples of stable hydroxycarbonyl complexes, including *trans*-$[PtCl(PEt_3)_2(COOH)]$, actually been intercepted and characterized.[15-18] Such complexes tend to be unstable and to decompose upon warming or upon reaction with water, with loss of CO_2 to form the corresponding hydrides. An unresolved mechanistic question is whether such decomposition, especially in the presence of water, involves the direct transfer of hydrogen to the metal (β-elimination of CO_2) according to Eq. (10a) or deprotonation to yield an intermediate CO_2 complex (or metallacarboxylate) according to Eq. (10b). Both processes are inherently plausible and it is possible that both occur in appropriate circumstances.



It is likely that the $[Hg(COOH)]^{\oplus}$ intermediate **1** in reaction (6) is formed by external nucleophilic attack of water on the transient mercury(II)-carbonyl complex **2** [Eq. (11)], analogous to the mercury(II)-olefin complexes (or mercurinium ions) **3** that have been postulated as intermediates in the closely related olefin oxymercuration reactions [Eq. (12)].[19]

$$Hg^{2\oplus} + CO \rightleftharpoons \underset{\mathbf{2}}{[Hg(CO)]^{2\oplus}} \xrightarrow{H_2O} [Hg(COOH)]^{\oplus} + H^{\oplus} \qquad (11)$$

$$Hg^{2\oplus} + CH_2{=}CH_2 \rightleftharpoons \underset{\mathbf{3}}{[Hg(CH_2{=}CH_2)]^{2\oplus}} \xrightarrow{H_2O}$$
$$[Hg(CH_2CH_2OH)]^{\oplus} + H^{\oplus} \qquad (12)$$

To the extent that such prior coordination of CO is an important component of the CO oxidation pathway, the scope of such oxidations would appear to be constrained by the limited tendency of CO to coordinate to metal ions in high oxidation states (for example, potential oxidants such as Co^{III}). It appeared to us that a possible approach to get around this limitation and thereby to extend the scope for possible metal-ion oxidations of CO (and related unsaturated molecules) would be to start with a stable metal-carbonyl complex in a low (i.e., non-oxidizing) oxidation state and to oxidize the pre-formed complex to a higher oxidation state of the metal ion which would not normally coordinate CO.

This approach was applied successfully to effect the oxidation of CO in the mixed ligand Co^I complex $[Co^I(CN)_2(PEt_3)_2(CO)]^{\ominus}$ (abbreviated $[L_nCo^I(CO)]^{\ominus}$), using $[Fe(CN)_6]^{3\ominus}$ (abbreviated $X^{3\ominus}$) as oxidant.[20] $[L_nCo^I(CO)]^{\ominus}$ was found to undergo two successive one-electron oxidations in aqueous solution to form the CN-bridged binuclear Co^{III} complex $[(NC)_5Fe^{II}(CN)Co^{III}(CN)_2(PEt_3)_2(CO)]^{3\ominus}$ (abbreviated $[XL_nCo^{III}(CO)]^{3\ominus}$). The fate of the latter is determined by the pH of the solution [Eq. (13)]; the paths (13a), (13b), and (13c) predominate in the pH ranges <4.5, 4.5—11.5, and >11.5, respectively. The rate constants $k_{(13b)}$ and $k_{(13c)}$ at 25° are 1.0×10^{-3} and $3.4\ s^{-1}$, respectively.

$$[L_nCo^I(CO)]^{\ominus} \underset{X^{4\ominus}}{\overset{X^{3\ominus}}{\rightleftharpoons}} [L_nCo^{II}(CO)] \xrightarrow{X^{3\ominus}}$$

$$[XL_nCo^{III}(CO)]^{3\ominus} \xrightarrow{H_2O} [XL_nCo^{III}(H_2O)]^{3\ominus} + CO \qquad (13a)$$
$$OH^{\ominus}\Updownarrow$$
$$[XL_nCo^{III}(COOH)]^{4\ominus} \xrightarrow{k_{(13b)}} [XL_nCo^{I}]^{5\ominus} + CO_2 + H^{\oplus} \qquad (13b)$$
$$OH^{\ominus}\Updownarrow H_2O$$
$$[XL_nCo^{I}(CO_2)]^{5\ominus} \xrightarrow{k_{(13c)}} [XL_nCo^{I}]^{5\ominus} + CO_2 \qquad (13c)$$

In the presence of excess $[Fe(CN)_6]^{3\ominus}$ the L_nCo^I produced in reaction (13b) or (13c) is irreversibly oxidized to a Co^{III} complex [Eq. (14)], resulting in the overall stoichiometry of Eq. (15). Under these conditions the effective reducing power of the coordinated CO, as well as of the Co^I ion, is utilized to supply electrons for the reduction of $[Fe(CN)_6]^{3\ominus}$ so that $[L_nCo^I(CO)]^{\ominus}$ acts as a 4-electron reductant.

$$[XL_nCo^I]^{5\ominus} + 2X^{3\ominus} + H_2O \longrightarrow [XL_nCo^{III}(H_2O)]^{3\ominus} + 2X^{4\ominus} \qquad (14)$$

$$[L_nCo^I(CO)]^{\ominus} + 4X^{3\ominus} + 2OH^{\ominus} \longrightarrow$$
$$[XL_nCo^{III}(H_2O)]^{3\ominus} + 3X^{4\ominus} + CO_2 \qquad (15)$$
$$CO_2 + 2OH^{\ominus} \rightleftharpoons CO_3^{2\ominus} + H_2O$$

The apparent reversibility of the sequence of steps corresponding to Eq. (16), and the relatively slow decomposition of the intermediate CO_2 complex, $[XL_nCo^I(CO_2)]^{5\ominus}$ ($k_{(13c)}=3.4\ s^{-1}$), identifies a pathway for the reduction of coordinated CO_2 to CO (i.e., by Co^I). Since CO_2 has been demonstrated to coordinate to other Co^I complexes,[21] this suggests a possible approach to the homogeneous catalytic reduction of CO_2, an objective of considerable current interest. The recently reported catalytic reduction of CO_2 to CO at carbon electrodes modified with cobalt phthalocyanine probably involves related chemistry.[22]

$$[XL_nCo^{III}(CO)]^{3\ominus} \overset{OH^\ominus}{\rightleftharpoons} [XL_nCo^{III}(COOH)]^{4\ominus} \overset{OH^\ominus}{\underset{H_2O}{\rightleftharpoons}} [XL_nCo^I(CO_2)]^{5\ominus} \quad (16)$$

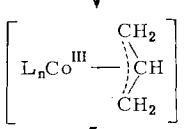
Because of the effectiveness of CO_2 as a leaving group, redox pathways such as (17) may result in the formation of "coordinatively unsaturated" species, e.g., $[XL_nCo^I]^{5\ominus}$ (or $[L_nCo^I]^\ominus$, which presumably is formed readily from $[XL_nCo^I]^{5\ominus}$ by loss of $X^{4\ominus}$), with high affinities for a variety of ligands, notably those (e.g., olefins) that are effective in stabilizing low oxidation states. This opens up the possibility of synthetic approaches involving the "oxidative substitution" of CO by other ligands to generate complexes that are not readily synthesized by other methods, such as **4** and **5** [Eq. (17)–(19)].[20]

$$[L_nCo^I(CO)]^\ominus \xrightarrow[-X^{4\ominus}\ -H_2O]{2\,X^{3\ominus}\ 2\,OH^\ominus} [XL_nCo^I(CO_2)]^{5\ominus} \xrightarrow[-X^{4\ominus}]{-CO_2} [L_nCo^I]^\ominus \quad (17)$$

$$[L_nCo^I]^\ominus \xrightarrow{CH_2=CHCN} [L_nCo^I(CH_2{=}CHCN)]^\ominus \quad (18)$$

4

$$[L_nCo^I]^\ominus \xrightarrow{CH_2=CHCH_2OH} [L_nCo^I(CH_2{=}CHCH_2OH)]^\ominus \xrightarrow{-OH^\ominus} \quad (19)$$



5

When the oxidation of $[L_nCo^I(CO)]^\ominus$ according to Eq. (13b) and (13c) is conducted in the presence of an excess of CO, the coordinatively unsaturated $[L_nCo^I]^\ominus$ intermediate is readily trapped by CO to reconstitute the initial $[L_nCo^I(CO)]^\ominus$ complex. This results in the establishment of a catalytic cycle for the oxidation of CO [Eq. (20)]. When the oxidant is $[Fe(CN)_6]^{3\ominus}$ the overall catalytic reaction corresponds to Eq. (21).[20]

$$\begin{array}{ccc} [Co^I(CO)] & \xrightarrow{-2\,e^\ominus} & [Co^{III}(CO)] \\ \uparrow{\scriptstyle [CO]} & & \downarrow{\scriptstyle 2\,OH^\ominus\ (-H_2O)} \\ [Co^I] & \xleftarrow{-CO_2} & [Co^I(CO_2)] \end{array} \quad (20)$$

$$CO + 2\,OH^\ominus + 2\,[Fe(CN)_6]^{3\ominus} \xrightarrow{[L_nCo^I(CO)]^\ominus} CO_2 + 2\,[Fe(CN)_6]^{4\ominus} + H_2O \quad (21)$$

Catalysis of the oxidation of CO also has been observed in the case of certain other metal-ion oxidants (e.g., Cu^{II} and Rh^{III}) whose reduction products (Cu^I and Rh^I) form stable CO complexes.[12] In such cases reduction may be autocatalytic as in the reduction of $RhCl_3$ by CO [Eq. (22)] where both uncatalyzed and autocatalytic pathways are observed [Eq. (23) and (24)], corresponding to the rate laws $k'[Rh^{III}][CO]$ and $k''[Rh^{III}][Rh^I(CO)_2]$, respectively.

$$[Rh^{III}] + 3\ CO + H_2O \longrightarrow [Rh^I(CO)_2] + CO_2 + 2\ H^\oplus \quad (22)$$

$$[Rh^{III}] \xrightarrow{CO} [Rh^{III}(CO)] \xrightarrow[-H^\oplus]{H_2O} [Rh{-}\overset{O}{\overset{\|}{C}}OH] \xrightarrow[-H^\oplus]{-CO_2} [Rh^I] \xrightarrow{2\,CO} [Rh^I(CO)_2] \quad (23)$$

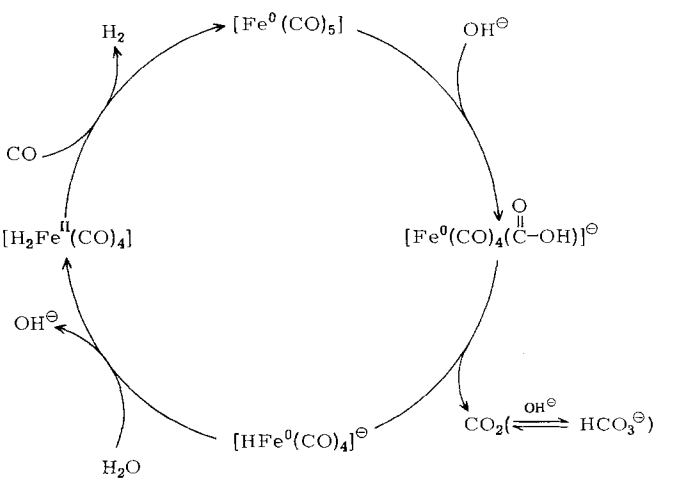
$$[Rh^{III}] + [Rh^I(CO)_2] \longrightarrow [Rh^I] + [Rh^{III}(CO)_2] \xrightarrow{H_2O,\ -H^\oplus} [Rh^{III}(CO)(COOH)] \xrightarrow{CO} [Rh^I(CO)] + CO_2 + H^\oplus \quad (24)$$

Other catalytic applications of the metal-carbonyl chemistry described above include catalysis of the water-gas shift reaction [Eq. (25)][12,23–25] and the use of combinations of CO and H_2O as a source of hydrogen or of electrons to effect hydrogenation, hydroformylation [Eq. (26)], or reduction [Eq. (27)].[23,26,27] Mechanistic schemes for reactions (25) and (26) are depicted in Schemes 1 and 2, respectively.

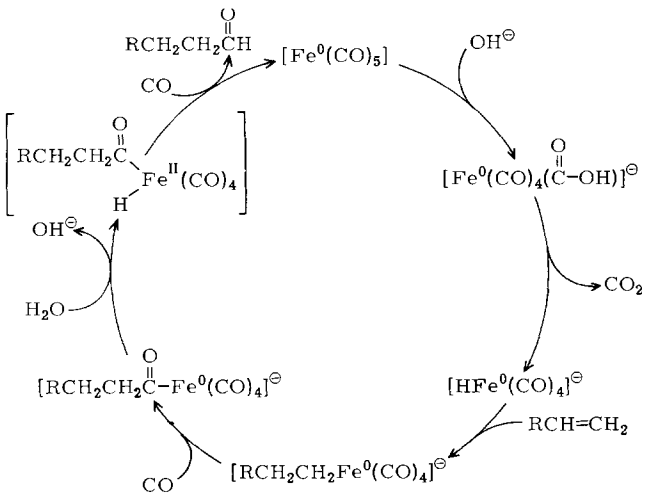
$$CO + H_2O \xrightarrow{[Fe(CO)_5]} H_2 + CO_2\ (\overset{OH^\ominus}{\rightleftharpoons} HCO_3^\ominus) \quad (25)$$

$$RCH{=}CH_2 + 2CO + H_2O \xrightarrow{[Fe(CO)_5]} RCH_2CH_2\overset{O}{\overset{\|}{C}}H + CO_2 \quad (26)$$

$$RNO_2 + 3CO + H_2O \xrightarrow{[Fe(CO)_5]} RNH_2 + 3CO_2 \quad (27)$$



Scheme 1. Mechanism of the $Fe(CO)_5$-catalyzed water-gas shift reaction [Eq. (25)].



Scheme 2. Mechanism of the $Fe(CO)_5$-catalyzed hydroformylation of alkenes [Eq. (26)].

The susceptibility of coordinated CO to nucleophilic attack by water and the instability of the resulting hydroxycarbonyl complexes usually precludes the direct detection and characterization of oxidized metal-carbonyl complexes in aqueous solution. In less nucleophilic solvents such as acetonitrile, oxidation may simply result in the liberation of coordinated CO and other ligands [Eq. (28) and (29), C_4H_6 = butadiene].[28]

$$[Fe(CO)_5] \xrightarrow{-e^{\ominus}} [Fe(CO)_5]^{\oplus}\ (?) \xrightarrow{-e^{\ominus}} Fe^{II} + 5CO \qquad (28)$$

$$[Fe(CO)_3(C_4H_6)] \xrightarrow{Fe^{III}\ or\ Ce^{IV}} Fe^{II} + 3CO + C_4H_6 \qquad (29)$$

In some cases the lifetimes of the oxidized species are sufficiently long that the electrochemical oxidations of metal carbonyls or mixed ligand carbonyl complexes to the corresponding 17-electron radical cations yield reversible cyclic voltammograms as in the example of Eq. (30) and the corresponding oxidations of $[Cr(CO)_5(PPh_3)]$,[29] $[CpMn(CO)(PPh_3)_2]$,[30] $[Fe(CO)_3(PR_3)_2]$,[31] $[Cr(CO)_5I]^{\ominus}$,[32] $[Ta(CO)_2(dmpe)_2Cl]^{\oplus}$,[33] $[CpCo(PPh_3)_2]$,[34] and $[Cr(CO)_6]$[35] (Cp = cyclopentadienyl; dmpe = bis(1,2-dimethylphosphino)ethane). Several such species have been characterized by electron absorption and EPR spectroscopy and at least one, $[Cr(CO)_4(PPh_3)_2]^{\oplus}$, has recently been isolated as a stable salt.[36] One decomposition pathway of such 17-electron radical cations in solution is through disproportionation [Eq. (31)].[37]

$$[Cr(CO)_6] \underset{e^{\ominus}}{\overset{-e^{\ominus}}{\rightleftharpoons}} [Cr(CO)_6]^{\oplus} \qquad (30)$$

$$2[Cr(CO)_6]^{\oplus} \longrightarrow [Cr(CO)_6] + [Cr(CO)_6]^{2\oplus}\ (\longrightarrow Cr^{II} + 6CO) \qquad (31)$$
unstable

3. Oxidation of Metal-Olefin Complexes

Metal ions such as Pd^{II}[38,39] and Tl^{III}[40,41] are useful oxidants for olefins, particularly in view of the distinctive selectivities which they characteristically exhibit. Mechanistic pathways for such reactions have been postulated which involve both π- and σ-bonded organometallic intermediates, an example being the widely accepted mechanism of the Wacker reaction [Eq. (32)].

$$[PdCl_4]^{2\ominus} \xrightarrow[-Cl^{\ominus}]{CH_2=CH_2} [PdCl_3(CH_2=CH_2)]^{\ominus} \xrightarrow[-H^{\oplus}]{H_2O}$$

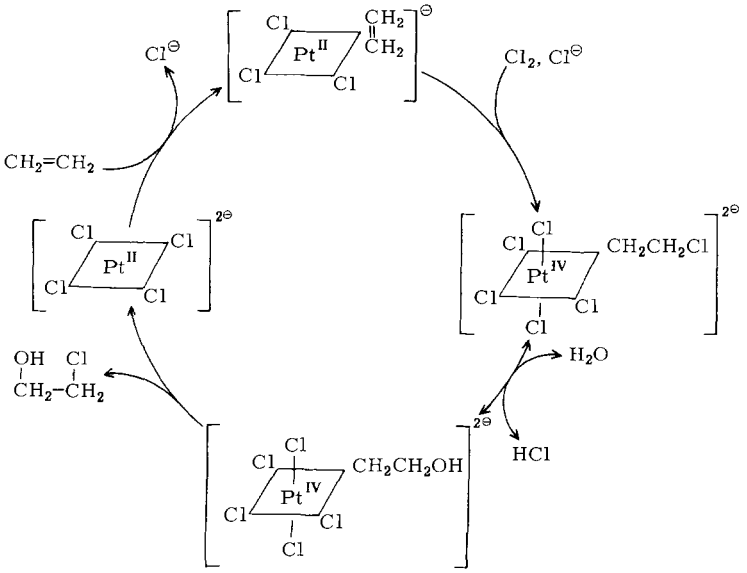
$$[PdCl_3(CH_2CH_2OH)]^{2\ominus} \longrightarrow Pd^0 + CH_3CHO + H^{\oplus} + 3Cl^{\ominus} \qquad (32)$$

The evidence upon which this mechanism rests is not entirely conclusive, particularly with respect to the intermediacy of the σ-bonded organometallic species $[PdCl_3(CH_2CH_2OH)]^{2\ominus}$ for which there is only indirect evidence[38,39] (although analogous $[Tl{\geqslant}C-C{\leqslant}OH]^{2\ominus}$ intermediates have been identified in the oxidations of certain olefins by Tl^{III}).[40a] To the extent that initial π-coordination of the olefins to the metal ion is an important component of the oxidation pathway, such oxidations (like the corresponding oxidations of CO discussed above)[20] would appear to be constrained by the limited tendencies of olefins to coordinate to metal ions in high oxidation states. Accordingly, one strategy for extending the scope of metal-ion oxidations (paralleling that described above for CO oxidation) would be to start with a stable olefin complex of a metal ion in a low oxidation state and to oxidize the pre-formed complex to a higher oxidation state with an external oxidant.

An illustration of the successful application of this approach is provided by the oxidation of Zeise's anion, $[Pt^{II}Cl_3(CH_2=CH_2)]^{\ominus}$, in aqueous HCl solution by Cl_2.[42] The addition of a stoichiometric amount of Cl_2 results in the oxidation of the coordinated ethylene to chlorohydrin [Eq. (33)]. Excess Cl_2 further oxidizes $[Pt^{II}Cl_4]^{2\ominus}$ to $[Pt^{IV}Cl_6]^{2\ominus}$.

$$[Pt^{II}Cl_3(CH_2=CH_2)]^{\ominus} + Cl_2 + H_2O \longrightarrow \qquad (33)$$
$$[PtCl_4]^{2\ominus} + \overset{Cl}{\overset{|}{CH_2}}-\overset{OH}{\overset{|}{CH_2}} + H^{\oplus}$$

A detailed study of this reaction has revealed that it proceeds according to the stepwise mechanism in Scheme 3.[42] The first step of this sequence apparently involves the rapid oxidative addition of Cl_2 to $[Pt^{II}Cl_3(CH_2=CH_2)]^{\ominus}$ to form $[Pt^{IV}Cl_5(CH_2=CH_2)]^{\ominus}$, followed by nucleophilic attack of $Cl^{\ominus}$ on the coordinated ethylene to form the σ-bonded complex $[Pt^{IV}Cl_5(CH_2CH_2Cl)]^{2\ominus}$. In the second step, a reversible solvolytic nucleophilic displacement of the chloride, apparently reflecting the activating influence of the β-Pt substituent, yields the β-hydroxy σ-complex $[Pt^{IV}Cl_5(CH_2CH_2OH)]^{2\ominus}$, the analogue of the postulated $[Pd^{II}Cl_3(CH_2CH_2OH)]^{2\ominus}$ intermediate in the Wacker reaction [Eq. (32)]. In the third step, reductive elimination of chlorohydrin takes place. The latter step exhibits a first-order kinetic dependence on the $Cl^{\ominus}$ concentration, suggesting that it actually proceeds via nucleophilic displacement at the Pt-bonded carbon atom by an external $Cl^{\ominus}$ ion [Eq. (34) and (35)]. This is consistent with our earlier suggestion that the mechanism of the reverse reaction, i.e., of "oxidative addition" of organic halides to low-valent d^8 metals such as iridium(I), also involves such a nucleophilic displacement.[5,43]



Scheme 3. Mechanism of the $[PtCl_4]^{2\ominus}$-catalyzed oxidation of ethylene by Cl_2 [42].

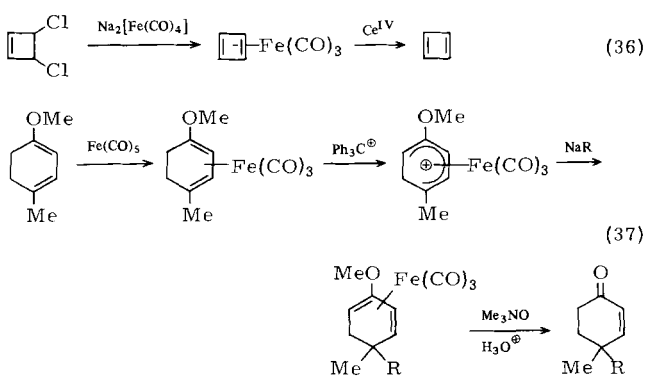
$$[Pt^{IV}Cl_5(CH_2CH_2OH)]^{2\ominus} + Cl^{\ominus} \longrightarrow [Pt^{II}Cl_5]^{3\ominus} + ClCH_2CH_2OH \quad (34)$$

$$[Pt^{II}Cl_5]^{3\ominus} \longrightarrow [Pt^{II}Cl_4]^{2\ominus} + Cl^{\ominus} \quad (35)$$

The known reaction of C_2H_4 with $[Pt^{II}Cl_4]^{2\ominus}$ to regenerate $[Pt^{II}Cl_3(CH_2{=}CH_2)]^{\ominus}$ completes a catalytic cycle for the highly selective oxidation of C_2H_4 to $ClCH_2CH_2OH$ (Scheme 3). All the intermediate species and the component steps of this catalytic cycle have been directly observed and characterized. This general approach would appear to be capable of extention to encompass the catalysis of the oxidation of olefins and related substrates by other metal complexes with potentially distinctive selectivities.

Few oxidation reactions of other metal-olefin complexes have been examined in any detail. Commonly, oxidation of metal-olefin complexes, and especially of mixed olefin-carbonyl complexes, results in liberation of the coordinated olefin (see, e.g., Eq. (29), C_4H_6 = butadiene).[28]

In recent years, "metal assisted syntheses", involving the construction or elaboration of organic molecules that are coordinated to metals (e.g., to fragments such as $Fe(CO)_3$ and $Cr(CO)_3$), have achieved increasing importance in synthetic organic methodology.[28,44] The application of this approach typically results in the production of the target organic molecule as a coordinated ligand. Oxidation of the



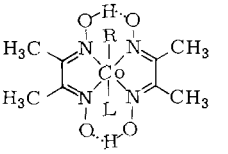
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(37)

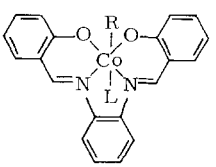
resulting complex has proved to be a useful method of liberating the organic product [Eq. (36)[28] and (37)[44]].

4. Oxidation of Cobalt Alkyl Complexes

The most extensive studies on the chemical and electrochemical oxidations of alkyl transition-metal compounds have been performed on organobis(dimethylglyoximato(1−))organocobalt(III) complexes $[RCo(Hdmg)_2L]$ (abbreviated [CoR]), **6**, where L is an axial ligand such as water or pyridine, and on related organocobalt complexes such as **7**, which have Schiff base compounds as ligands.[45-53,5] Such organocobalt compounds also have been studied extensively in other contexts because of their relevance as coenzyme B_{12} models.[54-56]



6, L = H_2O



7, L = py

[CoR] compounds (R = alkyl or benzyl) have been found to undergo reversible chemical and electrochemical one-electron oxidations in aqueous solution to generate the corresponding 17-electron radical cations, $[RCo(Hdmg)_2(H_2O)]^{\oplus}$ (abbreviated $[CoR]^{\oplus}$, Eq. (38)).[47,50]

$$[CoR] \rightleftharpoons [CoR]^{\oplus} \quad (38)$$

The $[CoR]^{\oplus}$ ions, which could also be generated by chemical oxidation with $[IrCl_6]^{2\ominus}$ [Eq. (39)], are unstable at room temperature and are decomposed by nucleophilic attack of water to form Co^{II} and ROH [Eq. (40)].[47,50] In accord with this scheme, the rate law of the overall reaction [Eq. (41)] was found to conform to Eq. (42).

$$[CoR] + [IrCl_6]^{2\ominus} \underset{k_{-39}}{\overset{k_{39}}{\rightleftharpoons}} [CoR]^{\oplus} + [IrCl_6]^{3\ominus} \quad (39)$$

$$[CoR]^{\oplus} + H_2O \xrightarrow{k_{40}} [Co^{II}] + ROH + H^{\oplus} \quad (40)$$

$$[CoR] + [IrCl_6]^{2\ominus} + H_2O \longrightarrow [Co^{II}] + ROH + [IrCl_6]^{3\ominus} + H^{\oplus} \quad (41)$$

$$\frac{-d[CoR]}{dt} = \frac{k_{39}k_{40}[CoR][IrCl_6^{2\ominus}]}{k_{-39}[IrCl_6^{3\ominus}] + k_{40}} \quad (42)$$

Values of $E_{1/2}$ for the electrochemical oxidations (determined by cyclic voltammetry) and of the kinetic parameters, determined from the kinetic measurements, are summarized in Table 1.[50] As expected, the trend of $E_{1/2}$ values is in the direction of increasing ease of oxidation with increasing electron donor power of R. At the same time the trend of lifetimes ($1/k_{40}$) of the $[CoR]^{\oplus}$ ions, i.e., CH_3, $C_2H_5 > i\text{-}C_3H_7$ and $p\text{-}NO_2C_6H_4CH_2 > C_6H_5CH_2 \gg p\text{-}CH_3OC_6H_4CH_2$, is consistent with a decomposition mode involving nucleophilic attack on R.

At −78 °C (in aqueous methanol or methylene chloride) the $[CoR]^{\oplus}$ ions (generated by oxidation with Ce^{IV} or

Table 1. Thermodynamic and kinetic parameters for the oxidation of **6** [50].

R	$E_{1/2}$ [V] [a]	k_{39} [L mol^{-1} s^{-1}]	K_{39} [b]	k_{40} [s^{-1}]
CH_3	0.902	—	$4.6\cdot10^{-4}$	$1.6\cdot10^{-2}$
C_2H_5	0.878	—	$1.1\cdot10^{-3}$	$0.9\cdot10^{-2}$
n-C_3H_7	0.867	—	$1.9\cdot10^{-3}$	$9.3\cdot10^{-3}$
i-C_3H_7	0.856	$3.5\cdot10^{5}$	$2.7\cdot10^{-3}$	32
p-$CH_3OC_6H_4CH_2$	—	$3.4\cdot10^{5}$		
p-$CH_3C_6H_4CH_2$	0.849	$1.4\cdot10^{5}$	$3.9\cdot10^{-2}$	$>10^2$
$C_6H_5CH_2$	0.859	$\approx5\cdot10^{4}$	$2.8\cdot10^{-2}$	8.3
p-$FC_6H_4CH_2$	0.873	$\approx5\cdot10^{4}$	$2.6\cdot10^{-2}$	9.1
p-$ClC_6H_4CH_2$	0.876	$\approx1\cdot10^{4}$	$1.7\cdot10^{-2}$	1.7
p-$NO_2C_6H_4CH_2$	0.907	$\lesssim1\cdot10^{2}$	$3.2\cdot10^{-3}$	$1.7\cdot10^{-2}$

[a] Relative to the saturated calomel electrode. [b] $K_{39}=k_{39}/k_{-39}$.

PbO_2) were found to be stable for many hours and could be characterized by EPR.[47-49] The results convincingly support the formulation of these ions as cobalt(IV) complexes, i.e., as $[Co^{IV}R^{\ominus}]^{\oplus}$ rather than $[Co^{III}R^{\odot}]^{\oplus}$. Warming such solutions (CH_3OH/H_2O, 4:1) of $[CoR]^{\oplus}$, $R=C_6H_5CH_2$, to ca. -20°C resulted in decomposition according to Eq. (40). On the other hand, when $R=C_2H_5$, decomposition followed a different course, the products and kinetics of which are consistent with Eq. (43) and (44).[50]

$$2[CoR]^{\odot} \underset{k_{-43}}{\overset{k_{43}}{\rightleftharpoons}} [CoR] + [CoR]^{2\oplus} \quad (43)$$

$$[CoR]^{2\oplus} \xrightarrow{k_{44}} [Co^{III}] + \text{olefin} \quad (44)$$

The reversible disproportionation of $[CoR]^{\oplus}$ [Eq. (43)] finds parallels in the corresponding reactions of other organometallic radical cations, e.g., $[Cr(CO)_6]^{\oplus}$ [Eq. (31)].[37] Failure to detect the disproportionative pathway in the case of the benzyl and *sec*-alkyl cobalt complexes presumably reflects the much higher reactivities of these complexes toward nucleophilically induced decomposition [Eq. (40)] as revealed by the values of k_{40} in Table 1.

Examination of the data in Table 1 reveals an unusual pattern of relationships between the rate constant (k_{39}) and equilibrium constant ($K_{39}=k_{39}/k_{-39}$) for reaction (39). For the series of *p*-substituted benzylcobalt complexes examined, the rate constant k_{39} exhibits a significantly larger dependence on the variation of R than the corresponding equilibrium constant K_{39}. These data give rise to a Marcus plot of $\log k_{39}$ vs $\log K_{39}$ with an anomalously large slope of ca. 2–3 instead of the slope of ca. 0.5 expected for a simple outer-sphere electron-transfer reaction (and found, for example, in the related oxidations of PbR_4 compounds by $[IrCl_6]^{2\ominus}$).[8] The results suggest that reaction (39) may actually be a stepwise process of the type depicted by Eq. (45) in which the second step presumably involves a structural rearrangement as well as an internal electron transfer. In such a case the measured rate constant and equilibrium constant would not refer to the same process. The testing of this suggestion calls for measurements on a faster time scale than can be achieved by the electrochemical and chemical oxidation procedures employed in these studies, e.g., pulse radiolysis.

$$[Co^{III}R^{\odot}]^{\oplus} \underset{\text{slow } (k_{45})}{\xrightarrow{-e^{\ominus}}} [Co^{III}R^{\odot}]^{\oplus} \xrightarrow[\text{fast}]{} [Co^{IV}R^{\ominus}]^{\oplus} \quad (45)$$

In related studies on the electrochemical oxidations of a variety of $[RCo(Hdmg)_2L]$ and [RCo(Schiff base)] complexes in acetonitrile solutions, the initially produced $[Co^{IV}R]$ radical cations were found to exhibit several different reactivity patterns, depending on the ligands used and on whether nucleophiles such as pyridine were added.[53] In addition to nucleophilic displacement of $R^{\odot}$ (either by pyridine [Eq. (46)], or by an oxygen atom of the Schiff base ligand) homolytic dissociation of the Co–R bond with formation of alkyl radicals was observed in some cases [Eq. (47)].

$$[Co^{IV}R]^{\oplus} + py \longrightarrow [Co^{II}] + Rpy^{\oplus} \quad (46)$$

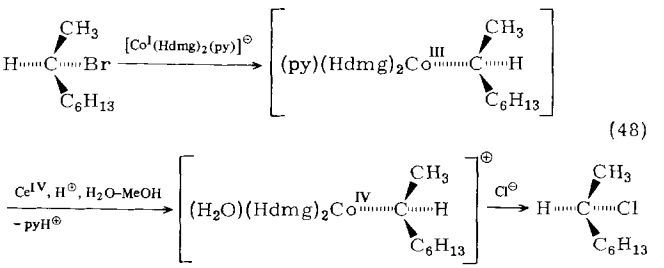
$$[Co^{IV}R]^{\oplus} \longrightarrow [Co^{III}] + R^{\odot} \quad (47)$$

Much of the research on the redox chemistry of organocobalt compounds such as $[RCo(Hdmg)_2(H_2O)]$ has been motivated, at least in part, by the relevance of such compounds as coenzyme B_{12} (5′-deoxyadenosylcobalamin) models. However, at this stage there is no evidence, and little reason to suspect, that oxidation or reduction of coenzyme B_{12} is involved in the cobalt-carbon bond dissociation step which triggers the coenzyme B_{12}-promoted rearrangement and in which the coenzyme's distinctive biochemical role is manifested.[54-56]

5. Implications for Halogen Cleavage of Metal-Alkyl Bonds

In contrast to the familiar halogen cleavage reactions of organomercurials, which typically proceed with retention of configuration at the metal-bonded α-carbon atom, and which have been interpreted as front-side electrophilic displacement processes,[57] halogen cleavage of alkyl transition-metal complexes, e.g., $[RCo(Hdmg)_2(H_2O)]$ and $[RFe(\eta^5\text{-}C_5H_5)(CO)_2]$, commonly proceeds with inversion of configuration.[58,59] The latter reactions have been alternatively interpreted as proceeding through (1) direct backside electrophilic attack at the α-carbon atom,[58] or (2) one-electron oxidation of the metal alkyl followed by nucleophilic attack of halide ion on the resulting radical cation.[46,59]

The demonstration that stable $[RCo(Hdmg)_2(H_2O)]^{\oplus}$ radical cations could be generated in solution by oxidation of $[RCo(Hdmg)_2(H_2O)]$ permitted a direct test of interpretation (2) to be made. Employing the sequence of steps depicted by Eq. (48), it was demonstrated that $Cl^{\ominus}$ does indeed react directly with $[RCo(Hdmg)_2(H_2O)]^{\oplus}$, displacing $R^{\oplus}$ with virtually quantitative inversion of configuration of the α-carbon atom. Accordingly, such a process does ap-



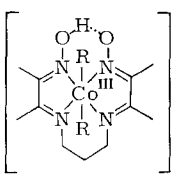
(48)

pear to be a viable step in halogen cleavage reactions of metal-carbon bonds that occur with inversion of configuration.[52]

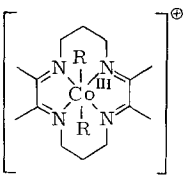
6. Oxidation of Dialkyl Transition-Metal Compounds. Oxidatively Induced Reductive Elimination

Diverse reactivity patterns have been observed in studies on the oxidation of dialkyl transition-metal compounds.

One-electron oxidation of *trans*-[Me_2Co^{III}(dpnH)] **8**[*] or *trans*-[Me_2Co^{III}(tim)] **9**[*] in acetonitrile to the corresponding Co^{IV} complexes was found to be irreversible (by cyclic voltammetry) and generally to result in homolysis of one of the Co–C bonds, yielding a stable monoalkyl Co^{III} compound and a free $CH_3^{\oplus}$ radical whose fate (dimerization, H abstraction, or oxidation by excess oxidant) depends on the reaction conditions [Eq. (49)].[60]



[R_2Co(dpnH)] **8**



[R_2Co(tim)] **9**

$$[Me_2Co^{III}(chelate)]^{n\oplus} \xrightarrow{-e^{\ominus}} [Me_2Co^{IV}(chelate)]^{(n+1)\oplus} \longrightarrow [MeCo^{III}(chelate)]^{(n+1)\oplus} + Me^{\odot} \quad (49)$$

Oxidation of *cis*-[$R_2Pt^{II}(PR'_3)_2$] ($R = CH_3$, C_2H_5; $PR'_3 = PMe_2Ph$, PPh_3) complexes by $[IrCl_6]^{2\ominus}$ in acetonitrile afforded two types of products, depending on the nature of R and PR'_3 ($X = Cl^{\ominus}$, CH_3CN, etc.). *cis*-[$Me_2Pt(PMe_2Ph)_2$] reacted predominantly according to Eq. (50a), whereas *cis*-[$Et_2Pt(PPh_3)_2$] reacted predominantly according to Eq. (50b). For *cis*-[$Me_2Pt(PPh_3)_2$], competition between the two pathways was observed.[61a]

$$[R_2Pt^{II}(PR'_3)] \xrightarrow{2\,[IrCl_6]^{2\ominus}} [R_2Pt^{IV}(PR'_3)_2X_2] \quad (50a)$$

$$[R_2Pt^{II}(PR'_3)] \xrightarrow{2\,[IrCl_6]^{2\ominus}} [RPt^{II}(PR'_3)_2X] + RCl \quad (50b)$$

Oxidation of *cis*-[R_2Fe^{II}(bpy)$_2$] ($R = Me$, Et, *n*Pr, etc.) revealed still other reactivity patterns [Eq. (51)].[61b]

$$cis\text{-}[R_2Fe^{II}(bpy)_2] \underset{e^{\ominus}}{\overset{-e^{\ominus}}{\rightleftharpoons}} \underset{\mathbf{10}}{[R_2Fe^{III}(bpy)_2]^{\oplus}} \xrightarrow{-e^{\ominus}} \underset{\mathbf{11}}{[R_2Fe^{IV}(bpy)_2]^{2\oplus}}$$
$$\downarrow \qquad\qquad \downarrow$$
$$[Fe^{I}] + 2\,R^{\odot}(\longrightarrow R_2 \text{ etc.}) \qquad [Fe^{II}] + R_2 \quad (51)$$

The one-electron oxidation product, **10**, whose formation was electrochemically reversible, was sufficiently stable to be isolated and characterized by EPR. The decomposition products (C_4H_{10}, C_2H_6, and C_2H_4 when $R = C_2H_5$) were interpreted as arising from cage reactions of a pair of $R^{\odot}$ radicals. On the other hand, the two-electron oxidation product, **11**, whose formation is irreversible, apparently undergoes a *concerted* reductive elimination to yield R_2 directly.[62]

Other reported examples of oxidatively induced reductive elimination include that depicted by Eq. (52) (R = alkyl or aryl, L = PEt_3).[62]

$$[(Aryl)(R)Ni^{II}L_2] \xrightarrow{-e^{\ominus}} [(Aryl)(R)Ni^{III}L_2] \longrightarrow Aryl\text{–}R + [Ni^{I}L_2] \quad (52)$$

Reductive elimination from a Ni^{III} intermediate according to Eq. (53)–(55) has been invoked to interpret the cross-coupling reactions of aryl halides (ArylX) with arylnickel complexes ($ArylNiXL_2$, L = PEt_3 and similar ligands) to yield biaryls [Eq. (56)].[63]

$$[Ni^{I}XL_2] + ArylX \longrightarrow [ArylNi^{III}X_2L_2] \quad (53)$$

$$[ArylNi^{III}X_2L_2] + [ArylNi^{II}XL_2] \longrightarrow [Aryl_2Ni^{III}XL_2] + [Ni^{II}X_2L_2] \quad (54)$$

$$[Aryl_2Ni^{III}XL_2] \longrightarrow Aryl_2 + [Ni^{I}XL_2] \quad (55)$$

$$[ArylNi^{II}XL_2] + ArylX \longrightarrow [Ni^{II}X_2L_2] + Aryl_2 \quad (56)$$

7. Oxidation of Non-Transition Metal Alkyls

Extensive studies also have been conducted on chemical and electrochemical oxidations of non-transition metal alkyl compounds such as R_4Pb, R_4Sn, and R_2Hg.[8] The course of the oxidation of Me_4Pb in acetic acid is typical of that found for such systems [Eq. (57)–(60)].

$$[Me_4Pb] + [IrCl_6]^{2\ominus} \xrightarrow{\text{rate-determining}} [Me_4Pb]^{\ominus} + [IrCl_6]^{3\ominus} \quad (57)$$

$$[Me_4Pb]^{\oplus} \xrightarrow{\text{fast}} Me^{\odot} + [Me_3Pb]^{\oplus} \left(\xrightarrow{HOAc} [Me_3PbOAc] + H^{\oplus}\right) \quad (58)$$

$$Me^{\odot} + [IrCl_6]^{2\ominus} \longrightarrow MeCl + [IrCl_5]^{2\ominus} \quad (59)$$

$$[Me_4Pb] + 2[IrCl_6]^{2\ominus} \xrightarrow{HOAc} [Me_3PbOAc] + MeCl + [IrCl_6]^{3\ominus} + [IrCl_5]^{2\ominus} \quad (60)$$

Differences between this behavior and that found for related oxidations of alkyl transition-metal compounds include the following: 1) Step (57) appears to be essentially irreversible and the postulated $[R_4Pb]^{\oplus}$ (or $[R_2Hg]^{\oplus}$) radical cations are too short-lived to be detected kinetically, electrochemically, or spectroscopically. 2) In contrast to the oxidized organo-transition metal complexes, for which alternative decomposition modes, including nucleophilic attack, disproportionation, or reductive elimination, usually are observed, $[R_4Pb]^{\oplus}$ and $[R_2Hg]^{\oplus}$ decompose exclusively by metal-carbon bond homolysis. The origin of these differences may be that the highest occupied molecular orbital (HOMO) from which the electron is removed in the oxidation of [R_4Pb] presumably is a metal-carbon σ-bonding orbital, whereas in the case of most transition metal complexes, such as $[R_nCo^{III}]$ or $[R_nFe^{II}]$, it is a nonbonding d-orbital.[64]

[*] dpnH = 2,3,9,10-tetramethyl-1,4,8,11-tetraaza-1,3,8,10-undecatetraen-11-ol-1-olate; tim = 2,3,9,10-tetramethyl-1,4,8,11-tetraaza-1,3,8,10-cyclotetradecatetraene.

Finally it should be noted that not all processes in which oxidation of an organometallic compound apparently occurs actually proceed through such a step. Thus oxidative cleavage of the Cr–C bond in $[PhCH_2Cr^{III}(H_2O)_5]^{2\oplus}$ by oxidants such as $Fe^{3\oplus}$, $Cu^{2\oplus}$, O_2, and H_2O_2 in aqueous solution exhibits first-order kinetics that are independent of the nature or concentration of the oxidant [Eq. (61)].[65]

$$[PhCH_2Cr^{III}(H_2O)_5]^{2\oplus} \xrightarrow{\text{rate-determining}} PhCH_2^{\oplus} + Cr^{2\oplus}aq \quad (61)$$
$$PhCH_2^{\oplus} \xrightarrow{\text{oxidation fast}} PhCH_2OH$$
$$Cr^{2\oplus}aq \xrightarrow{\text{oxidation fast}} Cr^{3\oplus}aq$$

8. Oxidatively Induced CO Insertion

There is extensive evidence that one-electron oxidation of transition metal complexes containing both alkyl and CO ligands promotes migratory insertion of CO into the metal-alkyl bond [Eq. (62)]. Specific examples encompassing this phenomenon are shown in Eq. (63) and (64).[66–68]

$$\left[L_nM\begin{matrix}CO\\R\end{matrix}\right] \xrightarrow{-e^{\ominus}} \left[L_nM\begin{matrix}CO\\R\end{matrix}\right]^{\oplus} \longrightarrow \left[L_nM{-}\overset{O}{\overset{\|}{C}}{-}R\right]^{\oplus} \quad (62)$$

$$[R{-}Fe(CO)_2(\eta^5{-}C_5H_5)] \xrightarrow[CuCl_2]{R'OH,\ CO} R\overset{O}{\overset{\|}{C}}OR' \quad (63)$$

$$[R{-}Mo(CO)_3(\eta^5{-}C_5H_5)] \xrightarrow[Ce^{IV}]{MeOH} R\overset{O}{\overset{\|}{C}}OCH_3 \quad (64)$$

It has been shown that such CO insertion reactions proceed with *retention* of configuration at the α-carbon atom.[66] Oxidatively induced migratory insertion of CO has been utilized in synthetic applications such as β-lactam synthesis [Eq. (65), $Cp=\eta^5$-C_5H_5].[69]

$$\left[Cp(CO)_2Fe\begin{matrix}R\\NHCH_2Ph\end{matrix}\right] \xrightarrow{-e^{\ominus}} \left[Cp(CO)_2Fe\begin{matrix}R\\NHCH_2Ph\end{matrix}\right]^{\oplus} \quad (65)$$
$$\longrightarrow \left[Cp(CO)Fe\begin{matrix}\overset{O}{\overset{\|}{C}}\\NH\ R\\CH_2Ph\end{matrix}\right]^{\oplus} \longrightarrow \begin{matrix}R\\N\\PhCH_2\end{matrix}\!\!\overset{O}{\overset{\|}{C}}$$

9. Redox-Catalyzed Reactions of Organometallic Compounds

The distinctive reactivity patterns of oxidized organometallic compounds may be incorporated into catalytic cycles which proceed through electron-transfer-propagated chain mechanisms.

An example of such catalysis is provided by the substitution reactions of metal carbonyls such as *cis*-$[L_2W(CO)_4]$ (L = MeCN or py), whose rates are enhanced by chemical or electrochemical oxidation according to the mechanism of Eq. (66)–(69), for which the chain length has been estimated to be ca. 20.[70]

$$\text{Initiation:} \quad [L_2W(CO)_4] \xrightarrow{-e^{\ominus}} [L_2W(CO)_4]^{\oplus} \quad (66)$$

$$\text{Propagation:} \quad \begin{cases} [L_2W(CO)_4]^{\oplus} + PPh_3 \longrightarrow [LW(CO)_4(PPh_3)]^{\oplus} + L & (67) \\ [LW(CO)_4(PPh_3)]^{\oplus} + [L_2W(CO)_4] \longrightarrow & \\ \qquad [LW(CO)_4(PPh_3)] + [L_2W(CO)_4]^{\oplus} & (68) \end{cases}$$

$$\text{Net reaction:} \quad [L_2W(CO)_4] + PPh_3 \longrightarrow [LW(CO)_4(PPh_3)] + L \quad (69)$$

Analogous mechanisms [Eq. (70)–(72)] have been invoked to account for the oxidatively induced migratory insertion reaction of $[(\eta^5\text{-}C_5H_5)(PPh_3)(CO)Fe(CH_3)]$ (abbreviated [Fp–CH_3]) [Eq. (73)].[71]

$$\text{Initiation:} \quad [Fp{-}CH_3] \xrightarrow{-e^{\ominus}} [Fp{-}CH_3]^{\oplus} \quad (70)$$

$$\text{Propagation:} \quad \begin{cases} [Fp{-}CH_3]^{\oplus} + CO \longrightarrow [Fp{-}\overset{O}{\overset{\|}{C}}{-}CH_3]^{\oplus} & (71) \\ [Fp{-}\overset{O}{\overset{\|}{C}}{-}CH_3]^{\oplus} + [Fp{-}CH_3] \longrightarrow & \\ \qquad [Fp{-}\overset{O}{\overset{\|}{C}}{-}CH_3] + [Fp{-}CH_3]^{\oplus} & (72) \end{cases}$$

$$\text{Net reaction:} \quad [Fp{-}CH_3] + CO \longrightarrow [Fp{-}\overset{O}{\overset{\|}{C}}{-}CH_3] \quad (73)$$

These processes parallel other examples of "electron-transfer catalysis", the principle of which has been recognized for some time also in other contexts.[72–74]

10. Concluding Remarks

The study of the oxidation reactions of organometallic compounds constitutes a relatively new field of research which has developed almost entirely within the past decade. The results yielded by the limited studies conducted thus far already reveal a rich and versatile array of chemistry associated with the primary redox processes themselves, with the distinctive electronic structures and reactivity patterns of the species produced by oxidation of stable organometallic compounds, and with the synthetic and catalytic applications of oxidatively induced organometallic reactions. At the same time many problems, both of understanding and of application, remain to be addressed. Research activity in this field continues at a high level and with great promise for the realization of important new discoveries and insights.

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η^3-Allylpalladium Compounds**

By Peter W. Jolly*

Dedicated to Professor Günther Wilke on the occasion of his 60th birthday

The use of transition-metal complexes as homogeneous catalysts for the production of organic chemicals is of considerable industrial significance. Although palladium complexes have not attained the same importance as, for example, those of rhodium or cobalt, palladium is nonetheless one of the most versatile metals for synthetic organic purposes. An understanding of the role played by the metal in these reactions is essential for their optimal utilization. This necessarily entails a detailed study of the chemistry of the palladium-carbon bond. In this article we concentrate on η^3-allylpalladium complexes, which are frequently involved as intermediates in the Pd-catalyzed transformations of dienes. The study of their behavior gives a deeper insight into the individual steps of a catalytic cycle.

1. Introduction

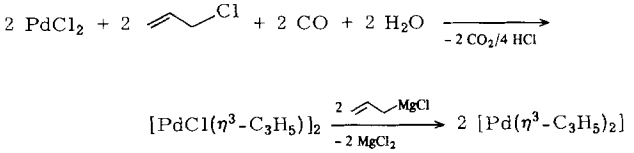
The η^3-allyl complexes of palladium have played an important role in the development of organotransition metal chemistry. $[PdCl(\eta^3\text{-}C_3H_5)]_2$, which was reported in 1959, was the first complex for which the presence of a symmetrically bonded η^3-allyl group was postulated[1] and confirmed in solution[7] and in the crystal.[8] In addition, the fluxional behavior of the allyl group in this molecule in the presence of donor ligands, which was noted soon after its isolation,[9] was to have a significant and lasting influence on the development of the NMR spectroscopy[10] of organotransition metal complexes.

The synthesis of homoleptic η^3-allyl metal complexes such as $[Pd(\eta^3\text{-}C_3H_5)_2]$ by *G. Wilke* et al. introduced a new dimension as did the recognition that such complexes are a convenient source of the metal component in homogeneous catalysts and are involved, as intermediates, in a variety of transition-metal-catalyzed transformations of organic molecules.[11, 12] In this article we discuss some recent developments in η^3-allylpalladium chemistry.

2. Bis(η^3-allyl)palladium Complexes

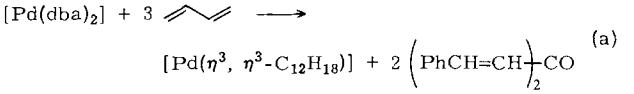
2.1. Preparation

The first bis(η^3-allyl)palladium complex, $[Pd(\eta^3\text{-}C_3H_5)_2]$, reported in 1963, was prepared by reacting $PdCl_2$ with allylmagnesium chloride.[11-15] Subsequently, complexes containing η^3-1-MeC_3H_4, η^3-2-MeC_3H_4, η^3-1,1-$Me_2C_3H_3$, and η^3-1,3-$Me_2C_3H_3$ groups have been synthesized and there seems to be no reason why this list should not be extended. Highest yields (ca. 80%) are obtained by carrying out the reaction in two stages: the dichloride is first converted into $[PdCl(\eta^3\text{-}C_3H_5)]_2$[16] and this is then reacted with the Grignard reagent in ether at $-50°$ (Scheme 1).[17, 18] $[Pd(\eta^3\text{-}C_3H_5)_2]$ and $[Pd(\eta^3\text{-}2\text{-}MeC_3H_4)_2]$ are conveniently isolated from the reaction mixture by high-vacuum sublimation at 0° or by extraction and recrystallization from pentane.



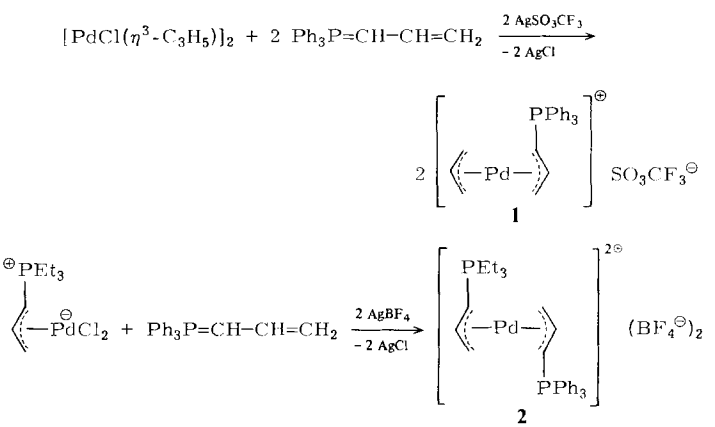
Scheme 1.

Recently, we have succeeded in preparing bis(η^3,η^3-dodecatrienediyl)palladium by reacting bis(dibenzylideneacetone)palladium(0) $[Pd(dba)_2]$ with butadiene [Reaction (a)].[19]



(a)

A series of ionic η^3-allyl(ylide)palladium complexes, e.g., **1** and **2**, have been prepared by reacting the appropriate organopalladium chloride with an allylidene phosphorane in the presence of a silver salt (Scheme 2).[20]



Scheme 2.

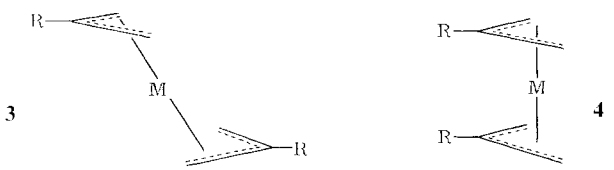
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[**] Based on work carried out by *B. Henc, P. W. Jolly, T. Joswig, B. Raspel, G. Schenker, K. P. Schick,* and *H. Trinh.*

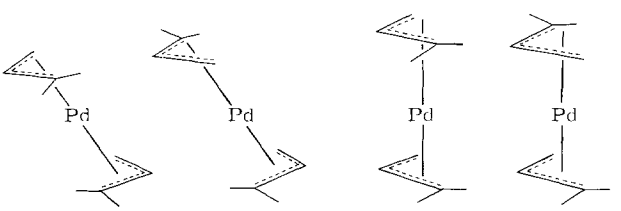
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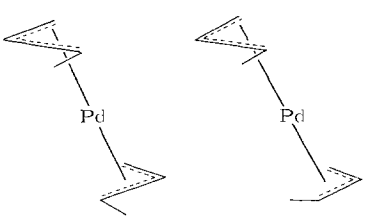
2.2. Structure and Bonding

The NMR spectra of the bis(η^3-allyl)palladium complexes[13-15,21-23] indicate that, as in the case of the corresponding complexes of nickel and platinum, isomers are present in solution. Although, surprisingly, no crystal structure determination of a palladium complex has been reported, the four complexes of nickel that have been studied, viz., [Ni(η^3-cyclooctenyl)$_2$], [Ni(η^3-2-MeC$_3$H$_4$)$_2$], [Ni(η^3-pinenyl)$_2$], and [Ni(η^3-C$_3$H$_5$)$_2$],[15,24-26] as well as [Pt(η^3-2-MeC$_3$H$_4$)$_2$][27] all contain η^3-allyl groups that are mutually *trans* (see **3**). It is generally assumed, although direct evidence is still lacking, that in the other isomer the η^3-allyl groups adopt a *cis* configuration, as in **4**. It should be noted that a neutron diffraction study of [Ni(η^3-C$_3$H$_5$)$_2$] has shown that the hydrogen atoms do not lie in the plane formed by the carbon atoms; the *syn*- and *meso*-hydrogen atoms are bent towards the metal by 8.9(4)° and 15.8(1)°, respectively, while the *anti*-hydrogen atoms are bent 29.4(7)° away from the metal. The direction and magnitude of this distortion is reproduced in an ab initio SCF calculation.[26]



The NMR spectra of [Pd(η^3-C$_3$H$_5$)$_2$] indicate that the two isomers are in equilibrium with each other; whether interconversion involves the intermediate formation of an η^1-allyl species or direct rotation about the η^3-allyl-metal axis has not been decided.[14,21,22] It has even been suggested that both mechanisms may be operating simultaneously.





Additional isomers are possible for complexes containing unsymmetrically substituted η^3-allyl groups. For example, the NMR-spectra of [Pd(η^3-1,1-Me$_2$C$_3$H$_3$)$_2$] indicate the presence of the four possible isomers **5**—**8** (Fig. 1). In the case of [Pd(η^3-1-MeC$_3$H$_4$)$_2$] additional isomers, e.g., **9** and **10**, are possible, depending upon the *syn*- or *anti*-arrangement of the methyl groups. In addition to the four main isomers, which have been shown to contain methyl groups in *syn* positions, two additional isomers are present in low (<5%) concentration.[15] The ionic η^3-allyl(ylide) complexes **1** and **2** also exist in solution as a mixture of isomers.[20]

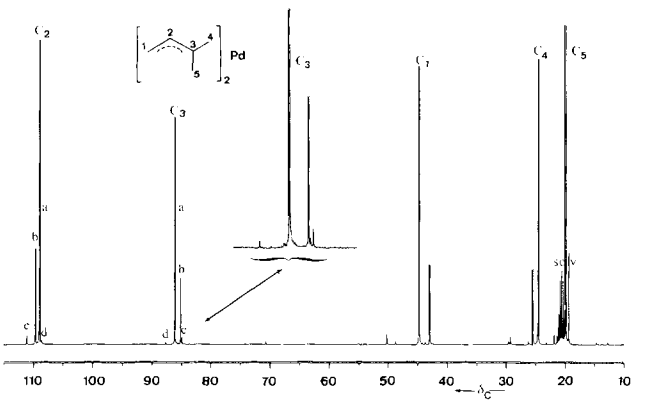
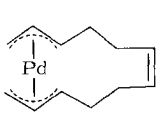
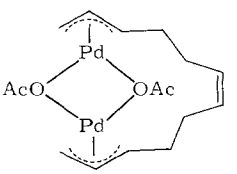


Fig. 1. The ^{13}C{^{1}H}-NMR spectrum of [Pd(η^3-1,1-Me$_2$C$_3$H$_3$)$_2$] (**5**—**8**) in [D$_8$]toluene at −30°C; a:b:c:d = 73:22:4:1.

The NMR spectra of [Pd(η^3,η^3-C$_{12}$H$_{18}$)] **11** at −30°C indicate a symmetrical arrangement of the dodecatrienediyl chain around the metal atom with *syn*-η^3-allyl groups and an uncomplexed *cis* double bond. It has still to be decided whether the η^3-allyl groups are mutually *cis* or *trans*. A similar arrangement is found in [Pd$_2$(OAc)$_2$(η^3,η^3-C$_{12}$H$_{18}$)] **12**, which can be prepared by reacting [PdOAc(η^3-C$_3$H$_5$)]$_2$ with butadiene.[19,28] **11** and **12** should be compared with the related complexes of nickel, [Ni(η^3,η^3-C$_{12}$H$_{18}$)],[15] ruthenium, [RuCl$_2$(η^3,η^3-C$_{12}$H$_{18}$)],[29] and molybdenum and tungsten, [M(CO)$_2$(η^3,η^3-C$_{12}$H$_{18}$)] (M = Mo, W),[30] all of which contain a metal-complexed *trans*-alkene but differ in the *anti* (Ni) or *syn* (Ru, Mo, W) substitution of the η^3-allyl groups. Below −80°C, the six signals observed in the ^{13}C-NMR spectrum of **11** split, suggesting either that at these temperatures the C$_{12}$-chain adopts an unsymmetrical arrangement or, more probably, that two symmetrical isomers exist whose interconversion is only slow enough below −80°C to be detected by NMR spectroscopy.[19]





The IR[13,31-33] and the Raman[15,32-35] spectra of [Pd(η^3-2-RC$_3$H$_4$)$_2$] (R = H, Me) have been studied extensively, and the low-frequency (50—800 cm^{-1}) absorptions have been recorded by inelastic neutron scattering.[36] The Raman spectra are particularly informative and the observation of only three Raman-active metal-ligand vibrations in [Pd(η^3-C$_3$H$_5$)$_2$] supports a centrosymmetric arrangement.

The He(I) photoelectron spectra of [Pd(η^3-C$_3$H$_5$)$_2$] and [Pd(η^3-2-MeC$_3$H$_4$)$_2$] have been recorded and the results

compared with those for the corresponding complexes of nickel and platinum.[37] The assignments of the bands to a particular molecular orbital should, however, be viewed with caution since the model used assumes that the carbon and hydrogen atoms of the allyl ligands are coplanar, which, at least for $[Ni(\eta^3\text{-}C_3H_5)_2]$, has been shown not to be the case (see above),[26] and a reassignment of the energy levels will be necessary.

2.3. Reactions

Reactions of the bis(η^3-allyl)palladium complexes with donor ligands, which lead to formation of η^1-allylpalladium compounds, are discussed in Sections 3 and 4. Reaction of bis(η^3-allyl)palladium complexes with excess tertiary phosphanes leads to coupling of the allyl groups and formation of $[PdL_n]$ species.[14]

$[Pd(\eta^3\text{-}C_3H_5)_2]$ is a yellow, unpleasant smelling compound that decomposes at 50 °C liberating mainly propene.[13] Reaction with H_2 occurs instantaneously at room temperature to give propene and palladium metal,[13] which is active for the catalytic hydrogenation of olefins,[38] as is the catalyst prepared by reacting bis(η^3-allyl)palladium with the surface hydroxy groups of a variety of supports, such as La_2O_3.[39]

$$2\ [Pd(\eta^3\text{-}C_3H_5)_2] + 2\ Et_2NH \longrightarrow [PdNEt_2(\eta^3\text{-}C_3H_5)]_2 + 2\ C_3H_6 \quad (b)$$

Controlled protonolysis of bis(η^3-allyl)palladium with HCl,[13] H_2S,[40,41] or Et_2NH [Reaction (b)][42] results in cleavage of one η^3-allyl group. The reaction with H_2S proceeds in a stepwise manner to give ultimately η^3-allylpalladium-sulfur clusters [Reaction (c)] which may also be formed by reacting bis(η^3-allyl)palladium with trithiopentalene derivatives or S_8. Reaction of bis(η^3-allyl)palladium with $[Ni(SH)(\eta^3\text{-}C_3H_5)]_2$ leads to mixed metal clusters [Reaction (d)].

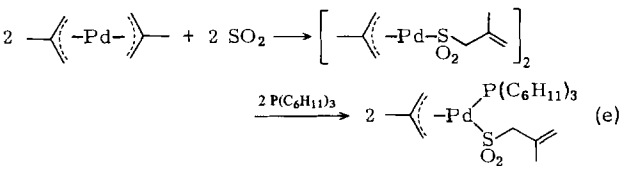
$$2\ [Pd(\eta^3\text{-}C_3H_5)_2] + 2\ H_2S \xrightarrow[-2\,C_3H_6]{} [Pd(SH)(\eta^3\text{-}C_3H_5)]_2 \quad (c)$$

$$\xrightarrow[-2\,C_3H_6]{2\,[Pd(\eta^3\text{-}C_3H_5)_2]} \frac{2}{n}\,[(\eta^3\text{-}C_3H_5)Pd\text{-}S\text{-}Pd(\eta^3\text{-}C_3H_5)]_n$$

$$2\ [Pd(\eta^3\text{-}C_3H_5)_2] + [Ni(SH)(\eta^3\text{-}C_3H_5)]_2 \xrightarrow[-2\,C_3H_6]{} \frac{2}{n}\,[(\eta^3\text{-}C_3H_5)Pd\text{-}S\text{-}Ni(\eta^3\text{-}C_3H_5)]_n \quad (d)$$

Whereas bis(η^3-allyl)palladium is inert towards CO_2 under mild conditions,[43,44] it reacts with SO_2 at −78 °C:[43,45] reaction with bis(η^3-2-methallyl)palladium gives a dimer [Reaction (e)] in which the arrangement of the bridging atoms is not yet known. A ^{1}H-NMR study indicates that two isomers are present in solution. These are interconvertible and differ presumably in the arrangement of the sulfur-bonded and η^3-bonded methallyl groups. The dimer is cleaved upon treatment with tricyclohexylphosphane.

The reaction of SO_2 with $[Pd(\eta^3\text{-}C_3H_5)_2]$ is temperature dependent: at −78 °C a dimer, presumably related to that discussed above, is formed, whereas at −40 °C a monomer



(e)

$[PdSO_2C_3H_5(\eta^3\text{-}C_3H_5)]$ **13** of unknown structure results. The S–O stretching frequencies at 1020 and 1130 cm^{-1} in the infrared spectrum would seem to rule out a structure containing an η^1-bonded SO_2 molecule such as **13a**, while the presence of an uncomplexed double bond (IR band at 1625 cm^{-1}) makes **13b** unlikely. **13** reacts with tricyclohexylphosphane to give $[PdSO_2C_3H_5\{P(C_6H_{11})_3\}(\eta^3\text{-}C_3H_5)]$.



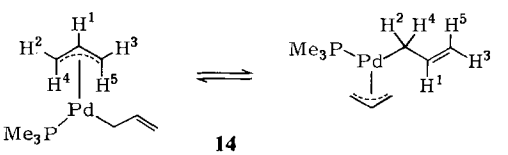
13a **13b**

The formation of $[PdCl(\eta^3\text{-}C_3H_5)]_2$ in the reaction of $PdCl_2$ with $[Pd(\eta^3\text{-}C_3H_5)_2]$ was one of the first examples of the intermetallic transfer of an organic ligand.[13]

3. Bis(η^1,η^3-allyl)palladium Complexes

3.1. Preparation and Structure

Although it has been known for many years that bis(η^3-allyl)palladium forms adducts with P-donor ligands,[13] it is only recently that their nature has been established. Reaction of the palladium complex with monodentate donor ligands results in the conversion of one η^3-allyl group into the η^1-allyl form; for example, with trimethylphosphane, **14** is formed.



14

The rearrangement of **14** is reflected in the temperature dependence of the ^{1}H-NMR spectra (Fig. 2): at −109 °C the rearrangement is too slow to be observed (on the NMR time scale); on raising the temperature the allyl groups exchange—without dissociation of the phosphane. The coalescence temperature for the exchange is ca. −50 °C which corresponds to a free energy of activation for the process of 9.6 ± 1.5 kcal/mol.[46,47] The η^1,η^3-arrangement of the allyl groups has been confirmed by X-ray crystallography for a related platinum complex (Fig. 3).[18]

$[Pd(\eta^3\text{-allyl})(\eta^5\text{-}C_5H_5)]$ reacts with donor ligands to form an adduct that also exists in two isomeric forms; these interconvert rapidly at room temperature [Equilibrium (f)]. An NMR study indicates that at low temperatures the isomer with the η^1-cyclopentadienyl group predominates. An X-ray diffraction study has established this structure in the crystal for the complex where L = P*i*Pr$_3$ and R = *t*Bu[48].

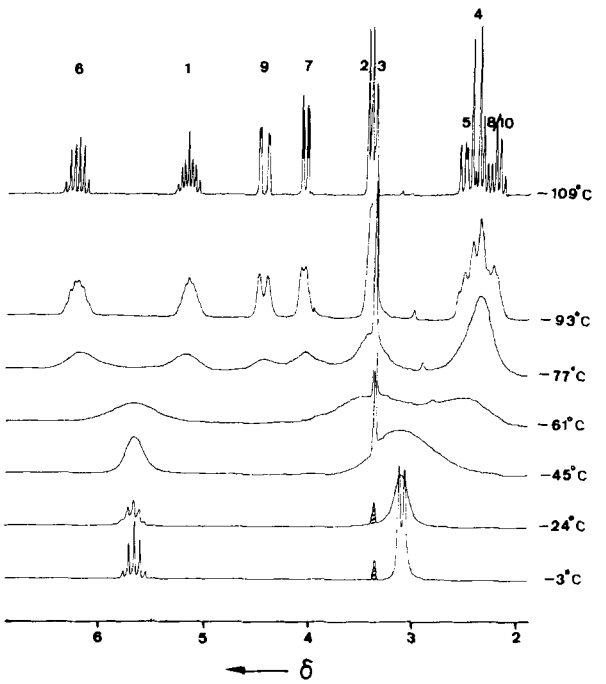


Fig. 2. The ^{1}H-NMR spectra of $[Pd(PMe_3)(\eta^1,\eta^3\text{-}C_3H_5)_2]$ **14** at different temperatures [46]. The numbers 1 — 10 above the peaks refer to the ten protons of the two allyl groups.

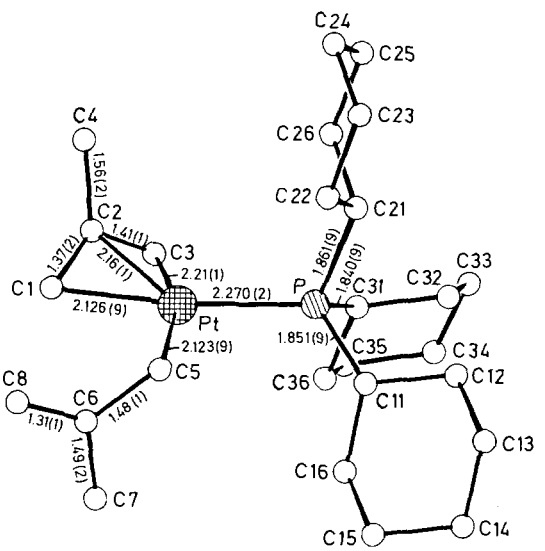


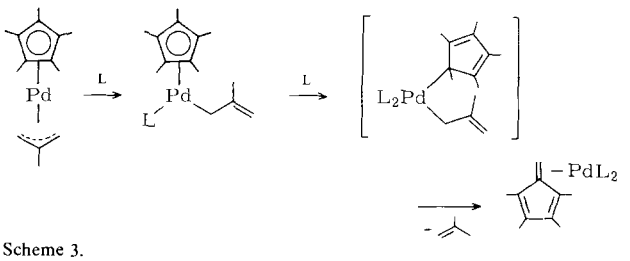
Fig. 3. The crystal structure of $[Pt\{P(C_6H_{11})_3\}(\eta^1,\eta^3\text{-}2\text{-}MeC_3H_4)_2]$ [18].

The rearrangement (f) forms the basis of a palladium-induced fulvene synthesis starting from substituted cyclo-



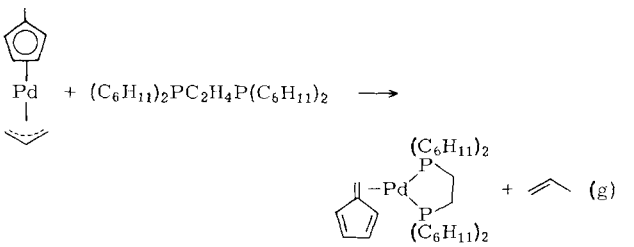
(f)

pentadienyl derivatives (Scheme 3). The final step in this reaction is a β-hydrogen transfer from the η^1-C_5Me_5 moiety to the η^1-allyl group.

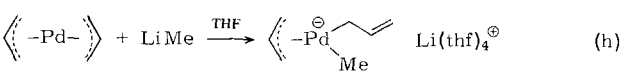


Scheme 3.

This reaction seems to be general and has, for example, been used to convert a methylcyclopentadienylpalladium complex into a fulvene complex [Reaction (g)].[49]

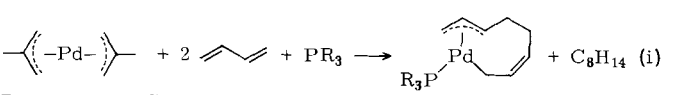


The conversion of an η^3-allyl group into the η^1-allyl form upon reaction with donor ligands is not limited to tertiary phosphanes but is also observed on treating bis(η^3-allyl)palladium with carbanions: ionic ate-complexes result. Such compounds have been isolated from reactions with methyl-, vinyl-, and phenyllithium [Reaction (h)].[50] Similar complexes involving nickel or platinum have been isolated; in the case of $[NiMe(\eta^1,\eta^3\text{-}C_3H_5)_2]^{\ominus}$, it was shown by NMR spectroscopy that η^1-η^3-allyl exchange occurs.



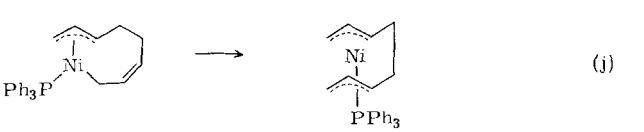
(h)

An important class of bis(η^1,η^3-allyl)palladium complexes—the η^1,η^3-octadienediyl complexes—may be prepared by reacting bis(η^3-allyl)palladium with butadiene in the presence of a donor ligand [Reaction (i)].[18,19,51]



R = Me, *i*Pr, C_6H_{11}, NMe_2, Ph

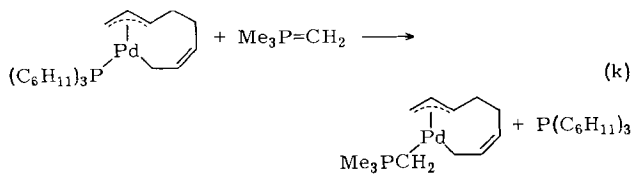
Interestingly, the complex stabilized by PPh_3 shows no tendency up to its decomposition point (> -25 °C) to rearrange in the manner established for the corresponding nickel complex [Reaction (j)]:[52]



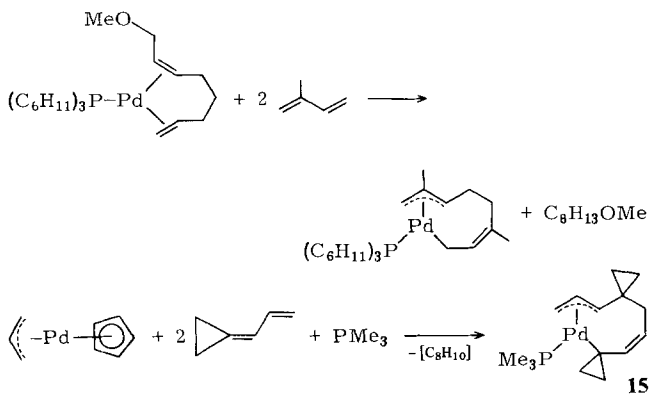
(j)

Reaction (i) has been shown to proceed in a stepwise manner via $[Pd(PR_3)(\eta^1,\eta^3\text{-allyl})_2]$ and $[Pd(PR_3)(\mu\text{-}\eta^3\text{-al-}$

lyl)]$_2$ species. The η^1,η^3-octadienediyl complexes can also be prepared by reacting butadiene with [Pd(dba)$_2$], [Pd(η^3-C_3H_5)(η^5-C_5H_5)], or $PdCl_2$/Mg(anthracene)[53] in the presence of a phosphane or by reaction with bis(alkene)(phosphane)palladium complexes. In addition, a trimethylmethylenephosphorane-complex has been prepared by ligand exchange [Reaction (k)].[54]



Reaction (i) is not limited to butadiene; isoprene, 3-methylene-1-heptene, and allylidenecyclopropane react similarly[19,55] (Scheme 4).



Scheme 4.

The structure of the η^1,η^3-octadienediyl complexes has been verified by spectroscopic methods. The $^{13}C\{^1H\}$-NMR spectrum of [Pd(PMe$_3$)(η^1,η^3-C_8H_{12})] is shown in Figure 4 and should be compared with that of the analogous nickel complex.[52]

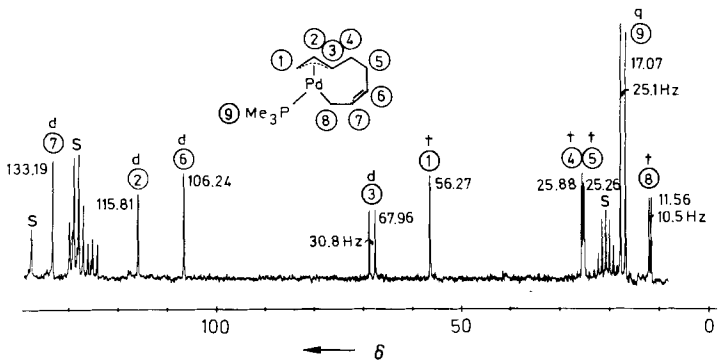


Fig. 4. The 25.2-MHz $^{13}C\{^1H\}$-NMR spectrum of [Pd(PMe$_3$)(η^1,η^3-C_8H_{12})] in [D$_8$]toluene at −30 °C [18].

Diagnostic for the structure is the high-field shift of the Pd-bonded carbon atom C-8 and its coupling to phosphorus ($J_{P,C\text{-}8}$ = 10.5 Hz), along with the large *trans* coupling between the terminal C-atoms of the η^3-allyl group and phosphorus ($J_{P,C\text{-}3}$ = 30.8 Hz) and the small *cis* coupling ($J_{P,C\text{-}1}$ = 1.4 Hz). The *syn*-substitution of the η^3-allyl group and the *cis*-configuration of the uncomplexed double bond follow from a detailed analysis of the 400-MHz ^{1}H-NMR spectrum. The X-ray structure determination indicates that the configuration in the crystal is the same as that in solution (Fig. 5). Disorder prevented a more exact determination of the bond distances; these are, comparable, however, with those found for the related nickel complex [Ni{P(C_6H_{11})$_3$}(η^1,η^3-2,6-$Me_2C_8H_{10}$)].[56] A similar disorder is found in the corresponding platinum complex which is,

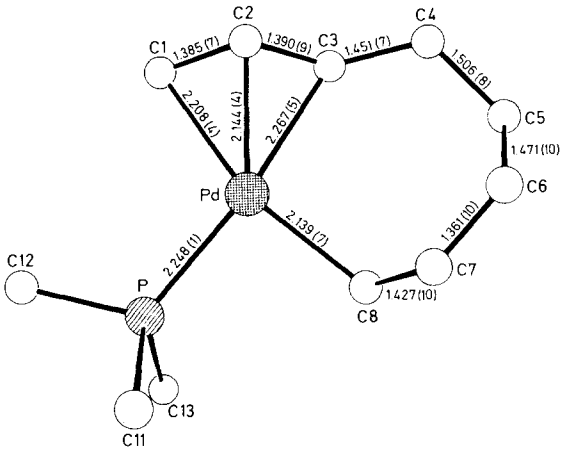


Fig. 5. The crystal structure of [Pd(PMe$_3$)(η^1,η^3-C_8H_{12})] [18].

moreover, isomorphous with the palladium complex discussed here.[57] More precise structural parameters have been obtained for the complex **15** derived from allylidenecyclopropane (Fig. 6).

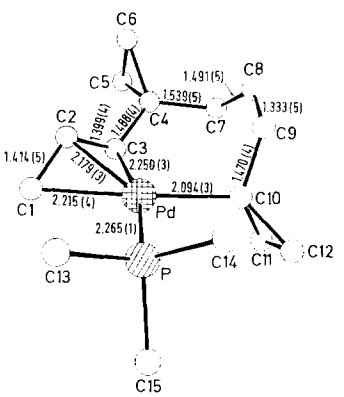


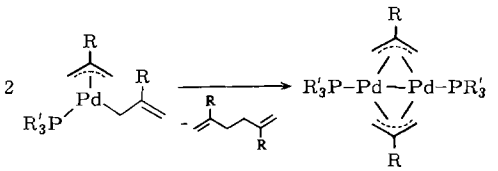
Fig. 6. The crystal structure of **15** [55].

Of the four possible products of the reaction of two isoprene molecules at palladium (cf. Reaction (i)) only two are formed, viz., [PdL(η^1,η^3-2,6-$Me_2C_8H_{10}$)] and [PdL(η^1,η^3-2,7-$Me_2C_8H_{10}$)]. These result from head-tail and tail-tail coupling of the two diene molecules; it has been shown that the 2,6-disubstituted isomer is the product of a kinetically controlled reaction; the 2,7-isomer is thermodynamically more stable.[19]

3.2. Reactions

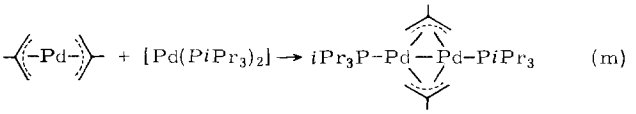
The [Pd(PR$_3$)(η^1,η^3-allyl)$_2$] complexes react further in solution at room temperature to give binuclear complexes

having bridging η^3-allyl groups [Reaction (l)].[18, 19, 58] Complexes of this type had previously been prepared by reacting bis(η^3-allyl)palladium with $[Pd(PR_3)_2]$ complexes [Reaction (m)].[59]



(1)

R = H; R' = Me, C_6H_{11}, Ph;
R = Me; R' = iPr_3, NMe_2, OC_6H_4Ph



(m)

The X-ray structure determination has confirmed the structure of the triphenylphosphane-substituted derivative (Fig. 7). The allyl groups are not symmetrically bonded to the metal atoms, suggesting a partial localization of the electrons within the organic ligands.

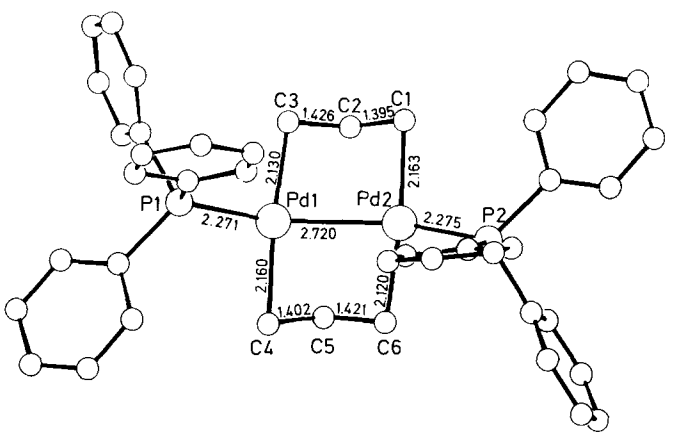


Fig. 7. The crystal structure of $[Pd(PPh_3)(\eta^3\text{-}C_3H_5)]_2$ [58].

The bis(η^1,η^3-allyl)(phosphane)palladium complexes react with CO_2, SCO, and SO_2 with insertion into the Pd–C bond (Scheme 5).[43, 60] The structure of **16** has been confirmed by X-ray structure determination (Fig. 8).

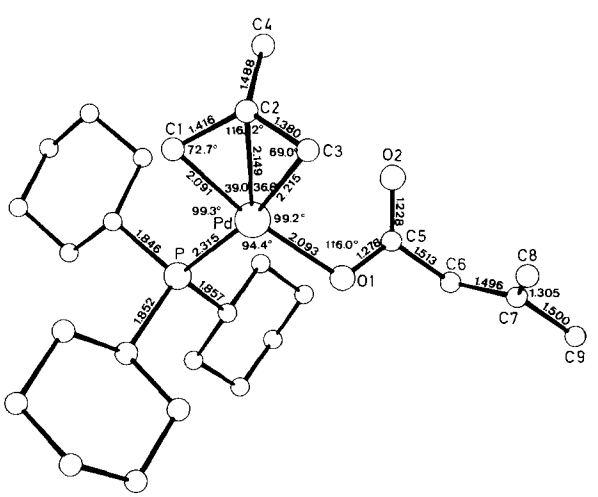
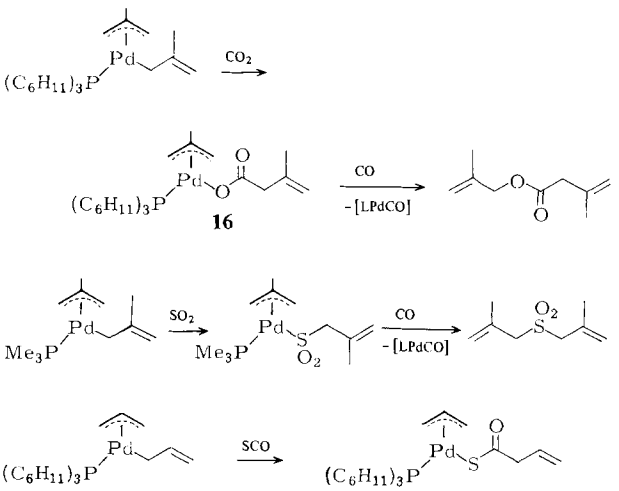


Fig. 8. The crystal structure of **16** [18].

The η^3-allyl group in this molecule is asymmetric and is bonded unsymmetrically to the metal atom: the Pd–C bond *trans* to the phosphane is elongated and the allylic C–C bond shortened. For the complex shown in Scheme 5, the direction of insertion of SCO has also been confirmed by X-ray structure determination, although a satisfactory refinement of the data was hindered by disorder in the η^3-allyl group.[61]



Scheme 5.

Reaction of the η^3-allylpalladium carboxylate and S-sulfinate complexes with CO results in reductive coupling and elimination of an ester or sulfone (Scheme 5).[43, 60] On the other hand, the reaction of $[Pd(PMe_3)(\eta^1,\eta^3\text{-}C_8H_{12})]$ or $[Pd\{(C_6H_{11})_3\}(\eta^1,\eta^3\text{-}Me_2C_8H_{10})]$ with CO does not lead to reductive coupling and elimination of vinylcyclohexene or dimethylvinylcyclohexene (as observed for the analogous nickel compounds).[52] Instead, cleavage of the C_8-chain occurs with elimination of butadiene or isoprene.[18, 19] In the case of the trimethylphosphane-substituted complex this has been shown to be accompanied by the formation of a novel cluster compound $[Pd(PMe_3)(CO)]_7$. An X-ray structure determination (Fig. 9) has established that this compound is one of the few examples of a seven-metal-atom cluster in which the atoms are arranged in a face-capped octahedron. A phosphane molecule is bonded terminally to each palladium atom, whereas the CO molecules are both edge- and face-bridging.

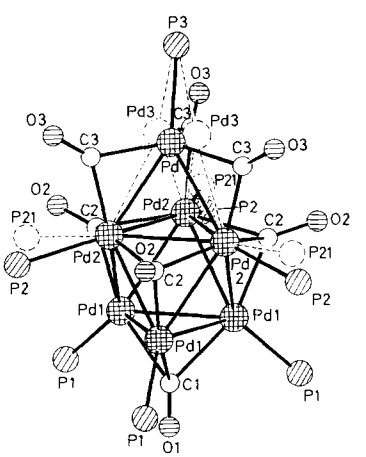
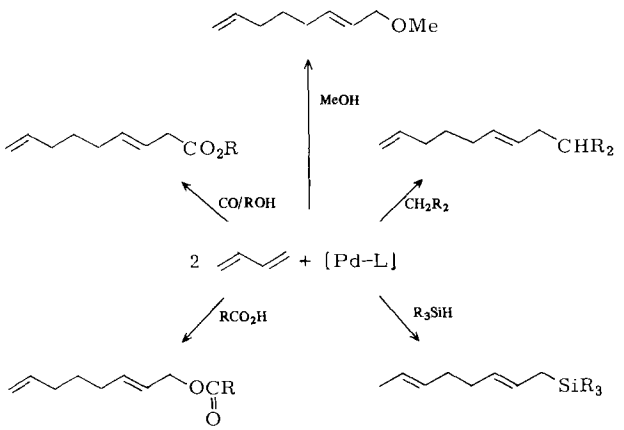


Fig. 9. The crystal structure of $[Pd(PMe_3)(CO)]_7$ [62].

The significance of the [PdL(η^1,η^3-C_8H_{12})] complexes lies in their role as intermediates in palladium-catalyzed butadiene telomerization reactions, some of which are of considerable importance in organic synthesis (see Scheme 6).



Scheme 6 [63].

The relevance of the η^1,η^3-octadienediylpalladium species to these reactions is best illustrated by two examples: the reaction of [Pd(PMe_3)(η^1,η^3-C_8H_{12})] with methanol[18,51] and of [Pd{$P(C_6H_{11})_3$}(η^1,η^3-C_8H_{12})] with ethyl acetoacetate.[54] The ^{31}P-NMR spectra of the mixture obtained from the reaction of [Pd(PMe_3)(η^1,η^3-C_8H_{12})] with methanol at various temperatures is shown in Figure 10. The starting material [$\delta(^{31}P) \approx -13.6$] is converted via intermediate **A** [$\delta \approx -16.0$] into the product **B** [$\delta \approx -25.6$]; **A** and **B** have been identified as an η^2,η^3-octadienylpalladium complex and an η^2,η^2-1-methoxy-2,7-octadienepalladium complex, respectively. A plausible mechanism for the telomerization reaction is shown in Scheme 7. The reaction of **B** with butadiene with regeneration of the original η^1,η^3-octadienediylpalladium complex and displacement of methoxyoctadiene has been confirmed in a separate reaction.

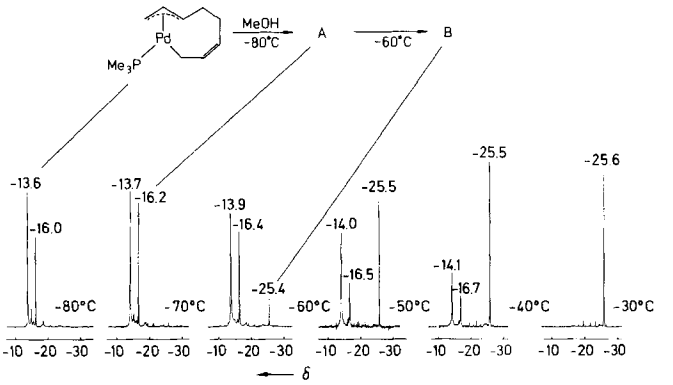
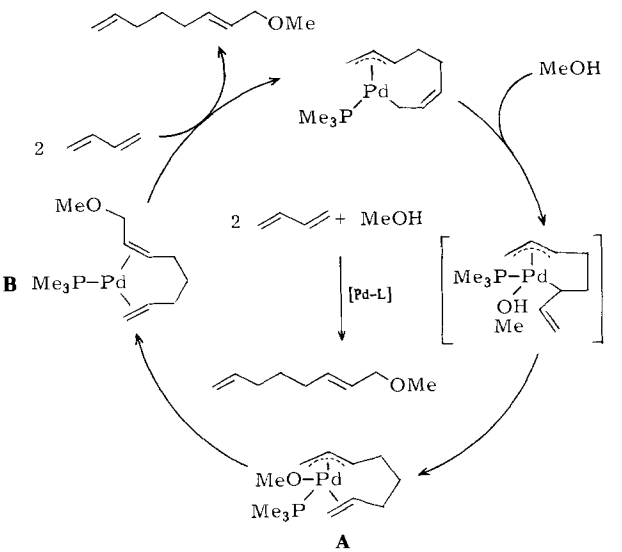
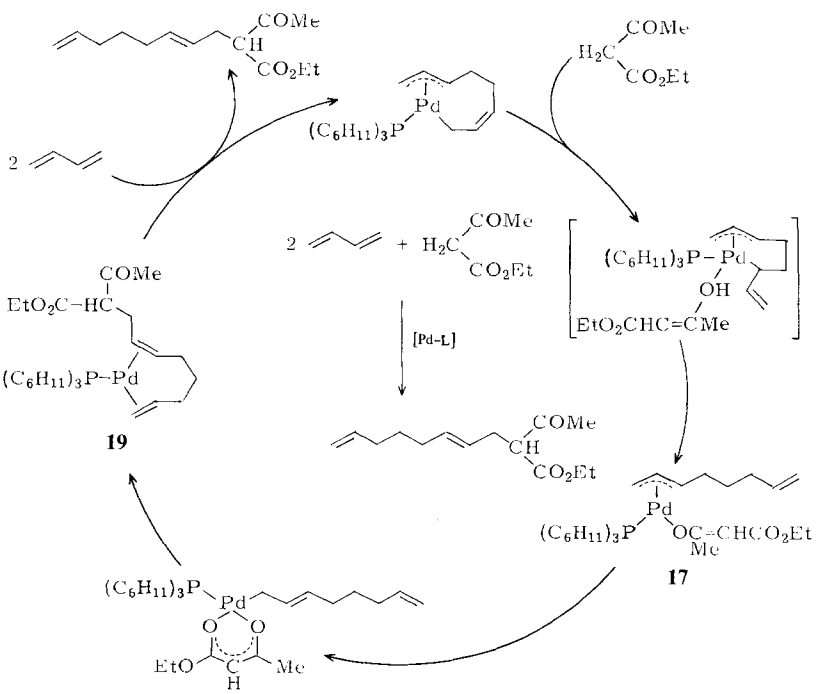


Fig. 10. ^{31}P-NMR spectra of the reaction mixture obtained from [Pd(PMe_3)(η^1,η^3-C_8H_{12})] and MeOH at different temperatures [18].

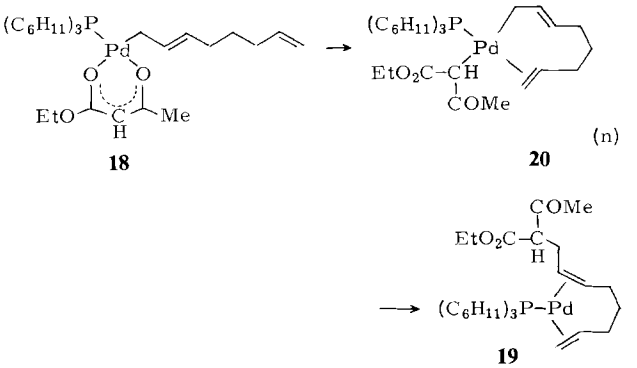


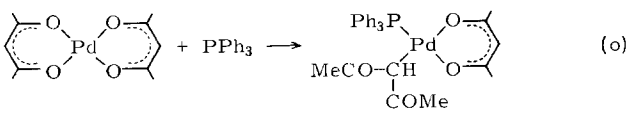
Scheme 7.



Scheme 8.

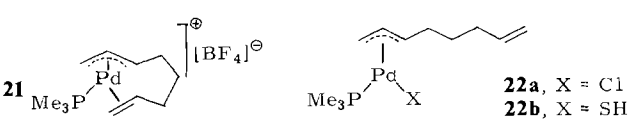
The reaction between $[Pd\{P(C_6H_{11})_3\}(\eta^1,\eta^3\text{-}C_8H_{12})]$ and ethyl acetoacetate, forming 2,7-octadienyl acetate, is more complicated. By a combination of chemical analysis and NMR spectroscopy, three intermediates, **17**, **18**, and **19**, could be identified; these support the catalytic cycle shown in Scheme 8. Apparently, the ethyl acetoacetate reacts through the enol form to give initially **17**. The rearrangement of **18** to **19** presumably proceeds via the intermediate formation of **20** in which a second Pd–C bond is formed; the rearrangement is instigated by complexation of the terminal double bond in **18** to the metal [Reaction (n)]. This rearrangement has precedence in that of palladium acetylacetonate in the presence of donor ligands [Reaction (o)].[64]



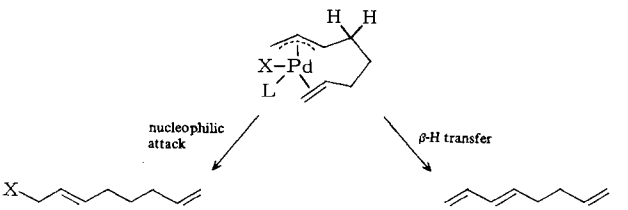


A number of questions concerning these reactions remain to be answered. In both cases it is suggested that the original η^1,η^3-octadienediyl chain rearranges, under the influence of the reactant, to give a vinyl-substituted isomer. This rearrangement explains directly the observed exclusive deuteration of C-6 on reaction with MeOD (or CH_3CO_2D in the analogous reaction with acetic acid). However, alternative explanations, e.g., direct attack on the uncomplexed *cis* double bond in the η^1,η^3-octadienediyl species, are possible. In addition, it has still to be decided whether **A** in Scheme 7 is better described by a covalent or by an ionic structure: the NMR data for **A** and for $[Pd(PMe_3)(\eta^1,\eta^3\text{-}C_8H_{13})]^{\oplus}[BF_4]^{\ominus}$ **21**, which has been shown by conductivity measurements to be ionic, are very similar.

Intermediates similar to those shown in Schemes 7 and 8 have also been isolated from the reactions of $[Pd(PR_3)(\eta^1,\eta^3\text{-}C_8H_{12})]$ complexes with Me_2CHOH, $H_2C(CO_2Et)_2$, $H_2C(CN)_2$, $H_2C(CN)CO_2Me$, $MeCO_2H$, and $PhCH(OH)CO_2H$. HBF_4 reacts to give **21a**, whereas HCl and H_2S give the non-ionic η^3-allyl complexes **21b** and **21c**, respectively.[54]



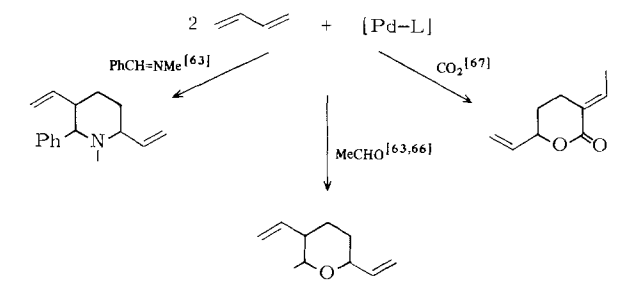
The η^2,η^3-octadienylpalladium species is a key "switch" intermediate: nucleophilic attack leads to the formation of a telomer, whereas β-hydrogen transfer leads to liberation of a linear dimer (Scheme 9). The addition of tertiary amines—which are known to promote the telomerization of,



Scheme 9.

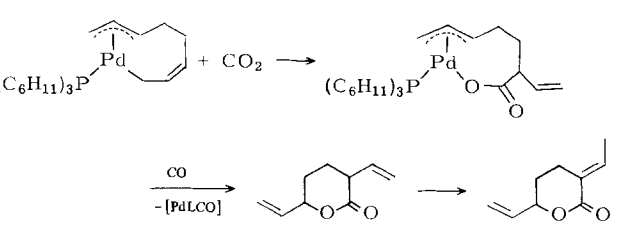
for example, acetic acid with butadiene[65]—presumably provides additional donor molecules, which displace the olefinic moiety in the octadienyl ligand from the metal atom and promote the rearrangement of the η^3-allyl group to the η^1-allyl form and its reductive coupling with acetate. Secondary or primary amines, in contrast, compete with the acetic acid in complexing with the metal, resulting in the formation of octadienylamines.

The η^1,η^3-octadienediylpalladium species are probably involved in the Pd-catalyzed cyclooligomerization of butadiene with heteroolefins (Scheme 10). Here, too, stoi-



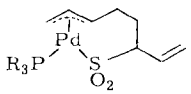
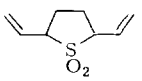
Scheme 10.

chiometric reactions throw some light on the course of reaction. For example, it has been shown that these organopalladium complexes react with CO_2 via insertion into the Pd–C bond. Reaction of the intermediate η^3-allylpalladium carboxylate with CO results in reductive coupling and displacement of a γ-lactone, which was shown to undergo facile thermal isomerization at room temperature to the lactone formed in the catalytic reaction (Scheme 11).[19,43]



Scheme 11.

Phenyl isocyanate reacts similarly.[18] SO_2 also inserts into the Pd–C bond of the η^1,η^3-octadienediylpalladium complexes to give the palladium-S-sulfinate complex **22**.[43] This complex might well be involved in the cooligomerization of SO_2 with butadiene to give 2,5-divinylsulfolane **23**. This reaction is catalyzed, albeit inefficiently, by a triphenylphosphane-modified palladium catalyst.[68]

22  **23** 

Complexes analogous to **22** have also been isolated from reactions involving nickel. For the reaction between $[Ni\{P(C_6H_{11})_3\}(\eta^1,\eta^3\text{-}3,6\text{-}Me_2C_8H_{10})]$ and SO_2, the crystal structure of the product has been established by X-ray crystallography (Fig. 11).

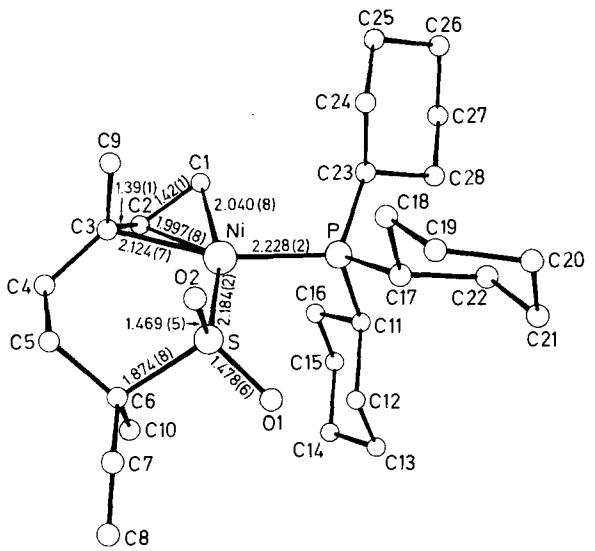
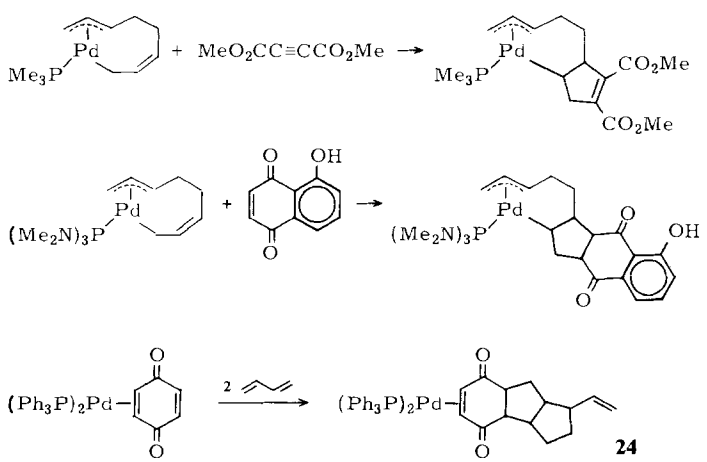


Fig. 11. The crystal structure of the product of the reaction of SO_2 with $[Ni\{P(C_6H_{11})_3\}(\eta^1,\eta^3\text{-}3,6\text{-}Me_2C_8H_{10})]$ [43, 61].

The reaction of the η^1,η^3-octadienediylpalladium complexes with unsaturated organic molecules takes a different course: electron-deficient alkynes and olefins undergo 1,3-addition to the η^1-allyl fragment (Scheme 12).[54] These



Scheme 12.

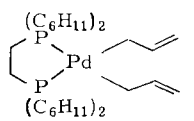
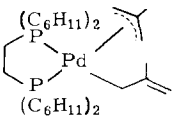
reactions are reminiscent of that between bis(triphenylphosphane)(η^2-*p*-benzoquinone)palladium and butadiene from which, the palladium complex **24** has been isolated.[69]

The reactivity of systems derived from substituted dienes should be similar to that of the η^1,η^3-octadienediylpalladium complexes. Preliminary investigations of the $[Pd(PR_3)(\eta^1,\eta^3\text{-}Me_2C_8H_{10})]$ complexes derived from isoprene have confirmed this for reactions with methanol, acetic acid, and mandelic acid.[19]

4. Bis(η^1-allyl)palladium Complexes

4.1. Preparation and Structure

Treatment of bis(η^3-allyl)palladium with two equivalents of a donor ligand could convert both η^3-allyl groups into the η^1-arrangement; indeed, this is observed in some cases upon reaction with chelating bidentate phosphanes. The course of the reaction is dependent upon the nature of both the phosphane and the allyl group: whereas bis(dicyclohexylphosphino)ethane reacts with $[Pd(\eta^3\text{-}C_3H_5)_2]$ as expected to give **25**, it reacts with $[Pd(\eta^3\text{-}2\text{-}MeC_3H_4)_2]$ to give the η^1,η^3-compound **26** in which the allyl groups undergo intramolecular exchange.[18, 19, 70]

25   **26**

25 is unstable at room temperature (hexadiene is eliminated to give $[(L_2Pd)_2C_6H_{10}]$). The analogous platinum compound, however, is stable, and the η^1-arrangement of the allyl groups has been confirmed by X-ray structure determination (Fig. 12).

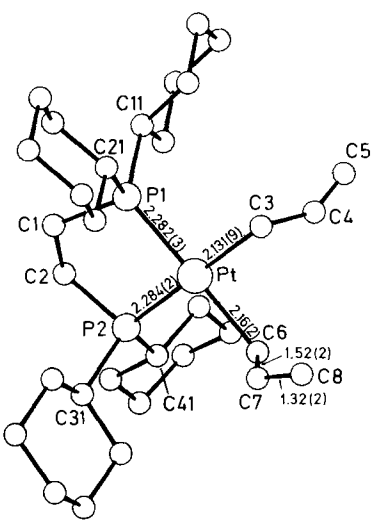
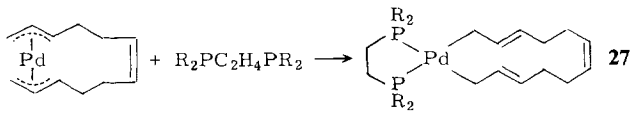


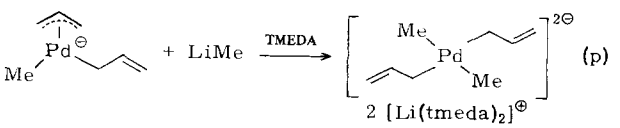
Fig. 12. The crystal structure of $[Pt\{(C_6H_{11})_2PCH_2CH_2P(C_6H_{11})_2\}(\eta^1\text{-}C_3H_5)_2]$ [61, 70].

$[Pd(\eta^3,\eta^3,C_{12}H_{18})]$ reacts similarly on treatment with a variety of dialkyl-substituted bidentate phosphanes: the 13-membered palladium ring system **27** is formed—presumably a record for metallacycle size.



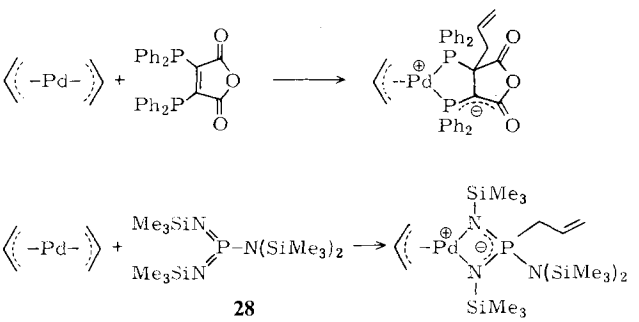
27

Although the reactions of the $[Pd(PR_3)(\eta^1,\eta^3\text{-allyl})_2]$ complexes with a second monodentate ligand have still to be investigated carefully, the anionic bis(η^1,η^3-allyl)(methyl)palladium complex has been shown to react with a second equivalent of methyllithium to form a tetraorganopalladate [Reaction (p)].[50] The reaction was carried out in the presence of tetramethylethylenediamine (TMEDA).



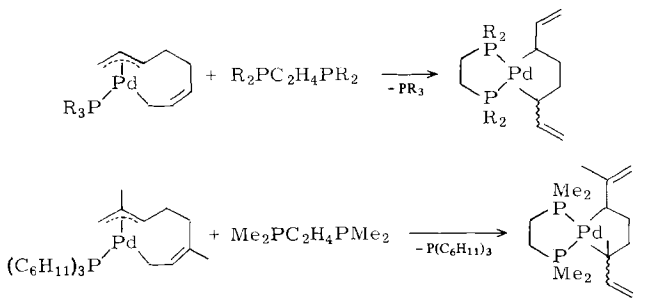
(p)

A few, rather exotic, bidentate ligands react anomalously with bis(η^3-allyl)palladium: bis(diphenylphosphino)maleic anhydride reacts with transfer of an allyl group from the metal to the ligand to give a zwitterion;[71] similar behavior is also observed in the reaction with the amino[bis(imino)]ylide **28**[72] (Scheme 13). In both cases the structure of the product has been confirmed by X-ray structure determination.



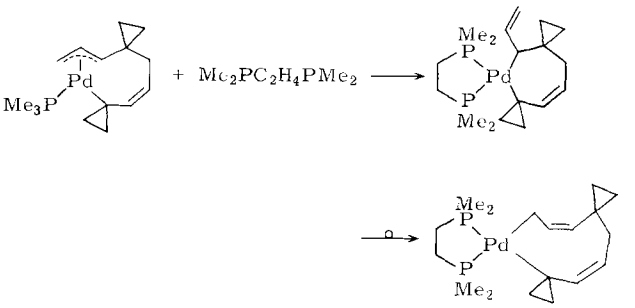
Scheme 13.

Treatment of the $[Pd(PR_3)(\eta^1,\eta^3\text{-}C_8H_{12})]$ complexes with chelating phosphanes frequently leads to ligand exchange and formation of a bis(η^1-allyl)palladium system. For example, 1,4-divinylpalladacyclopentane derivatives may be prepared in this way as a mixture of *cis* and *trans* isomers. A similar reaction is observed with the dimethyl-substituted octadienediyl derivatives[19] (Scheme 14).



Scheme 14. R = Me, *i*Pr, C_6H_{11}; R' = Me, Ph, NMe_2.

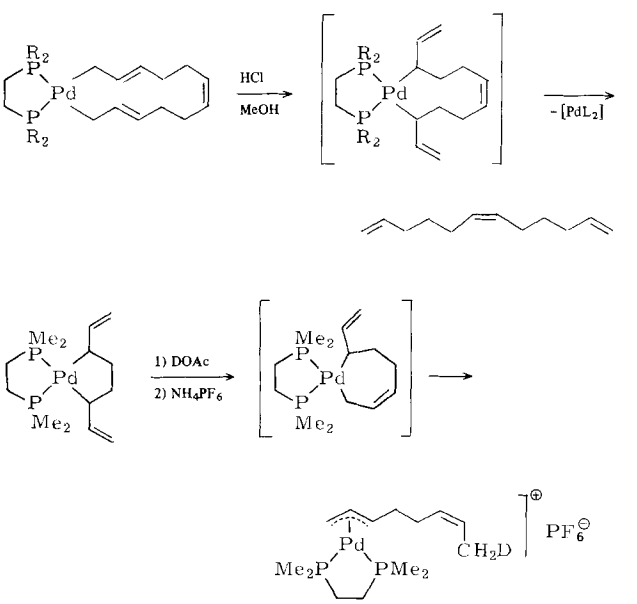
The cyclopropane-substituted analogue reacts somewhat differently (Scheme 15): initially a palladacycloheptene derivative is formed which then rearranges to a palladacyclononadiene species whose structure has been verified by X-ray crystallography.[55]



Scheme 15.

4.2. Reactions

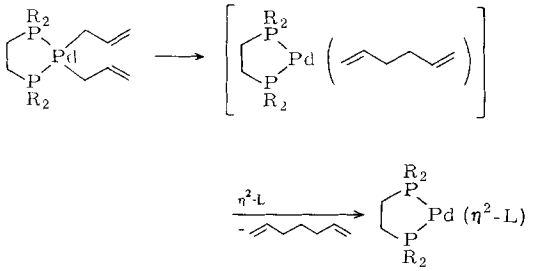
The $[PdL_2(\eta^1\text{-allyl})_2]$ complexes behave as typical dialkylpalladium systems. For example, the Pd–C bond can be cleaved by acids, and reactions with donor ligands lead to reductive coupling of the allyl groups or (where possible) to β-hydrogen transfer. Two non-trivial examples are the treatment of the palladacyclotridecatriene with methanolic HCl, from which *cis*-1,6-11-dodecatriene is liberated, and the reaction of a palladacyclopentane derivative with deuteroacetic acid, which results in deuteration of a terminal C-atom (Scheme 16).[19] The first reaction is of interest



Scheme 16. R = Me, *i*Pr, C_6H_{11}.

because it establishes the presence of a *cis*-double bond in the reacting metallacycle. Whether these reactions proceed via the palladacyclononene and palladacycloheptene derivatives shown in Scheme 16 is not known; direct attack of the acid on the double bond is possible.

Ligand-induced or spontaneous reductive coupling of the allyl groups is observed for the simple $[PdL_2(\eta^1\text{-allyl})_2]$ species. There is some evidence that the resulting diene, which is initially complexed to the metal, can be displaced, providing a convenient access to a variety of $[L_2Pd]$ complexes of unsaturated organic molecules (Scheme 17).[18,70]

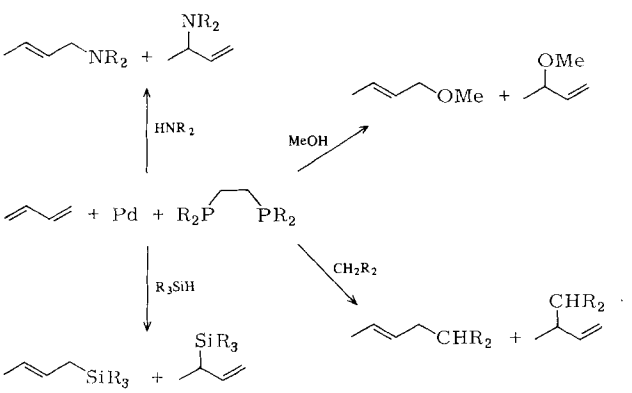


Scheme 17. R = *i*Pr, *t*Bu, C_6H_{11}.

The behavior of the palladacycles (Scheme 16) with excess donor ligand is anomalous: the palladacyclotridecatriene reacts with β-hydrogen transfer (presumably via the same nine-membered-ring intermediate) to give a mixture of dodecatetraene isomers; the palladacyclopentane derivative reacts with ring cleavage and liberation of butadiene.[19]

5. η^3-Allylpalladium Complexes with Bidentate Ligands[70]

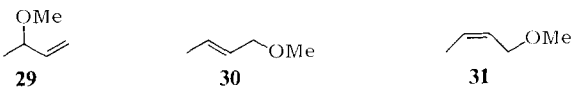
η^3-Allylpalladium complexes with bidentate ligands are presumably involved as intermediates in the numerous 1:1-telomerization reactions of butadiene with nucleophiles. Such reactions are catalyzed by palladium in the presence of chelating bidentate phosphanes or an excess of a monodentate phosphane (Scheme 18).[63]



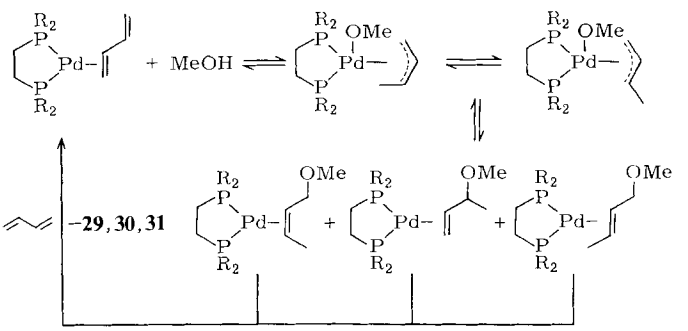
Scheme 18.

The stoichiometric reaction of the $[PdL_2(\eta^2\text{-}C_4H_6)]$ complexes (prepared as shown in Scheme 17) with nucleophiles has provided insight into the mechanism of the reactions shown in Scheme 18. The reaction with methanol will be described in detail; similar results have been obtained with acetic acid and amines.

The reaction between butadiene and methanol is catalyzed by $[Pd\{(C_6H_{11})_2PCH_2CH_2P(C_6H_{11})_2\}(\eta^2\text{-}C_4H_6)]$; after 3 h at 100°C, practically the only product is a mixture of the three methoxybutene isomers **29**, **30**, and **31** in an approximate ratio of 7:4:1 and with a butadiene conversion of 40%. If the bis(diphenylphosphino)ethane-stabilized complex is used as the catalyst, the main product is the 2:1 telomer methoxyoctadiene.



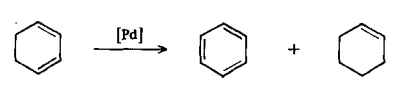
An NMR spectroscopic investigation of the stoichiometric reaction between the η^2-butadienepalladium complex and methanol in tetrahydrofuran established that a multistep reaction occurs: initially at −80°C an *anti*-η^3-1-methallylpalladium complex is formed which, after rearrangement to the *syn*-isomer, reacts further at ca. −30°C by reductive coupling to give the expected η^2-methoxybutenepalladium complexes (Scheme 19).



Scheme 19. R = C_6H_{11}.

The reversibility of all these steps could be demonstrated in separate reactions with the individual methoxybutene isomers. Treatment of the complexes with butadiene leads to displacement of the olefins.

An attempt to carry out a similar reaction with the analogous η^2-1,3-cyclohexadienepalladium complex failed—instead, disproportionation to benzene and cyclohexene was observed. Catalysis of this disproportionation by elemental palladium was first reported in 1933.[73] In the early



1970s, a number of homogeneous transition-metal catalysts[74] were investigated. The addition of methanol to $[Pd\{(C_6H_{11})PCH_2CH_2P(C_6H_{11})_2\}(\eta^2\text{-}1,3\text{-}C_6H_8)]$ produces a catalyst which, although less active than elemental palladium, is much more stable. The reaction presumably proceeds through the intermediate formation of η^3-cyclohexylpalladium species in a manner analogous to that proposed for the Rh-catalyzed reaction.[75]

6. Outlook

The main objective of this article has been to demonstrate how a study of the chemistry of model complexes can provide information relevant to the individual steps of a catalytic process. Although we have limited ourselves here to reactions involving η^3-allylpalladium complexes and dienes, a similar approach can be applied to other systems and other metals. For example, a study of the chemistry of alkylpalladium complexes can give insight into the mechanism of the palladium-catalyzed transformations of alkenes. Investigations of this kind only partly elucidate the catalysis. A well-founded mechanism must incorporate kinetic data, which, however, is notoriously lacking in organometallic chemistry.

Much of the progress that has been made is not based so much upon new principles—the basic reactions involved in homogeneous catalysis were clearly identified more than two decades ago—but rather on the increasing sophistication of the spectroscopic tools available. It requires no particular enlightenment to predict that this development will continue. In particular, the routine use of variable temperature NMR spectroscopy will continue to be a cornerstone of these studies, whereby it is to be anticipated that, above and beyond the continued use of the established nuclei (^{1}H, ^{13}C, ^{31}P, etc.), the routine measurement of the metal-atom chemical shift will introduce a new dimension. Unfortunately, ^{105}Pd (natural abundance 22%) has a spin of 5/2 and the absorptions are broad, so that the data will not be as useful as those of other metals (e.g., Pt and Rh). However, the increased facility with which these measurements can be carried out has the inherent danger that many important processes in which paramagnetic species are involved will be neglected.

Although emphasis has been placed in this article on catalytic reactions, it should at least be mentioned that many synthetically valuable reactions, e.g., the coupling of palladium-bonded organic groups and the nucleophilic attack on complexed alkenes, are of a stoichiometric nature.[63, 76] Attempts are being made to carry out these reactions catalytically. Their success, however, will clearly depend on a detailed understanding of the chemistry of the organopalladium complexes involved.

I would like to thank Professor G. Wilke for his continuous support of this work without which it would not have been possible. It is a pleasure to acknowledge the stimulating cooperation of Professor C. Krüger, Dr. R. Goddard, Dr. Y.-H. Tsay, and their coworkers, who were responsible for the X-ray diffraction studies, and of Dr. R. Benn, Miss B. Gabor, Dr. R. Mynott, Dr. A. Rufińska, and Mr. G. Schroth, who were responsible for the NMR investigations. I am also indebted to Mr. A. Döhring and Mrs. S. Holle for their dedicated and skillful technical assistance.

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Reactive Organometallic Compounds Obtained from Metallocenes and Related Compounds and Their Synthetic Applications**

By Klaus Jonas*

Dedicated to Professor Günther Wilke on the occasion of his 60th birthday

Progress in the synthesis of organometallic compounds via the partial or total degradation of metallocenes and related compounds under mild reaction conditions is reviewed. These degradation reactions permit highly reactive organo-transition metal complexes to be prepared which can in turn be used in a wide range of synthetic reactions. Examples include catalytic reactions such as the cobalt-catalyzed hydrogenation of benzene and the manganese-catalyzed cyclotrimerization of butadiene as well as stoichiometric syntheses of mono- and polynuclear transition metal complexes, some of which have novel structural features.

1. Introduction

As reported in a number of previous publications, metallocenes, alkali metals, and olefins can be used to prepare transition metal-olefin- or alkali metal-transition metal-olefin complexes.[1] More recently, developments arising from this synthetic approach have been having an impact on other areas of organometallic chemistry. The present paper reviews these and other current developments in this field.

The review is divided into two main parts. The first part deals primarily with those reaction schemes that have been studied in the Institute in Mülheim by which metallocenes and related compounds with pentacyclic ligands can be

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[**] Based on studies by *G. Burkart, K. Cibura, E. Deffense, A. Duff, D. Habermann, K. Jonas, J. Klocke, G. Koepe, H. Priemer, L. Schieferstein*, and *V. Wiskamp*. The author wishes to tank his co-workers for their enthusiastic cooperation in the research described here.

degraded, while the second part demonstrates that these degradation reactions can provide access to highly reactive organometallic compounds which have wide synthetic applications.

2. Synthesis of Reactive Organometallic Compounds by Partial or Total Degradation of Metallocenes and Related Compounds

This section describes reactions by which metallocenes and related compounds can be converted into reactive organometallic compounds, i.e. complexes of transition metals having readily accessible coordination sites. These reactions have in common that the cleavage of the transition metal five-membered ring ligand bonds takes place under especially mild reaction conditions. We have investigated the two following types of reaction[2] by which this can be achieved easily and which can be used for synthetic purposes:

A: Removal of the five-membered ring ligands by reaction with an alkali metal and olefin and/or another complexing agent (removal of one or both rings)

B: Exchange of the five-membered ring ligands by metathetical reactions with organometallic compounds or hydrides of the main group elements, especially of the alkali metals, either in the presence or absence of complexing agents (exchange of one or both rings)

In addition, reactions of type A and B can be combined in a synthesis, whereby one ring is removed from the transition metal by method A and the other by method B. Two-stage degradation reactions of this kind will be referred to as type C reactions in this publication.

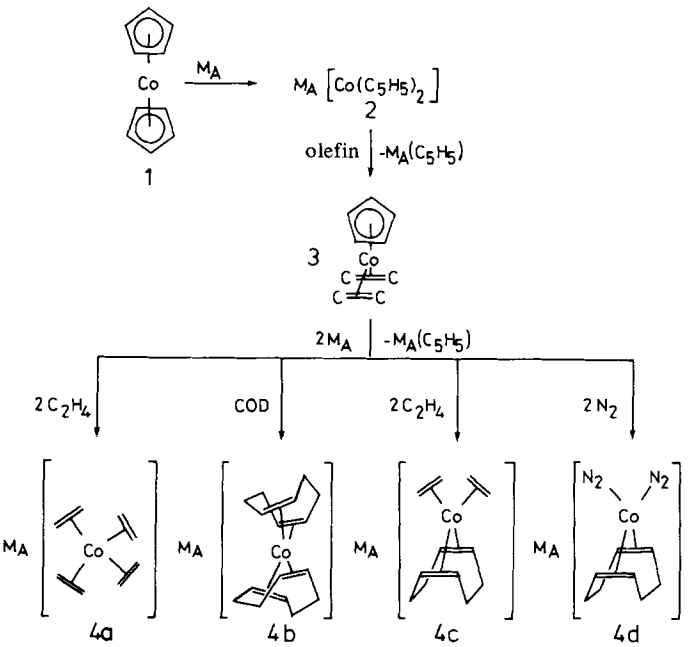
C: A and B combined (removal of both rings)

2.1. Degradation of Metallocenes and Related Compounds by Reaction with Alkali Metal and Olefin and/or Another Complexing Agent

2.1.1. Reactive Olefin Complexes of Cobalt and Iron

In 1973 we reported the synthesis and properties of tris(ethylene)nickel.[3] This compound, the first metal-olefin complex made up only of ethylene and a metal atom, is a beautiful example of "naked nickel".[4] Its discovery presented a challenge—could metal complexes with a similarly large number of ethylene ligands be prepared with transition metals further left in the periodic table? Today, such highly reactive ethylene complexes are also known for cobalt and iron,[1,2] thanks to the efficiency of the metallocene degradation of type A. Scheme 1 outlines the preparation of cobalt-ethylene and other cobalt-olefin complexes from cobaltocene **1**.

The first step in the reductive degradation of cobaltocene is the formation of 1 : 1 adducts between cobaltocene and an alkali metal atom M_A (M_A = Li, K) (see **2** in Scheme 1). The final products are cyclopentadienyl-free alkali metal cobaltates(−1) **4**, which contain readily replaceable olefin ligands, e.g. four coordinated ethylene molecules (**4a**). Further intermediates in the degradation are the half-sandwich complexes of type **3**, of which the most reactive is again the ethylene complex (**3a**). In practice, **3a** and **4a** are prepared by stirring cobaltocene **1** with the alkali metal in a reaction vessel connected to a gas bottle filled with ethylene. When diethyl ether is used as the solvent only one cyclopentadienyl ligand is removed, whereas when the reaction is carried out in THF both ring ligands are removed [Eq. (1) and (2)].[5]



Scheme 1. The preparation of cobalt-ethylene and other cobalt-olefin complexes from cobaltocene **1**. For clarity, the n-donor ligands tetrahydrofuran (THF), tetramethylethylenediamine (TMEDA) or diethyl ether (Et_2O) bonded to the alkali metal atoms M_A have been omitted from this and all other reaction schemes and equations in this publication.—Olefin = ethylene, butadiene, cyclohexadiene, cyclooctadiene etc.

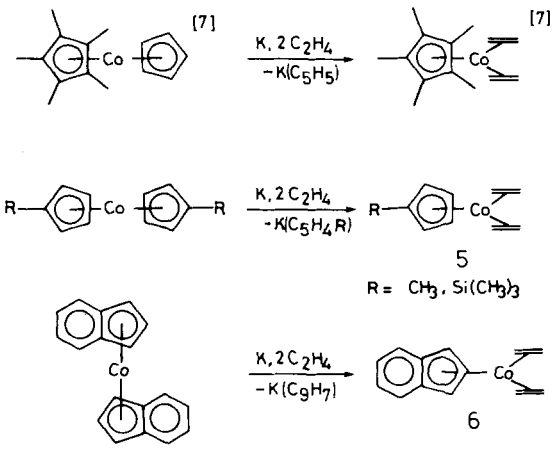
$$(C_5H_5)_2Co + K + 2C_2H_4 \xrightarrow[-K(C_5H_5)]{Et_2O} (C_5H_5)Co(C_2H_4)_2 \qquad (1)$$
1 **3a**

$$(C_5H_5)_2Co + 3M_A + 4C_2H_4 \xrightarrow[-2M_A(C_5H_5)]{THF} M_A[Co(C_2H_4)_4] \qquad (2)$$
1 **4a**

All these degradation reactions, including those where alkali metals are used in the presence of other complexing agents (see Scheme 1), proceed practically without side reactions and almost quantitatively (i.e., for **3** and **4** the yield is over 90%) and the alkali metal cyclopentadienides can be separated from the cobalt complexes **3** and **4** without difficulty.[*]

[*] This point is important enough to warrant further detail. For example, the $K(C_5H_5)$ formed according to Scheme 1 and Equation (2) is rather insoluble in THF at −78 °C compared to the potassium cobaltates **4a** and **4b**. Furthermore, it is precipitated in a form ideal for separation by filtration. Solid **4a** or **4b** is formed on evaporation of the THF-filtrate. The last traces of $K(C_5H_5)$ can be removed from the products by washing with diethyl ether, since the potassium cyclopentadienide is much more soluble in ether than in THF at 20 °C, while for the cobalt complexes exactly the reverse is true.

In order to develop a general method for the synthesis of cobalt(I)-ethylene complexes with substituted cyclopentadienyl ligands, the principle of reductive degradation of metallocenes has recently been extended to cobaltocene derivatives (Scheme 2). A particularly interesting variant of the $(C_5H_5)Co(C_2H_4)_2$ synthesis [Eq. (1)] is the preparation of the new indenylcobalt compound **6**.[6] This complex is unstable above 0°C and its reactivity can be expected to exceed that of the parent compound **3a**, which is stable at room temperature. This would be consistent with the known differences in reactivity of different half-sandwich complexes with carbonyl ligands.[8]



Scheme 2. Cobalt(I)-ethylene complexes prepared by reductive abstraction of five-membered ring ligands.

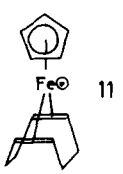
The potential of the reductive degradation of metallocenes is further illustrated by the fact that not only cobaltocene **1** and nickelocene **23** (electron-rich metallocenes)[1,9] can be degraded, but also that such a stable 18e compound as ferrocene **7** is a suitable starting material for the preparation of reactive iron-olefin complexes [Eqs. (3) to (5)]. Ferrocene reacts with lithium and ethylene to yield the iron-ethylene complexes **8**[10a] and **10**,[10b] while the corresponding reaction with 1,5-cyclooctadiene (COD) instead of ethylene produces **9**.[10a]

$$\underset{\mathbf{7}}{(C_5H_5)_2Fe} \xrightarrow[-Li(C_5H_5)]{2\,Li,\ 2\,C_2H_4} \underset{\mathbf{8}}{Li[(C_5H_5)Fe(C_2H_4)_2]} \qquad (3)$$

$$\underset{\mathbf{7}}{(C_5H_5)_2Fe} \xrightarrow[-Li(C_5H_5)]{2\,Li,\ COD} \underset{\mathbf{9}}{Li[(C_5H_5)Fe(cod)]} \qquad (4)$$

$$\underset{\mathbf{7}}{(C_5H_5)_2Fe} \xrightarrow[-2\,Li(C_5H_5)]{4\,Li,\ 4\,C_2H_4} \underset{\mathbf{10}}{Li_2[Fe(C_2H_4)_4]} \qquad (5)$$

Compound **9** can be delithiated with trityl chloride[10a] to produce **11** (Scheme 3). This mononuclear iron(I)-olefin complex, which has one unpaired electron, has been studied in detail by X-ray crystallography (for details, see the review by *Krüger* et al.).[11]



11

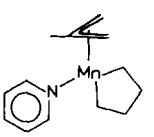
Scheme 3. Cyclooctadiene(cyclopentadienyl)iron(I) **11**—an iron-olefin complex with one unpaired electron.

2.1.2. The Reaction of Manganese(II) Cyclopentadienide with Alkali Metals and Olefins and Subsequent Reactions

When manganese(II) cyclopentadienide **12** is stirred with potassium at low temperatures (−60 to −20°C) in diethyl ether or THF, the surface of the potassium rapidly becomes coated with metallic manganese. The same is observed in the presence of ethylene or other olefins. Thus, compound **12**, which tends to dissociate into ions,[12] cannot be used in this way for organometallic syntheses. It is also unable to function as an alkali metal carrier, apparently because the $[(C_5H_5)_2Mn]^{\ominus}$ anion is unstable. For the metallocenes of Ni,[13] Co,[13–15] Cr and V,[13] the reversible one-electron reduction to the anion has been demonstrated by cyclic voltammetry, while $(C_5H_5)_2Co$ **1** (Scheme 1), $(C_5H_5)_2V$ **14** and $(C_5Me_5)V(C_5H_5)$ **15** (Section 2.1.3) and $(C_5Me_5)_2Mn$[17] form 1:1 adducts with alkali metals.

$Mn(C_5H_5)_2$ **12**

In order to prevent the deposition of manganese, the reactions have been carried out in the presence of conventional alkali metal carriers instead of the alkali metal alone.[18] This recent modification has proved to be most significant. Thus, the reaction of **12** in THF with naphthalenepotassium $[K(C_{10}H_8):Mn=3:1]$ and ethylene at −60°C to −40°C yields $K(C_5H_5)$, which is sparingly soluble in THF, in the amount calculated $[K(C_5H_5):Mn=2:1]$, together with a filtrate containing potassium and manganese in the ratio 1:1. On addition of methallyl chloride and then pyridine to the filtrate, the new metallacyclic mononuclear complex **13** can be isolated (Scheme 4).



13

Scheme 4. Proposed structure for η^3-methallyl(pyridine)manganacyclopentane **13**.

If iodine is added to the above filtrate instead of methallyl chloride ($K:Mn:I_2=1:1:1$) followed by $Li(C_5H_5)$ or $Li(C_5Me_5)$, novel binuclear complexes are isolated in which each manganese atom bears a five-membered ring ligand. Again, as found for **13**, these compounds are not manganese-ethylene complexes but contain manganese atoms coordinated to $(CH_2)_4$ ligands that have been formed from two ethylene molecules.

2.1.3. Olefin and Allyl Complexes of Vanadium from Vanadocene

When vanadocene **14** or pentamethylvanadocene **15** (Section 3.3.2) is reduced with potassium in THF at

-78 °C, a deep red solution is formed from which **16** or **17**, respectively, can be precipitated by addition of Et_2O or pentane [Eq. (6) and (7)].

$$\underset{\mathbf{14}}{(C_5H_5)_2V} + K \xrightarrow[-78\,^\circ C]{THF} \underset{\mathbf{16}}{K[(C_5H_5)_2V]} \quad (6)$$

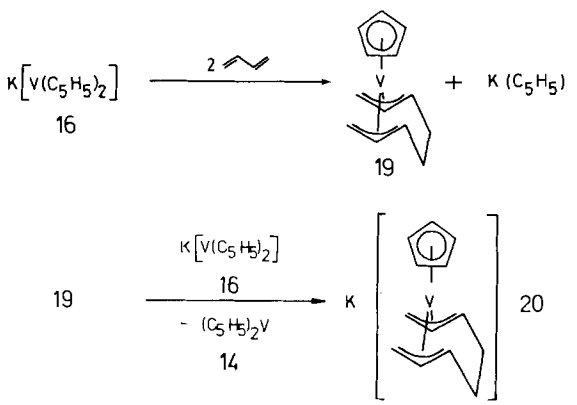
$$\underset{\mathbf{15}}{(C_5Me_5)V(C_5H_5)} + K \xrightarrow[-78\,^\circ C]{THF} \underset{\mathbf{17}}{K[(C_5Me_5)V(C_5H_5)]} \quad (7)$$

These new compounds **16**[19] and **17** are further examples of isolable alkali metal-reduced metallocenes or metallocene derivatives—other examples are **2** and $Na[(C_5Me_5)_2Mn]$.[17] Both these complexes **16** and **17** are, like the cobalt compounds **2**, particularly suitable for the synthesis of half-sandwich complexes.

Carbon monoxide reacts with **16** and **17** at -78 to 20 °C. These carbonylations lead to the formation of $K(C_5H_5)$ and $[(C_5H_5)V(CO)_4]$[20] or **18**, respectively.

$$\mathbf{16} + 4CO \xrightarrow[-K(C_5H_5)]{-78\,^\circ C \ldots 20\,^\circ C} (C_5H_5)V(CO)_4 \quad (8)$$

$$\mathbf{17} + 4CO \xrightarrow[-K(C_5H_5)]{-78\,^\circ C \ldots 20\,^\circ C} \underset{\mathbf{18}}{(C_5Me_5)V(CO)_4} \quad (9)$$



Scheme 5. The formation of **20** from **16** and butadiene.

When **16** is treated with butadiene in THF at -78 to 20 °C, the potassium vanadate **20** can be isolated.[19] The formation of **20** probably occurs as shown in Scheme 5. The intermediate potassium-free vanadium(III) complex **19** is formed by reaction of **16** with butadiene and is subsequently reduced to **20** by a second molecule of **16**. Thus, **16** has a double function since it not only provides the $(C_5H_5)V$ units [Eq. (10)] but also acts as a source of potassium [Eq. (11)].

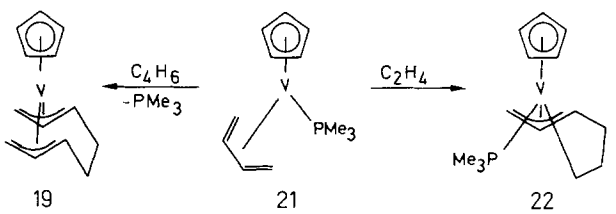
$$\underset{\mathbf{16}}{K[(C_5H_5)_2V]} \longrightarrow [(C_5H_5)V] + K(C_5H_5) \quad (10)$$

$$\underset{\mathbf{16}}{K[(C_5H_5)_2V]} \longrightarrow \underset{\mathbf{14}}{(C_5H_5)_2V} + K \quad (11)$$

The reaction of complex **16** with butadiene must be distinguished from that of **16** with a mixture of butadiene and trimethylphosphane. In this case **16** acts only as a source of $(C_5H_5)V$ units [Eq. (10)] and the product is the olefin-vanadium complex **21**, which contains no alkali metal [Eq. (12)]. [Compare this with Eq. (25) in Section 3.3.2.]

$$\underset{\mathbf{16}}{K[(C_5H_5)_2V]} + C_4H_6 + PMe_3 \xrightarrow[-78\ldots20\,^\circ C]{THF} \underset{\mathbf{21}}{(C_5H_5)V(C_4H_6)PMe_3} + K[C_5H_5] \quad (12)$$

The reactions of **21** with butadiene or ethylene are particularly interesting because C–C coupling[21] of the olefin ligands occurs (Scheme 6). With butadiene, **19** and free trimethylphosphane are formed, but with ethylene the V–P bond is retained and **22** is produced. The structures of **21** and **22** were determined by X-ray crystallography.[22]



Scheme 6. Allylvanadium(III) complexes **19** and **22** prepared by reaction of the olefin-vanadium(I) complex **21** with olefins.

2.2. Degradation of Metallocenes and Related Compounds by Metathetical Reactions

For a long time, metathetical reactions of metallocenes with organometallic compounds of the main group metals were used remarkably little for synthetic purposes. In 1961 *Muetterties* et al., reported that nickelocene reacts with allylmagnesium chloride to afford the allylnickel complex $[(\eta^3\text{-}C_3H_5)Ni(C_5H_5)]$ [Eq. (13)].[23] Ten years later, two Russian groups reported the reactions of nickelocene and vanadocene with benzylmagnesium chloride or phenyllithium,[24,25] while in 1972 *Switzer* and *Rettig* described the successive exchange of C_5H_5 ligands on nickel, chromium and manganese by C_5D_5 groups [Eq. (14)].[26] Finally, in 1978 it was shown by *Seidel* and *Scholz* that a lithium vanadate(II) can be obtained from vanadocene **14** and mesityllithium [Eq. (15)].[27]

$$\underset{\mathbf{23}}{(C_5H_5)_2Ni} \xrightarrow[-C_4H_5MgCl]{C_4H_5MgCl} [(\eta^3\text{-}C_3H_5)Ni(C_5H_5)] \quad (13)$$

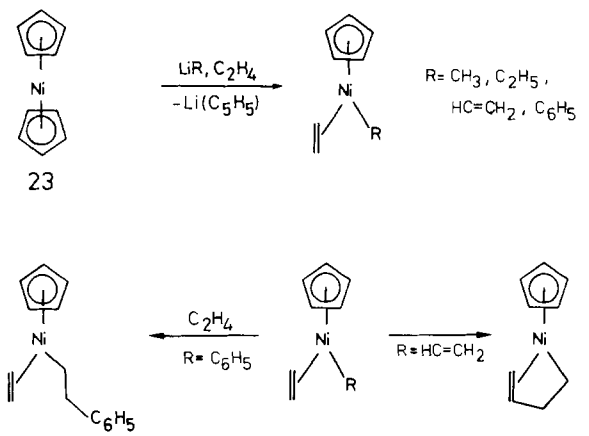
$$(C_5H_5)_2M \xrightarrow[-Li(C_5H_5)]{Li(C_5D_5)} [(C_5D_5)M(C_5H_5)] \xrightarrow[-Li(C_5H_5)]{Li(C_5D_5)} (C_5D_5)_2M \quad (14)$$
$M = Ni, Mn, Cr$

$$\underset{\mathbf{14}}{(C_5H_5)_2V} \xrightarrow[-Li(C_5H_5)]{2\,Li(C_9H_{11})} Li[(C_5H_5)V(C_9H_{11})_2] \quad (15)$$

2.2.1. Half-Sandwich Complexes and other Mononuclear Complexes of Nickel(II) from Nickelocene

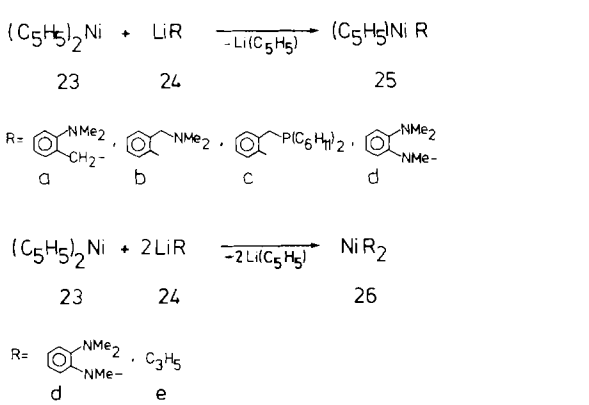
The are two major driving forces for the reactions of nickelocene with organometallic compounds of the main group metals which produce half-sandwich complexes. Firstly, the C_5H_5 ligand is the more strongly stabilized an-

ion and so binds preferentially with the more electropositive main group metal.[28] Secondly, one of the reactants is a sandwich compound with an electron-rich 20e system, while on the product side a nickel(II) compound is formed which always obeys the inert gas rule [see Eq. (13)]. *Lehmkuhl* et al., have used both factors to advantage in a wide range of syntheses of nickel complexes.[29] They have also used this principle to prepare nickel complexes which are model compounds for intermediates in metal-catalyzed conversions of olefins. Scheme 7 depicts the insertion of ethylene into the Ni–C σ-bonds of two nickel complexes that were prepared from **23**, an organolithium compound, and ethylene.[30]



Scheme 7. Insertion of ethylene into Ni–C σ-bonds.

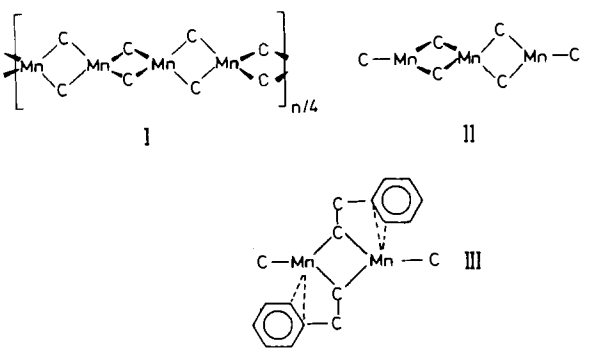
Recently, it was reported that the exchange of one of the Cp groups in nickelocene **23** can even be achieved by reaction with anhydrous lithium iodide. However, this reaction proceeds only when strong nucleophiles such as R_3P are added.[31] Finally, it should be mentioned that the reactions of nickelocene with the various organolithium compounds **24a–c** or the lithium amide **24d** lead to the formation of the new half-sandwich complexes **25a–d**.[6] Additionally, both C_5H_5 rings can be removed by treating **23** either with **24d** or with **24e** in the molar ratio 1:2 (Scheme 8).[6,30c]



Scheme 8. Exchange of one or both Cp moieties in nickelocene **23**.

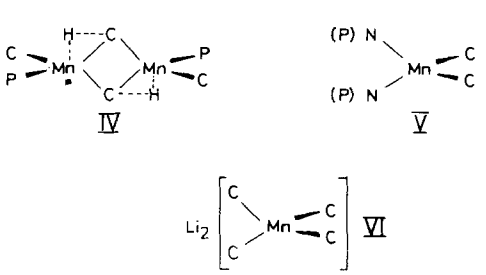
2.2.2. *Organomanganese(II) Compounds from Manganese(II) Cyclopentadienide*

The first dialkylmanganese compounds whose structures were determined by X-ray crystallography are $[Mn(CH_2SiMe_3)_2]_n$ and $[Mn(CH_2CMe_2Ph)_2]_2$, prepared in 1976 by *Wilkinson* et al. from $MnCl_2$ and the corresponding Grignard reagent or dialkylmagnesium.[32] In the polymeric compound, the organic groups are found exclusively in bridging positions, so that manganese is four-coordinate and has a tetrahedral environment (**I** in Scheme 9), while in the binuclear complex two of the neophyl groups act as bridging ligands and two are bound terminally. Nevertheless, the metal atoms are apparently four-coordinate because each manganese atom interacts with the phenyl group from one of the bridging ligands as shown in **III** of Scheme 9. On the other hand, while the central manganese atom in the trinuclear mesitylmanganese(II) complex $[Mn(C_6H_2Me_3)_2]_3$ reported by *Floriani* et al., in 1983[33] is four-coordinate, there can be no doubt that the two outer manganese atoms are three-coordinate (see **II** in Scheme 9).



Scheme 9. The greatly simplified structures of some homoleptic alkyl(aryl)manganese(II) complexes. **I** to **III**, see text.

Homoleptic alkyl(aryl)manganese(II) complexes are electron-deficient compounds. They add tertiary amines[32] or phosphanes[34,35] and react with organolithium compounds to form ate-complexes.[32] For example, the $[Mn(CH_2SiMe_3)_2]_n$ polymer discussed above reacts with PMe_3 to form the centrosymmetric binuclear complex $[Mn(CH_2SiMe_3)_2PMe_3]_2$. The geometry at manganese is a distorted tetrahedron, with each manganese atom coordinated to a PMe_3 ligand, a terminal Me_3SiCH_2 group, and two bridging Me_3SiCH_2 groups. The bridges are bound unsymmetrically: in each bridging methylene group one of the hydrogen atoms exhibits bonding interaction with the nearer manganese atom (**IV** in Scheme 10). Polymeric $[Mn(CH_2SiMe_3)_2]_n$ reacts with TMEDA to produce the mononuclear complex $[(tmeda)Mn(CH_2SiMe_3)_2]$ (type **V** in Scheme 10),[32] and with $Me_2P(CH_2)_2PMe_2$ to yield



Scheme 10. Greatly simplified structures of a manganate(II) complex (**VI**) and of alkylmanganese(II) compounds (**IV**, **V**) with phosphanes or amines as co-ligands. **IV** to **VI**, see text.

$[\{Me_2P(CH_2)_2PMe_2\}Mn(CH_2SiMe_3)_2]$ (also type **V**),[35] while treatment with $LiCH_2SiMe_3$ gives the ate-complex $Li_2[Mn(CH_2SiMe_3)_4]$ (**VI** in Scheme 10).[32] In all three high-spin d^5-complexes, manganese is tetrahedrally coordinated.

Before the following syntheses had been carried out, no alkyl- or arylmanganese(II) complexes with C_5H_5 ligands were known. Furthermore, no manganese(II) complexes had been reported in which the manganese is bound to different σ-bonded organyl groups.

The C_5H_5 ligands in manganese(II) cyclopentadienide **12** can be replaced by phenyl groups in a two-stage reaction with phenyllithium. The tetramethylethylenediamine, which is used in these reactions [Eq. (16) and (17)] as a complexing diamine, has a double function in both steps.[18] After **12** has reacted with LiC_6H_5 (molar ratio 1:1) in THF and the solution then evaporated to dryness, addition of a TMEDA/diethyl ether mixture at room temperature causes the TMEDA-stabilized manganese complex **27** to be precipitated. The product is very pure because $Li(C_5H_5)$ is highly soluble in Et_2O/TMEDA. The solubility relationships are equally favorable when **28** is prepared from **27**. While **28** probably has a geometry of type **V** in Scheme 10, the structures of **27** and $(C_6H_{11})_3PMn(C_6H_5)_2$[36] are unknown.

$$(C_5H_5)_2Mn + LiC_6H_5 \xrightarrow[-Li(C_5H_5)]{\text{1. THF, 2. } Et_2O/TMEDA} [(C_5H_5)Mn(C_6H_5)(tmeda)] \quad (16)$$
12 **27**

$$\mathbf{27} + LiC_6H_5 \xrightarrow[-Li(C_5H_5)]{\text{1. THF, 2. } Et_2O/TMEDA} [(C_6H_5)_2Mn(tmeda)] \quad (17)$$
28

When **24b** or **24a** is used instead of phenyllithium on replacement of the C_5H_5 rings, then either the new binuclear complexes **29** and **30** [Eq. (18)] or the known complexes **31** and **32**[37] [Eq. (19)] are formed, depending upon the stoichiometries employed. Like **29** and **30**, **32** is binuclear but **31** is mononuclear (cryoscopic determination).

$$2(C_5H_5)_2Mn \xrightarrow[-2Li(C_5H_5)]{2\ \mathbf{24b},\ THF} [(C_5H_5)Mn(C_6H_4CH_2NMe_2)]_2$$
12 **29**

$$2(C_5H_5)_2Mn \xrightarrow[-2Li(C_5H_5)]{2\ \mathbf{24a},\ THF} [(C_5H_5)Mn(CH_2C_6H_4NMe_2)]_2 \quad (18)$$
12 **30**

$$2(C_5H_5)_2Mn \xrightarrow[-4Li(C_5H_5)]{4\ \mathbf{24b},\ THF} 2[Mn(C_6H_4CH_2NMe_2)_2]$$
12 **31**

$$2(C_5H_5)_2Mn \xrightarrow[-4Li(C_5H_5)]{4\ \mathbf{24a},\ THF} [Mn(CH_2C_6H_4NMe_2)_2]_2 \quad (19)$$
12 **32**

It should be emphasized that the new complexes **29** and **30** can also be prepared by redistribution reactions (scrambling) on heating $(C_5H_5)_2Mn$ with **31** or **32** in toluene until a clear solution is formed. When the solution is cooled, highly pure **29** or **30** crystallizes out [e.g., Eq. (20)].

$$(C_5H_5)_2Mn + Mn(C_6H_4CH_2NMe_2)_2 \xrightarrow[\text{toluene}]{100\,^\circ C}$$
12 **31**

$$[(C_5H_5)Mn(C_6H_4CH_2NMe_2)]_2 \quad (20)$$
29

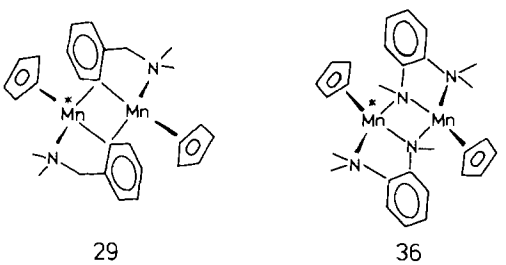
The new complexes **35**, which according to cryoscopic measurements in benzene are mononuclear, and the binuclear complex **36** can be prepared by the same method [Eqs. (21) and (22)]. The starting materials **33** and **34** were prepared in analogy to Equation (19) from **12** and $LiC_6H_4CH_2PR_2$ [$R = C_6H_{11}$ (**24c**), C_6H_5] or from **12** and **24d** (molar ratio 1:2), respectively.[18]

$$(C_5H_5)_2Mn + Mn(C_6H_4CH_2PR_2)_2 \xrightarrow[\text{toluene}]{40-70\,^\circ C}$$
12 **33**

$$2[(C_5H_5)Mn(C_6H_4CH_2PR_2)] \quad (21)$$
35

$$(C_5H_5)_2Mn + Mn(NMeC_6H_4NMe_2)_2 \xrightarrow[\text{toluene}]{60\,^\circ C}$$
12 **34**

$$[(C_5H_5)Mn(NMeC_6H_4NMe_2)]_2 \quad (22)$$
36

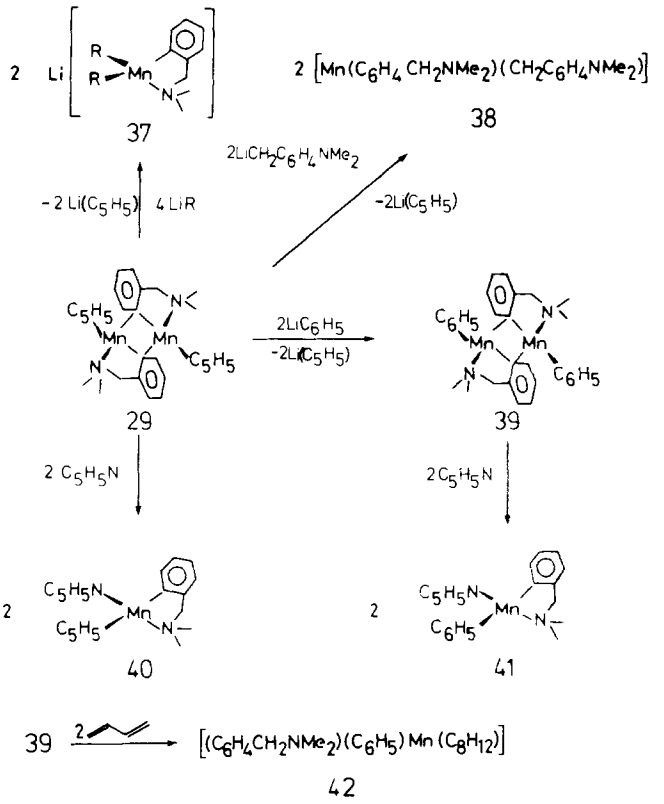


29 36

Scheme 11. The structures of crystalline **29** and **36** according to X-ray crystallography [22].

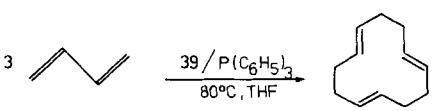
The manganese atoms have a pseudo-tetrahedral geometry in both the centrosymmetric binuclear complexes **29** and **36** (Scheme 11). The four coordination sites on manganese in **29** are taken up by a C_5H_5 ring, two bridging carbon atoms in unsymmetrical bridges, and a nitrogen atom; in **36**, each manganese atom is surrounded by a C_5H_5 ligand, two four-coordinate bridging nitrogen atoms in unsymmetrical bridges, and a terminal N-atom. The Mn–Mn distances in **29** and **36** lie between 2.428(6) and 2.632(7) Å and between 2.440(3) and 2.579(3) Å, respectively. They are thus considerably longer than the manganese-carbon distances for the centrally bound C_5H_5 ring in the dark brown modification of $Mn(C_5H_5)_2$ **12** (2.40–2.43 Å).[38]

Compound **29** reacts with LiR (R = CH_3, C_6H_5) (molar ratio 1:4) to afford the ate-complexes **37** and with $LiCH_2C_6H_4NMe_2$ **24a** or LiC_6H_5 (molar ratio 1:2) to yield **38** or the binuclear complex **39**, respectively.[18] Both the binuclear complexes **29** and **39** can be converted into mononuclear complexes (i.e. **40** and **41**, respectively) by treatment with pyridine. Much more interesting, however, is the reaction of the binuclear complex **39** with butadiene



Scheme 12. Some reactions of **29** and **39**.

at 0°C, which produces **42** (Scheme 12). This red compound is, like **39** itself, an excellent catalyst for the cyclotrimerization of butadiene (Scheme 13).

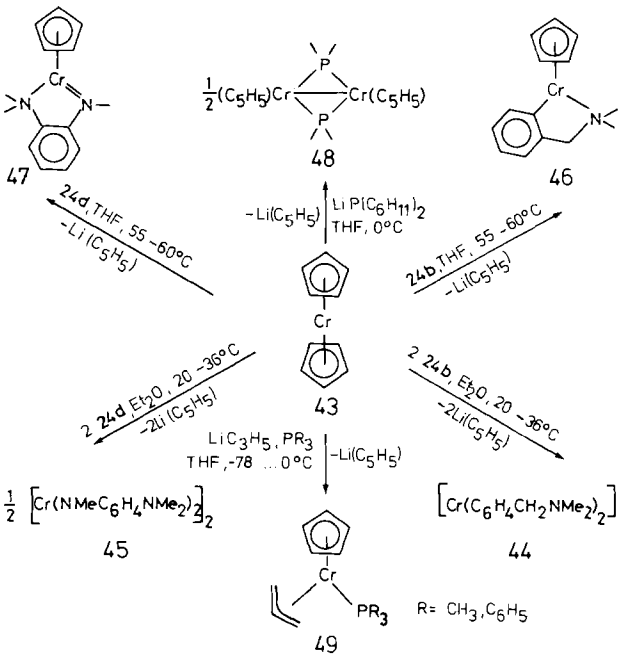


Scheme 13. The highly selective manganese-catalyzed cyclotrimerization of butadiene to *ttt*-cyclododecatriene.

A turnover number of ca. 5000 C_4H_6/Mn was achieved in 2.5 h at 80°C in the presence of **39** and $(C_6H_5)_3P$ in the molar ratio 1:1. The product was a mixture containing over 95% *ttt*-cyclododecatriene (yield 85%). Manganese catalysts based on $Mn(acac)_3/AlR_3$[39] or Mn/Et_2AlCl[40] are much less active and much less selective.

2.2.3. *Half-Sandwich Complexes and other Chromium(II) Complexes from Chromocene*

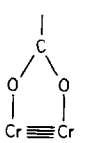
Cyclopentadienyl exchange reactions which proceed with retention of the oxidation state of the transition metal can also be carried out using chromocene **43**. Once again, particular organo-alkali metal compounds have proved to be suitable reagents,[41,42] but lithium amides or phosphides can also be used.[41] However, if the most effective use of the degradation in synthesis is to be achieved, the reaction conditions must be observed exactly in order to avoid the formation of a mixture of products. Whether only one C_5H_5-ligand or both ligands are exchanged or indeed whether both processes take place side by side is dependent not only upon the reactants involved and their stoichiometric ratio to chromocene, but also to a great extent upon the solvent and temperature (Scheme 14).



Scheme 14. Half-sandwich and other new chromium(II) complexes prepared from chromocene **43** [41]. According to X-ray crystallographic studies [22], the chromium atoms in both **46** and **47** are pseudo-trigonal planar.

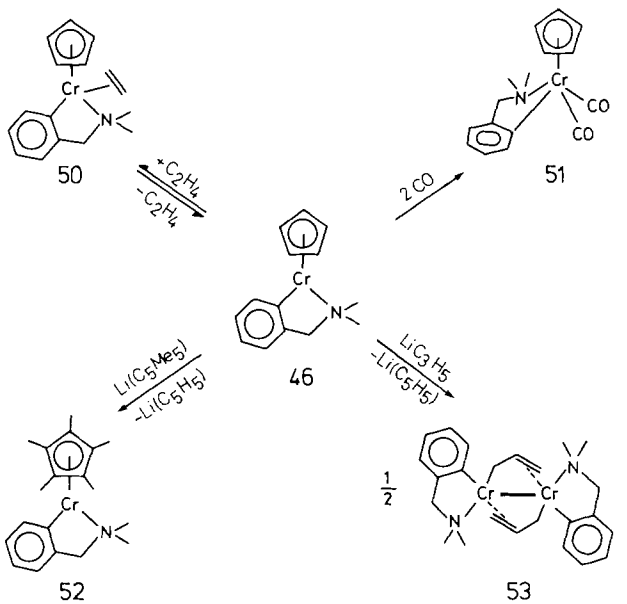
While both cyclopentadienyl groups are replaced by $Me_2NCH_2C_6H_4$ or $Me_2NC_6H_4NMe$ groups in ether at room temperature with the formation of only **44**[37] or **45**, respectively, the synthesis of the new half-sandwich complexes **46** and **47** requires more drastic reaction conditions (see Scheme 14) (yields 70—80%). Only a small quantity of **46** is formed in THF at temperatures below 0°C. Surprisingly, the major product under these conditions is the chromium(III) complex $Cr(C_6H_4CH_2NMe_2)_3$. This compound was first prepared by *Manzer*[43] from $CrCl_3$ and **24b** and it is also one of the products formed in the reaction of dichromium tetraacetate with **24b**.[44]

Quite remarkably, both the d^4 chromium complexes **46** and **47** are mononuclear. They are thus quite distinct from the numerous dimeric chromium(II) complexes, some of which have extremely short Cr—Cr distances.[45] *Cotton* has suggested that all these compounds have Cr—Cr quadruple bonds. The vast majority of these complexes have ligands (e.g., HCO_2, RCO_2, MeC_6H_3OMe) which bridge the chromium atoms to form dimetalla-five-membered rings (Scheme 15).



Scheme 15. Example of a three-membered bridging ligand in a binuclear chromium(II) complex.

The ligands forming the bridges in these systems nearly[*] always consist of three atoms, whereas bridges formed by the chelating groups *o*-$Me_2NCH_2C_6H_4$ and *o*-$Me_2NC_6H_4NMe$ are made up of four atoms. This difference is certainly important but it does not suffice to explain why **46** and **47** are mononuclear. Indeed, both the d^5 manganese complexes **29** and **36** (Scheme 11), which have the same set of ligands as the d^4 chromium complexes **46** and **47**, and some of the copper complexes characterized by *Noltes* and *van Koten*[47] show that the groups $Me_2NCH_2C_6H_4$ and $Me_2NC_6H_4NMe$ are perfectly capable of acting as bridging ligands. Furthermore, two binuclear complexes are known, $[V_2\{C_6H_3(OMe)_2\}_4(thf)_2]$[48] and $[Cr_2(CH_2SiMe_3)_4(PMe_3)_2]$,[49] which have metal-metal multiple bonds and have been shown by X-ray crystallography to contain in addition three-center bonds joining the metal atoms in M–C–M units.



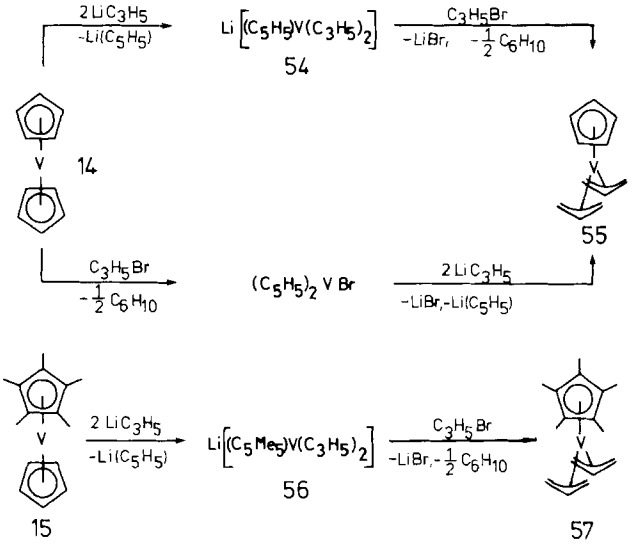
Scheme 16. Some reactions of **46**.

The new 14e complex **46** reacts with ethylene to afford the deep-green ethylene complex **50**, in which the olefin is only weakly bound. The diamagnetic 18e complex **51** is considerably more stable. NMR and IR spectra indicate that this complex contains a chiral chromium atom. The cyclopentadienyl ligand is exchanged when **46** is treated with $Li(C_5Me_5)$ or allyllithium. Like **46**, **52** is mononuclear, but **53** is a diamagnetic binuclear complex[41] (Scheme 16). The latter compound, the structure of which has clear similarities to that of tetraallyldichromium $[(\eta^3\text{-}C_3H_5)Cr(\mu\text{-}C_3H_5)]_2$,[50] is characterized by a very short Cr–Cr distance (1.973(1) Å) and unsymmetrical allyl bridges—the C-C bond lengths within these allyl groups are different and the distances between the terminal carbon atoms and the chromium atoms are unequal.[22]

[*] Dimetalla-six-membered rings together with dimetalla-five-membered rings are observed in $[M_2(O_2CCH_3)_2(o\text{-}NMe_2C_6H_4CH_2)_2]$, M = Cr, Mo [46].

2.2.4. *Allylvanadium Complexes from Vanadocene and Pentamethylvanadocene*

When we attempted the preparation of **54** and **55** in 1980, derivatives of these compounds were already known, i.e. the compounds **19** and **20** that were discussed in Section 2.1.3. Scheme 17 shows how simple it is to synthesize the parent compounds **54** and **55** starting with vanadocene **14**.[19]



Scheme 17. "One-pot" syntheses of allylvanadium(III) complexes.

Allyllithium **24e**, which is best prepared in pure form on a large scale by the treatment of C_3H_5MgCl with lithium metal,[51] reacts with vanadocene with C_5H_5/C_3H_5 exchange and addition at vanadium to form the ate-complex **54**. Treatment with allyl bromide leads to delithiation of the ate-complex and formation of the bis(allyl)cyclopentadienylvanadium **55**. Alternatively, if it is preferred to oxidize the vanadium in the first step by reacting **14** with allyl bromide, then $(C_5H_5)_2VBr$[52] is obtained as intermediate. Exchange of the bromine and one of the cyclopentadienyl rings by allyl groups leads, as before, to the formation of **55**. Both these degradation reactions and the third sequence of reactions given in Scheme 17, by which bis(allyl)pentamethylcyclopentadienylvanadium **57** was first prepared,[53] can be carried out as "one-pot" syntheses.

In 1984, *Teuben* et al.[54] reported the preparation of **55** by classical halide-organyl exchange [Eqs. (23) and (24)].

$$[VX_3(thf)_3] \xrightarrow[-3THF]{2PR_3} VX_3(PR_3)_2 \xrightarrow[-MX]{M(C_5H_5)} [(C_5H_5)VX_2(PR_3)_2] \quad (23)$$

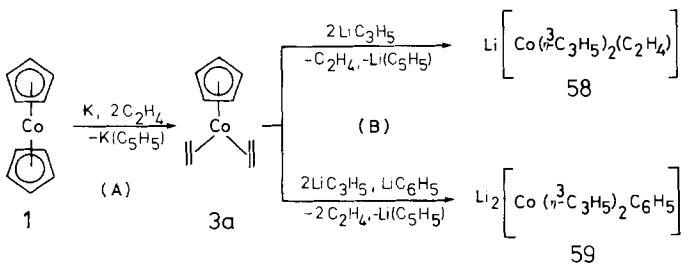
$$[(C_5H_5)VX_2(PR_3)_2] \xrightarrow[-2MgX_2,\ -2PR_3]{2C_3H_5MgX} \underset{\mathbf{55}}{[(C_5H_5)V(C_3H_5)_2]} \quad (24)$$

R = CH_3, C_5H_5

By comparison, this method has the disadvantage that intermediates of the type $[(C_5H_5)VX_2(PR_3)_2]$ must first be synthesized. These are stabilized by trialkylphosphane ligands, which are then liberated later in the synthesis. Furthermore, this procedure proved unsuitable for preparing **57**.

2.3. Metallocene Degradation by Combination of Metathetical Reactions and Reactions with Alkali Metals and Olefins

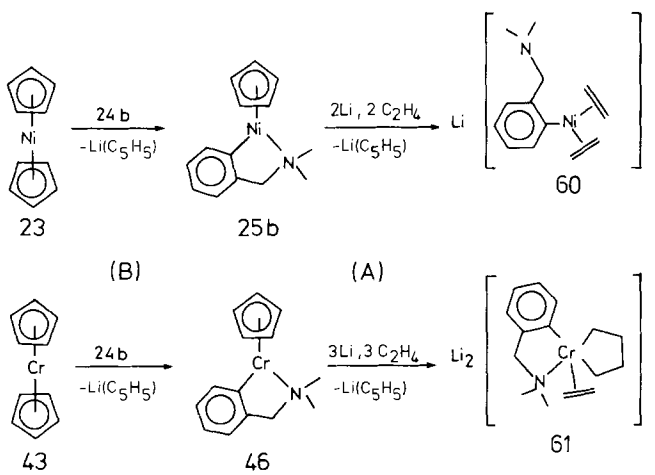
The removal of a C_5H_5 ring by method A can be combined with a metathetical reaction (type B) in the order A, B or B, A. Examples of type C reaction sequences A, B are the syntheses of the new lithium cobaltates(I) **58** and **59** (Scheme 18).[55]



Scheme 18. Syntheses of lithium cobaltates(I) from cobaltocene **1**, with cyclopentadienylbis(ethylene)cobalt **3a** as the intermediate.

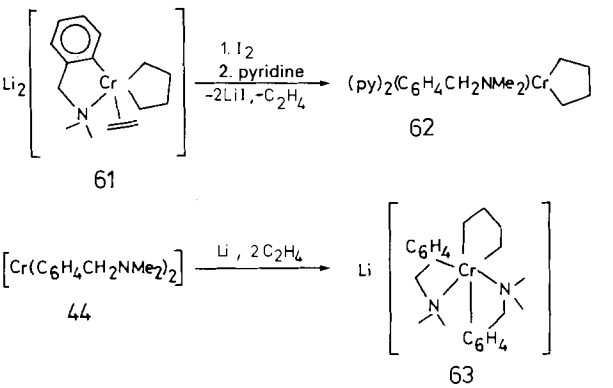
In the first step (type A reaction) the removal of the C_5H_5 ligand is accompanied by reduction of the metal from cobalt(II) (d^7) in the 19e complex **1** to cobalt(I) (d^8) in **3a**. However, in the subsequent reaction step (type B) the exchange of the cyclopentadienyl ligand, the displacement of the ethylene, and the formation of the ate-complex all proceed with retention of the formal oxidation number in both cases. The anions of the ate-complexes **58** and **59** are isoelectronic with tris(allyl)cobalt.[56]

Two degradation reactions with the order B, A having $(C_5H_5)_2Ni$ **23** and $(C_5H_5)_2Cr$ **43** as starting materials are compared in Scheme 19. In these reaction sequences, not only are the educts isostructural and have identical ligand sets—the same holds true of the intermediates as well. Nevertheless, they react with identical reactants (i.e., lithium and ethylene) to give different types of product (**60** and **61**).



Scheme 19. Synthesis of **60** and **61**.

The ethylene nickel complex **60**[6] is salt-like; such complexes have been described in detail elsewhere.[1] On the other hand, both the chromium complex **61**, which has been characterized by X-ray crystallography,[22] and its mode of formation are new.[41] Two ethylene molecules have coupled with the chromium atom to form a chromacyclopentane ring; the third molecule of ethylene taken up by the chromium is π-bonded. A striking feature of the structure is the close bonding contact of the lithium atoms with the metallacycle and the π-bonded ethylene.



Scheme 20. Synthesis of **62** and **63**.

It is possible to delithiate **61** with iodine; the lithium-free metallacyclic complex can be stabilized with pyridine **62** (Scheme 20). Finally, a third example of a chromium complex in which a metallacyclic $Cr(CH_2)_4$ unit has been formed by the coupling[*] of ethylene molecules with chromium is the new chromium(III) complex **63**.[41,22]

The reactions in Schemes 19 and 20 and the first results with organomanganese compounds described in Section 2.1.2 show that those systems where metallacyclopentane rings are formed by the coupling of simple olefins (ethylene) can be anticipated to involve transition metals predominantly to the left of Group VIII in the periodic table. Equally relevant to this classification are the preparations of the metallacyclic complexes of Ta,[58,59] Zr,[21c,60] and Hf[21e] which were reported somewhat earlier by *Schrock, Bercaw,* and *Erker.*

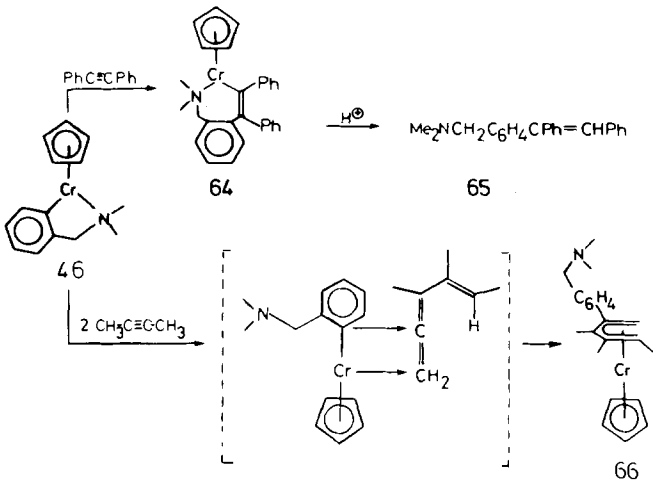
3. Syntheses Using Reactive Organometallic Compounds Prepared from Metallocenes

3.1. Reactions of Sandwich and Half-Sandwich Complexes with Alkynes under Mild Conditions

The reactions of metal complexes with alkynes or nitriles continue to be studied intensively. Complementary aspects of this field of research are stoichiometric synthesis, which has produced an extraordinarily wide range of different types of organometallic complexes,[61] and catalysis with metal complexes, by which organic compounds are obtained directly.[62-64] When the metal-containing component is a carbonyl or phosphane complex, it is frequently necessary to employ higher temperatures or photolysis to initiate the reaction. This can be a shortcoming

[*] Two other chromacyclopentane complexes that have been known for some time were prepared from chromium halides and 1,4-dilithiobutane [57].

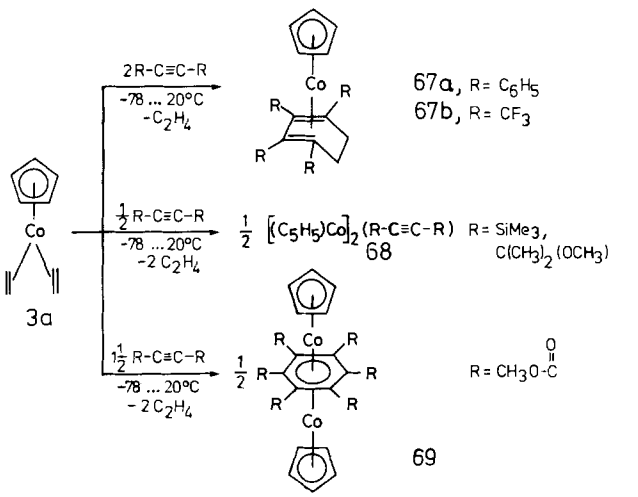
when the organic substrates are sensitive. Some thermal reactions of alkynes with carbonyl-free metal complexes which proceed at room temperature or lower are collected in Schemes 21, 22, and 23.



Scheme 21. Reactions of **46** with alkynes.

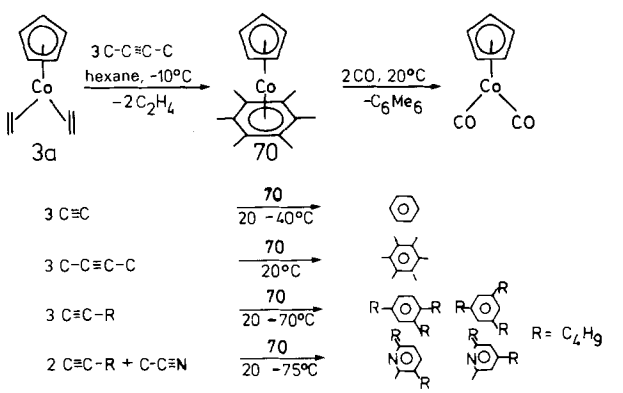
The mononuclear complex **46** obtained from chromocene **43** and **24b** reacts with diphenylacetylene to afford a chromium half-sandwich complex which probably has the structure **64**. In any case, the product of the protolysis of **64** is the styrene derivative **65**. **46** reacts with 2-butyne in excess to form the chromium(II) complex **66**. According to X-ray crystallography,[22] this compound has a sandwich-like arrangement of the cyclopentadienyl ring, chromium atom, and a pentadienyl ligand which lies practically parallel to the C_5H_5-ring in a manner reminiscent of chromocene. The nitrogen atom is no longer bonded to the chromium. The formation of **66** can be interpreted as a chromium-induced coupling of two butyne molecules to give the allene derivative 3,4-dimethyl-1,2,4-hexatriene (cf. the ene-reaction[65]), which inserts via the allene unit into the Cr–C σ-bond.[41]

Cyclopentadienylbis(ethylene)cobalt **3a**, which has also been finding increasing application in other groups as a starting material for synthesizing organocobalt compounds,[66–69] reacts with alkynes to form cobalt complexes whose modes of formation and structures can be very different from one another.



Scheme 22. Reaction of **3a** with alkynes.

For example, alkynes such as diphenylacetylene or hexafluorbutyne react with **3a** even below room temperature to produce the cobalt-complexed cyclohexadiene derivatives **67a**, **b**.[6] This should be contrasted with the synthesis of **67a** from the metallacyclic cobalt-phosphane complex $[(C_5H_5)CoC_4Ph_4(PPh_3)]$, when an ethylene pressure of 45 bar and a temperature of 150 °C are necessary.[71] From the reaction of **3a** with bis(trimethylsilyl)acetylene or with 2,5-dimethoxy-2,5-dimethyl-3-hexyne we obtained binuclear cobalt complexes **68** with alkyne bridges while **3a** and dimethyl acetylenedicarboxylate afford the cobalt complex **69**, the spectroscopic data of which are consistent with a triple-decker sandwich structure (34e complex).[6] A most interesting finding, especially in connection with the mechanism of the cobalt-catalyzed cyclization of alkynes, is the observation that **3a** reacts with 2-butyne at −10 °C to afford the arene complex **70** (Scheme 23).[5] In **70**, as in the isoelectronic cation of $[(C_6Me_6)_2Co]PF_6$,[71] the cobalt atom has two electrons more than required for a krypton electron configuration.



Scheme 23. Synthesis of the 20e sandwich complex **70** and the cobalt-catalyzed cyclization of alkynes and cocyclization of 1-hexyne and acetonitrile.

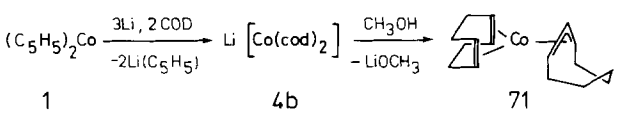
The fact that **70** is a 20e sandwich complex accounts for the ease with which the arene can be displaced by, for example, CO. It also explains why this paramagnetic cobalt complex, which can be recrystallized from boiling hexane, is (together with **3a**) the most reactive known complex containing the $(C_5H_5)Co$ unit capable of the cobalt-catalyzed cyclization of alkynes and cocyclization of alkynes and nitriles. When a mixture of 1-hexyne and THF or 1-hexyne and acetonitrile is treated with a catalytic amount of **70** at room temperature, no heating is required. Within a short time the mixtures reach boiling by themselves: the products are benzene and pyridine derivatives, respectively (for more details of the cobalt-catalyzed pyridine synthesis, see [72]).

3.2. Syntheses with Alkali Metal-Olefin Cobaltates(−I)

Another group of versatile reagents are the alkali metal cobaltates **4**, which are prepared from cobaltocene, alkali metal and olefin according to reaction Scheme 1 and

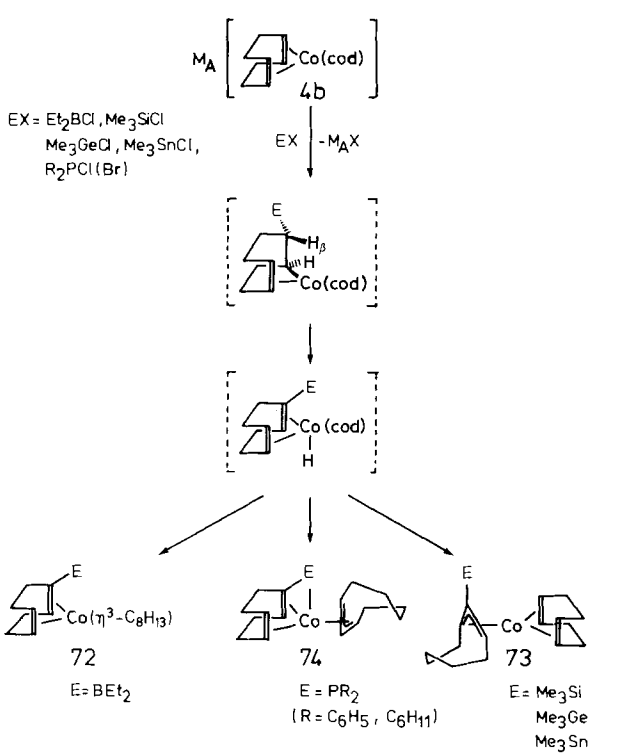
Equation (2). The anions in these reagents have a high nucleophilicity and, in contrast to the anions of $M_A[Co(CO)_4]$[73] and $M_A[Co\{P(OR)_3\}_4]$,[74] contain olefin ligands which are easily displaced from the cobalt atoms.

The reaction of **4b** with protonic acids such as methanol can be used to prepare highly pure **71**. This compound has also been prepared by the reduction of cobalt(II) chloride with sodium metal in THF/pyridine/COD[75] or from cobalt acetylacetonate and COD either electrochemically[76] or by reduction with R_2AlH[77] or $(C_2H_5)_3Al$[63]. When comparing this new synthetic route with those previously used, it must be remembered that a prerequisite for the synthesis of **71** according to Scheme 24 is the preparation of $Li[Co(cod)_2]$ **4b**, for which, in turn, cobaltocene is required. However, the preparation of cobaltocene, like that of other metallocenes, is not particularly difficult and the yield of highly pure **71** for both steps together is over 90%. Furthermore, it is not necessary to isolate **4b** for the subsequent reaction with methanol.



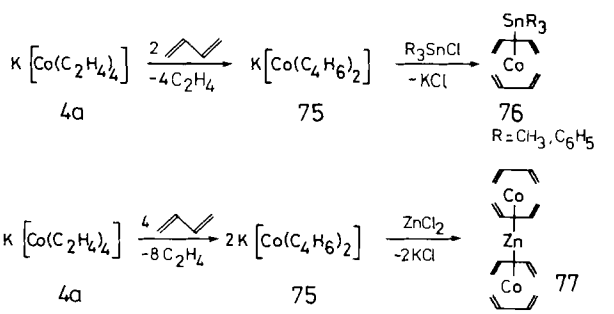
Scheme 24. Two stage synthesis of highly pure (η^4-1,5-cyclooctadiene)(η^3-cyclooctenyl)cobalt **71** starting with cobaltocene **1**.

Other electrophiles such as Et_2BCl, Me_3SiCl, Me_3GeCl, or Me_3SnCl react with **4b** to form the new cobalt complexes **72** and **73**. In these 16e complexes, the residue containing the main group element is bonded to one of the eight-membered ring ligands. In both the 18e complexes **74**, which are formed in the reaction of R_2PX compounds with **4b**, the R_2P groups are also bonded to cobalt[6]. All these reactions are probably initiated by *exo*-attack[78] of the organohalide compound of the main group element upon the complexed cyclooctadiene (Scheme 25), since only then can a β-H elimination take place to give a complexed double bond which bears the appropriate substituent. Whether the complex formed has the structure **72**, **73** or **74** is then only a question of the eight-membered ring to which the hydrogen atom of the cobalt hydride is transferred. In all cases, isomerization of the 1,4-enyl ligands leads to the formation of η^3-allyl units.



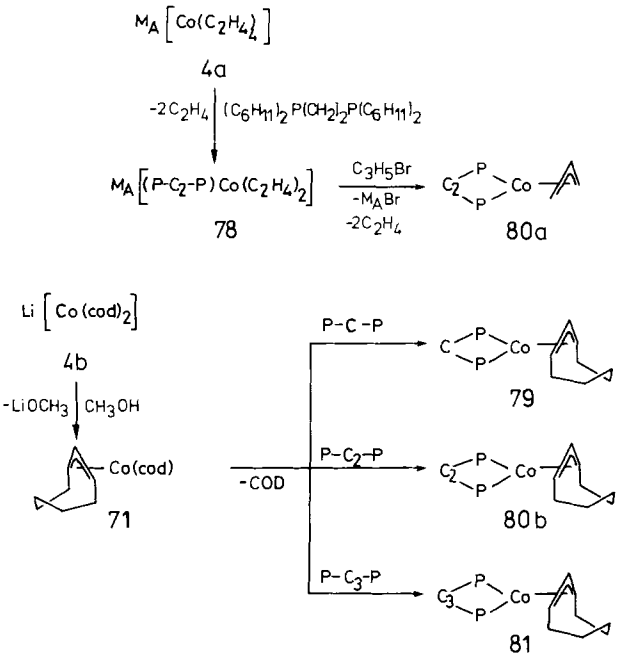
Scheme 25. *Exo*-attack of organohalides of the main group elements upon complexed cyclooctadiene. The products **72**—**74** have been examined in detail by ^{13}C-NMR spectroscopy [79]; **74** ($R=C_6H_5$) has also been studied by X-ray crystallography [22].

At the same time, the reactions of R_3SnCl or $ZnCl_2$ with alkali metal-olefin cobaltates containing complexed butadiene instead of cyclooctadiene show that electrophiles can attack the central cobalt atom directly (Scheme 26).[1,80] In the ^{13}C-NMR spectrum of the binuclear complex **76** (R = Me), spin-spin coupling between the terminal carbon nuclei of the η^4-butadiene ligands and ^{119}Sn is observed [$J(^{119}Sn\text{-}^{13}C) = 33$ Hz], indicating that an Sn—Co bond has been formed. Another highly symmetrical compound is the trinuclear complex **77**, in which four equivalent butadiene ligands are coordinated to the two cobalt atoms.[81] The corresponding trinuclear carbonyl complex $[Zn\{Co(CO)_4\}_2]$ was first reported as long ago as 1942.[82]



Scheme 26. Alkali metal-olefin cobaltates as cobalt nucleophiles.

Trityl chloride undergoes oxidative addition with $K[Co(cod)_2]$ at the cobalt(−1) ($d^{10} \rightarrow d^8$) to yield cyclooctadiene(trityl)cobalt.[6] The reactions of phosphane-stabilized olefin cobaltates with benzyl bromide or allyl halides are of the same type.[83] Suitable phosphorus ligands are bisphosphanes with bulky cyclohexyl groups on phosphorus.[1,2,83] Using this approach, which has previously proved useful for nickel,[84] it was possible to obtain (bisphosphane)cobalt(I) complexes which are coordinatively unsaturated. Scheme 27 shows how **80a**, which is dark blue, was synthesized.[2,83] Further examples of compounds of this type are the dark green complex **79**[85] and the dark blue complexes **80b**[2,83] and **81**.[85] It should be noted that the reaction of **71** with $CH_2[P(C_6H_{11})_2]_2$ to form the 16-electron complex **79**, containing a four-membered ring of cobalt, carbon, and two phosphorus atoms, proceeds much more slowly than the corresponding reactions with $(CH_2)_n[P(C_6H_{11})_2]_2$ (n = 2, 3) leading to **80b** and **81**.



Scheme 27. Synthesis of coordinatively unsaturated allylcobalt(I) complexes with bisphosphane ligands having bulky cyclohexyl groups on phosphorus.

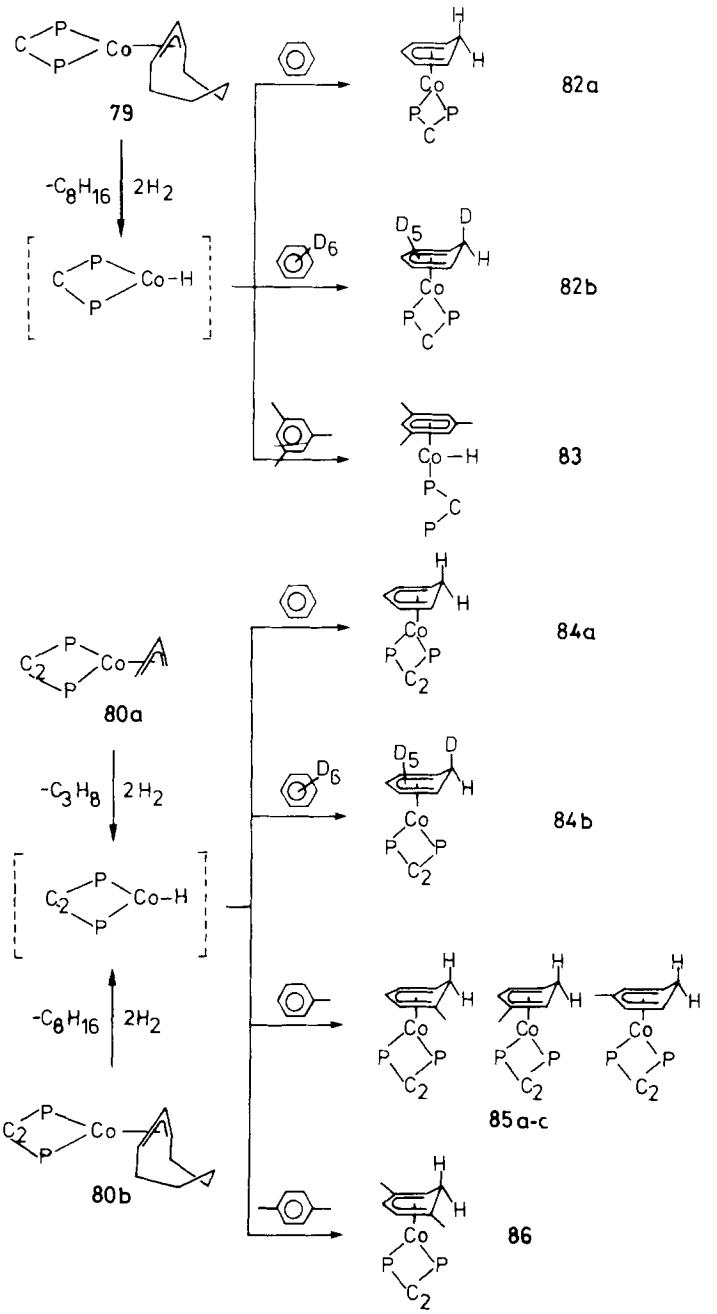
3.3. New Developments in the Organometallic Chemistry of Arenes

3.3.1. Hydrocobaltation and the Cobalt-Catalyzed Hydrogenation of Aromatic Hydrocarbons

A number of transition metal complexes are known which can act as homogeneous catalysts for the hydrogenation of aromatic hydrocarbons.[2,86-89] The cobalt-catalyzed arene hydrogenation with 18e catalyst precursors of the type $[(\eta^3\text{-}C_3H_5)Co\{P(OR)_3\}_3]$ has received most attention.[86] For several years it was assumed that the cobalt-bound allyl ligand in the precursor is retained in these systems under hydrogenation conditions and that this ligand stabilizes the catalytically active species so that it can retain its activity. However, in 1981 *Muetterties* et al.[90] reported that the allyl ligand is removed *before* the arene hydrogenation begins.

The new 16e cobalt complex **81** (Scheme 27) can also be used as a catalyst precursor for the homogeneous catalytic hydrogenation of arenes. However, **81** and compounds **79** and **80**[2] have a much greater significance as key compounds in a system that gives a detailed insight into the reaction course of metal-catalyzed arene hydrogenation.

When **79** or **80** is treated with H_2 (1 bar) in THF or hexane, the organic ligands are liberated even at -30 to 20°C as propane or cyclooctane, respectively. In addition, hydridocobalt complexes are formed, e.g. $[(C_6H_{11})_2P(CH_2)_2P(C_6H_{11})_2CoH_2]_3$,[2] which according to their cryoscopically determined molecular weights are polynuclear. How these products differ from the cobalt complexes obtained when solutions of **79** or **80** dissolved in aromatic hydrocarbon solvents are treated with H_2 at room temperature! Mononuclear cobalt complexes with η^5-cyclohexadienyl ligands (**82**, **84**—**86**) can be isolated in high yields. In mesitylene the novel hydridocobalt complex **83**



Scheme 28. Hydrocobaltation of benzene and alkylbenzenes with bisphosphanehydridocobalt species.

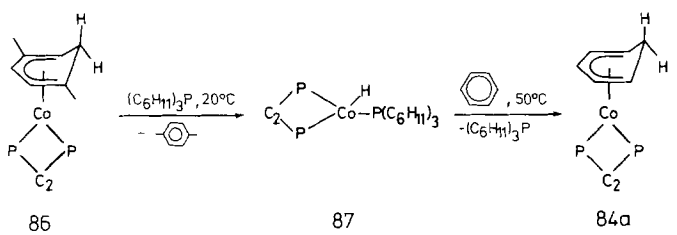
$[\nu(Co-H)$: 1890 $cm^{-1}]$ is produced. This compound has a η^6-coordinated arene ligand and is formed with the breaking of a Co—P bond and opening of the CoP_2C ring. According to IR spectroscopy, the hydrocobaltation of benzene and perdeuteriobenzene to form the cyclohexadienylcobalt complexes **82** and **84** proceeds via *cis*-addition of the bisphosphanehydridocobalt moiety to the aromatic ring, i.e. the hydrogen atom introduced by the cobalt goes into the *endo*-position. The compounds **82a** and **84a** show IR bands at 2760 and 2735 cm^{-1}, respectively, which in position and intensity are characteristic of metal complexes with η^5-cyclohexadienyl ligands $[\nu(C-H_{exo})$[91]]; these bands are missing in the IR spectra of **82b** and **84b**, which have absorbances at 2015 cm^{-1} and 2010 cm^{-1}, re-

spectively [ν(C–D_{exo})]. The hydrocobaltation of toluene leads to a mixture of the three positional isomers **85a–c**. The formation of the possible fourth isomer with the methyl group on the sp^3-carbon is not observed. Consistent with this, the hydrocobaltation of *p*-xylene results in just the one product, i.e. **86**.

The hydrocobaltation reactions summarized in Scheme 28 open up a new route to transition metal complexes with η^5-cyclohexadienyl ligands. They should be distinguished from the well established procedures for converting arene-metal cations into cyclohexadienyl complexes by reaction with hydrides of the main group metals.[92] In such reactions the arene has become activated towards nucleophilic attack by virtue of its coordination and the hydrogen from the hydride enters an *exo*-position on the ring.

The cyclohexadienylcobalt complexes **82** and **84–86** formed from bisphosphanehydridocobalt moieties and aromatic hydrocarbons are chemically rather labile compounds. This is particularly true of the product of hydrocobaltation of *p*-xylene **86**. The "retro"-hydrocobaltation occurs very easily, liberating the arene. While the arene regains its full aromaticity, the bisphosphanehydridocobalt fragment stabilizes itself by hydrocobaltation of another molecule or in some other way.

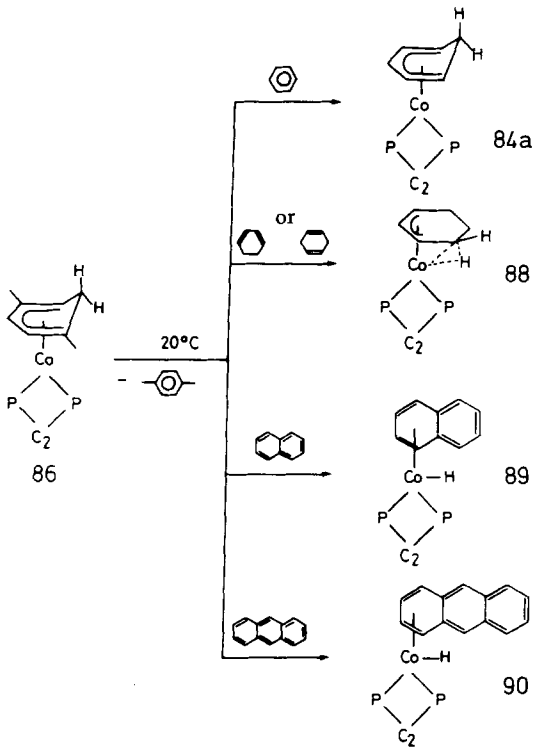
Using hydrocobaltated *p*-xylene **86** and tricyclohexylphosphane we obtained the dark blue 16e hydridocobalt complex **87** [ν(Co–H): 1763 cm^{-1}], which on reaction with benzene gave **84a** (Scheme 29).



Scheme 29. Hydrocobaltation of benzene by the stable hydridocobalt compound **87**.

This last reaction is a textbook example of an arene hydrometalation—both the product (**84a**) of the arene hydrometalation and the reacting metal hydride (**87**) on the educt side are stable enough to be isolated.

Compound **86** is labile and reacts with benzene at room temperature to form **84a**. With 1,3- or 1,4-cyclohexadiene, **86** produces the cyclohexenylcobalt complex **88**, which, in contrast to the corresponding cyclooctenyl compounds **79** (dark green), **80b**, and **81** (dark blue), is yellow. This suggests that the bonding relationship between cobalt and the eight-membered ring ligands differs from that between cobalt and the six-membered ring ligand. This was verified by NMR studies[79] and X-ray analysis[22] (see Fig. 2), which show that **88** is a fluxional molecule with an agostic[93] hydrogen atom. Finally, a further variant is found in compounds with a cobalt-bound terminal hydrogen atom as present in the hydridocobalt complexes **89** [ν(Co–H): 1910 cm^{-1}] and **90** [ν(Co–H): 1920 cm^{-1}], in which the arene is bound to the cobalt in a diene-like fashion (η^4) as in (C_5H_5)Co(anthracene)[5] (Scheme 30).



Scheme 30. Hydrocobaltated *p*-xylene **86** as a source of coordinatively unsaturated bisphosphanemonohydridocobalt fragments.

The structure of the (η^5-C_6H_7)Co unit in the 18e complex **84a** (Fig. 1) corresponds closely with those of other cyclohexadienyl transition metal complexes.[94] The carbon atoms C1, C2, C3, C5 and C6 are coplanar and bonded to cobalt. The angle between the plane of these carbon atoms and the plane C3, C4, C5 is 41°. The cyclohexenyl compound **88** (Fig. 2), which has two hydrogen atoms more than **84a**, must also be classified as an 18e complex, since in this and structurally related complexes (e.g. of Mn[95] and Fe[96]) a metal-H–C three-center bond is observed. Four coordination sites on the five-coordinate cobalt are occupied by the bisphosphane and the allyl group of the six-membered ring ligand, the fifth site is taken up by a

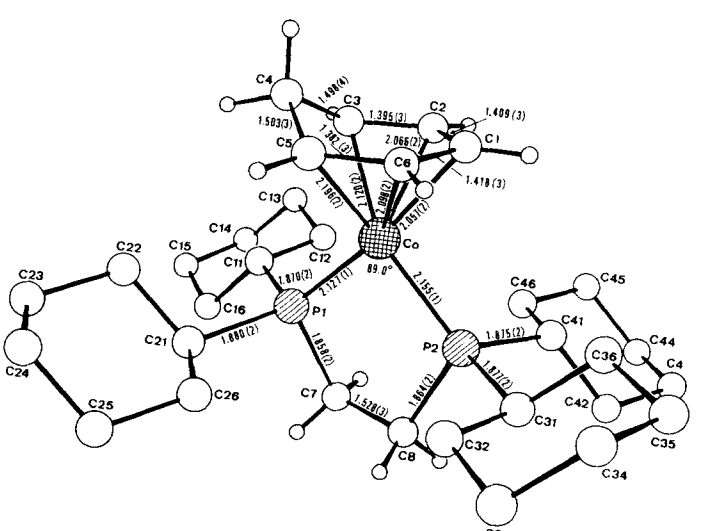


Fig. 1. Crystal structure of cyclohexadienyl[*P*,*P*'-ethylenebis(dicyclohexylphosphane)]cobalt **84a** formed by hydrocobaltation of benzene.

C–H_{endo} bond adjacent to the allyl unit. Characteristic of the $(C_6H_9)Co$ unit is a relatively large bond distance between Co and C27 (2.297(2) Å).

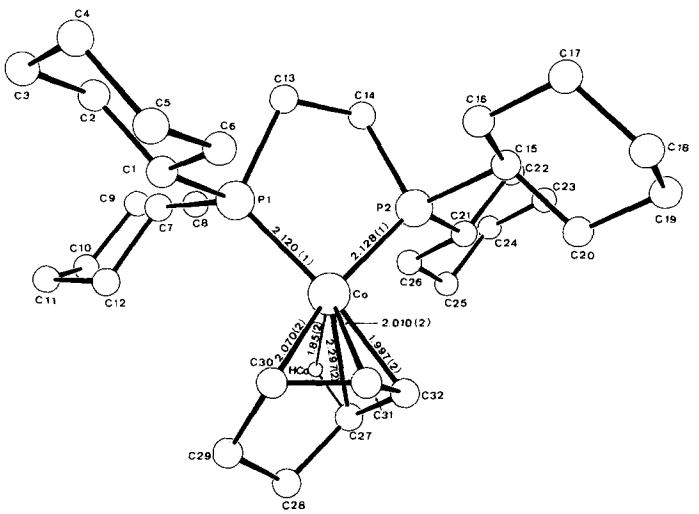
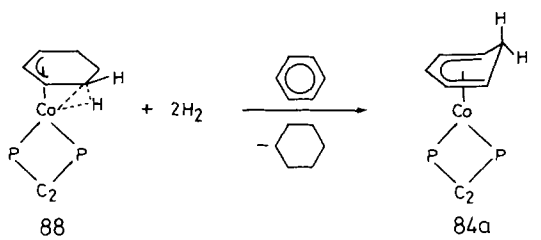


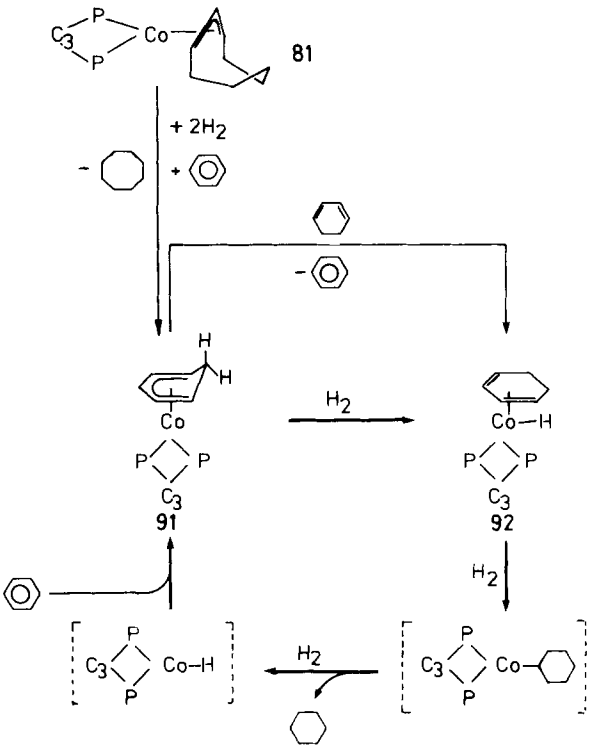
Fig. 2. Crystal structure of cyclohexenyl[*P,P'*-ethylenebis(dicyclohexylphosphane)]cobalt **88** formed by hydrocobaltation of cyclohexadiene.

In this cyclohexenylcobalt(I) complex **88** the cobalt and the two phosphorus atoms form part of a five-membered ring. Like the allylcobalt complexes **79** and **80** (Scheme 28), **88** reacts rapidly with hydrogen at room temperature. As to be expected, this reaction proceeds stoichiometrically in benzene solution to yield cyclohexane and **84a** (Scheme 31).



Scheme 31. Hydrogenolysis of **88** in benzene.

We were surprised, however, to discover that in benzene solution the hydrogenolysis of the cyclooctenylcobalt complex **81**, in which cobalt and the two phosphorus atoms are present in a less rigid six-membered ring (CoP_2C_3), by no means stops at the stage of the hydrocobaltated benzene. In this particular case, the benzene undergoes a cobalt-catalyzed hydrogenation to cyclohexane (Scheme 32). Thus, the cobalt complex **81** is a catalyst precursor for the hydrogenation of benzene. In addition, benzene solutions of **91** [ν(C–H_{exo}): 2760 cm^{-1}] or **92** [ν(Co–H): 1875 cm^{-1}], which are both sparingly soluble in aromatic solvents, can also take up hydrogen (1 bar) over a long period (30–40 h) at room temperature (e.g. 3.6×10^{-3} M solutions of **81** take up 216 H_2/Co in 6 h; this corresponds to 0.6 $H_2/(Co \cdot min^{-1})$.



Scheme 32. Cobalt-catalyzed benzene hydrogenation on $(CH_2)_3\{P(C_6H_{11})_2\}_2CoH$ fragments.

3.3.2. *Novel Types of Binuclear Complexes of Cobalt, Iron, and Vanadium with Benzene or Alkylbenzenes as Bridging Ligands*

Thirty years after the discovery of bis(benzene)chromium[97], mononuclear sandwich and half-sandwich complexes with arenes have become well established classes of compounds.[98] On the other hand, coordination compounds in which arenes are bonded to *two* metal centers and which have all six ring carbon atoms coordinated were not known until recently. In the past couple of years, no less than four different types of binuclear complex of this kind have been prepared in an astonishingly simple way in the Institute in Mülheim [Eqs. (25)–(28)]. Prerequisites for this were the educts **16**, **55**, and **11**, readily prepared from vanadocene and ferrocene, respectively, and the extraordinarily labile cobalt complex **86**, obtained by the hydrocobaltation of *p*-xylene.

$$2\,K[(C_5H_5)_2V] + \text{1,3-cyclohexadiene} \xrightarrow[-2\,K(C_5H_5)]{-78\ldots20\,^\circ C} [\{(C_5H_5)VH\}_2(\mu,\eta^4\!:\eta^4\text{-}C_6H_6)] \quad (25)$$

16 **93**

$$2[(C_5H_5)V(C_3H_5)_2] + \text{1,3-cyclohexadiene} \xrightarrow{100\,^\circ C} [\{(C_5H_5)V\}_2(\mu,\eta^6\text{-}C_6H_6)] + \cdots \quad (26)$$

55 **94a**

$$2[(C_5H_5)Fe(cod)] + 3\,R{-}C{\equiv}C{-}R \xrightarrow[-2\,COD]{20\,^\circ C} [\{(C_5H_5)Fe\}_2(\mu,\eta^4{:}\eta^4\text{-}C_6R_6)] \quad (27)$$

11

95a, $R = CH_3$

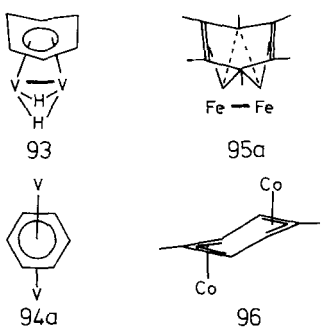
95b, $R = C_2H_5$

$$2[(CH_2)_2\{P(C_6H_{11})_2\}_2Co\{\eta^5\text{-}C_6H_5(CH_3)_2\}] \xrightarrow[-C_6H_4(CH_3)_2,\,-2H]{20\,^\circ C,\ hexane} [\{(CH_2)_2[P(C_6H_{11})_2]_2Co\}_2\{\mu,\eta^3{:}\eta^3\text{-}C_6H_4(CH_3)_2\}] \quad (28)$$

86

96

The structures of complexes **93**, **94a**, **95a**, and **96** were determined by X-ray crystallography.[99-101] In solution, **93**, **95a** and **95b** are fluxional. The most important structural features of these binuclear complexes are summarized in Scheme 33, while the full crystal structure of **94a** is illustrated in Figure 3.



Scheme 33. Binuclear transition metal-arene complexes in which benzene or alkylbenzenes act as bridging ligands and all six ring carbon atoms are coordinated to metal atoms.

Thus, the two metal atoms can be bound to one side of an arene ligand (synfacial) as in **93** and **95** or on opposite sides of the arene (antifacial) as in **94a** and **96**. Only in the binuclear vanadium complex **94a** (see Fig. 3), the first triple-decker sandwich complex with benzene as the "middle deck", does the benzene remain completely planar and retain equal C–C bond lengths in the coordinated state at room temperature. In all other binuclear complexes the arene ligands are either no longer planar (**93**) or are both non-planar and have different C–C bond lengths (**95**, **96**).

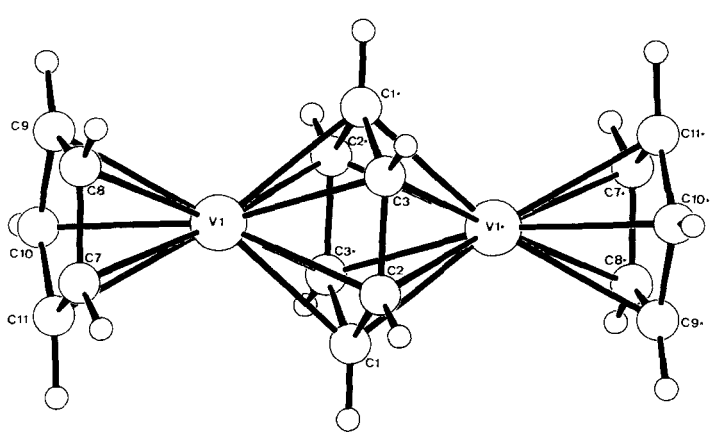
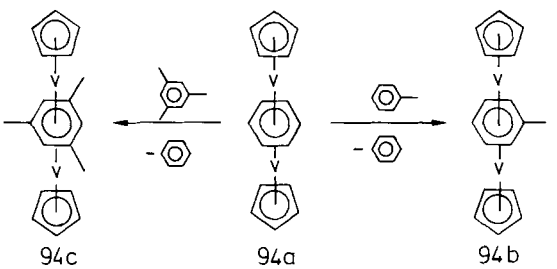


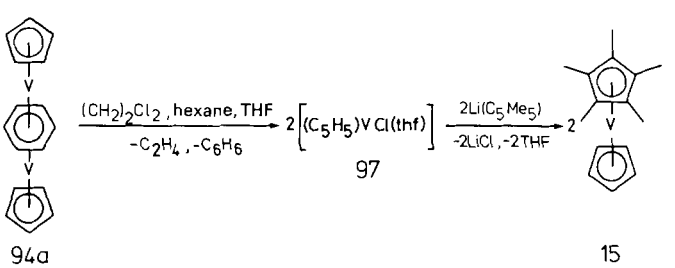
Fig. 3. Molecular structure of μ-benzenedicyclopentadienyldivanadium **94a**, the first triple-decker sandwich complex having complexed benzene as the "middle deck".

Remarkably, the coordinated benzene in **94a** can be displaced from the vanadium atoms by alkylbenzenes at 110 °C and this proceeds with retention of the triple-decker sandwich structure. For example, when **94a**, which is only sparingly soluble, is heated in toluene or mesitylene it goes into solution slowly. The new, much more soluble triple-decker sandwich complexes **94b** and **94c** are produced in which coordinated toluene or mesitylene now form the novel bridging group. An X-ray structure determination has also been carried out for **94c**[100] (Scheme 34).



Scheme 34. Replacement of complexed benzene in **94a** by toluene or mesitylene at 110 °C.

The triple-decker sandwich structure is lost when **94a** reacts with organic halides or iodine.[100] For example, when **94a** is treated with allyl chloride in THF, the vanadium(III) complex $[(C_5H_5)V(C_3H_5)Cl]$ is obtained, while treatment of **94a** with dichloroethane furnishes the vanadium(II) complex **97**. The reaction of **97** with lithium pentamethylcyclopentadienide forms pentamethylvanadocene **15** in high yield (Scheme 35), which in turn was used in the synthesis of **17** and **18** (Section 2.1.3) and of **56** and **57** (Section 2.2.4). In addition, **15** has proved to be a valuable starting material for a number of other syntheses.[102]



Scheme 35. Degradation of the triple-decker sandwich structure of **94a** and synthesis of **15**.

4. Conclusion

The use of cyclopentadienyl groups as ligands to stabilize transition metal atoms is one of the cornerstones of synthetic organo-transition metal chemistry. This situation has changed little in the three decades that have elapsed since the discovery of the metallocenes in the early 1950's. Indeed, the current literature shows a trend towards the use of alkylated five-membered ring ligands, frequently with the aim of forming even more stable systems.

In contrast, the properties of the C_5H_5 group as a mesomerically stabilized anionic leaving group have been neglected, and the consequent preparative applications have remained virtually unknown.

The degradation reactions based on this principle which have been described in this review are productive synthetic methods for preparing both coordinatively unsaturated transition metal complexes and those with labile ligands. These highly reactive compounds, many of which have not yet been prepared by other routes, are themselves suitable starting materials for a wide range of syntheses. We expect that numerous further examples will be discovered in the future. It also remains to be established whether this synthetic approach can also be successfully extended to cyclopentadienyl and related complexes of the f-elements.

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Formation of Organoaluminum Compounds in the Mixture $AlCl_3$–$TiCl_4$–Al–C_2H_4

By *Heinz Martin*,* *Helmut Bretinger*, and *Fritz Fürbach*

Dedicated to Professor Günther Wilke on the occasion of his 60th birthday

In the thirty-year history of the Ziegler catalysts, there has been no lack of efforts to attack, circumvent, or infringe the patent rights of *Karl Ziegler*. An earlier publication of *Max Fischer*,[2]

$$Al + AlCl_3 + TiCl_4 \xrightarrow[\text{heptane}]{C_2H_4} \text{polyethylene} + ? \quad (1)$$

in combination with work of *Hall* and *Nash*,[3,4]

$$Al + AlCl_3 \xrightarrow{C_2H_4} EtAlCl_2 + Et_2AlCl \quad (2)$$

played an important role in connection with a series of legal controversies in the USA, most recently against Dart,[1] which have meanwhile been resolved. These dealt with the question of whether, under the conditions of this ethylene polymerization [Eq. (1)], ethylaluminum sesquichloride forms from Al and $AlCl_3$ with ethylene according to Equation (2), and, via reaction with $TiCl_4$ to form a Ziegler catalyst,[5] could be made responsible for the formation of a solid, high-molecular-weight polyethylene. If this could be shown, then the catalyst patented by *Ziegler* for the polymerization of olefins would, in the opinion of the defendant, not be new and therefore not be patentable.

There has been mostly speculation on this question:[6–11] at least in situ, ethylaluminum chlorides, as well as $AlEt_3$,

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ought to have been formed. This conclusion could not be reached experimentally[9] since, in the reporting of analytical data, those for Al were absent, or since distillative separation of the ethylaluminum compounds supposedly formed, either from one another or from hydrocarbons in the C_{10}–C_{12} range, could not have led to the reported success under the given conditions: the vapor pressure curves of the possible Al compounds differ from each other and from those of the hydrocarbons to such a small extent that the separation of pure components would not have been thus possible.[12–14] Under the conditions of the Max Fischer patent, it is not possible to detect organoaluminum compounds in the product.

If an organoaluminum compound is formed at all as intermediate, it could only be a small amount of an Al compound with a Cl/Al ratio $\geqq 2$ mixed with a relatively large excess of $AlCl_3$, and not Et_2AlCl. This conclusion is arrived at by calculation alone, based on the mole ratio of Al powder and $AlCl_3$ used—especially in view of the results of *Hall* and *Nash*.

$$370\,\text{mmol Al} + 225\,\text{mmol AlCl}_3 \xrightarrow{C_2H_4} 225\,\text{mmol}\,(\text{EtAlCl}_2 + \text{Et}_2\text{AlCl}) + 145\,\text{mmol Al}^{[3,4]} \quad (3)$$

$$37\,\text{mmol Al} + 225\,\text{mmol AlCl}_3 \xrightarrow[\text{heptane}]{C_2H_4} 111\,\text{mmol EtAlCl}_2 + 151\,\text{mmol AlCl}_3^{[2]} \quad (4)$$

By the use of the catalytic mixture described by *Fischer*, solid polyethylenes were isolated as solid products mixed with excess oil having Friedel-Crafts character. The solid products are structurally highly branched and have melting points between 100 and 120 °C.

Without the addition of $TiCl_4$ under otherwise identical, or even milder, conditions, a dichloroaluminum compound forms in the heptane solution (detected by volumetric analysis). The ^{27}Al-NMR spectrum of the solution (104 MHz, [D$_8$]toluene) indicates a corresponding concentration of a hydrocarbon-containing dichloroaluminum compound ($\delta = +39.2$, $+5.8$; $EtAlCl_2$ $\delta = +35$, $+2.3$; $AlCl_3$ $\delta = 0$). The formation of Et_2AlCl ($\delta = +70$) is ruled out with certainty according to the analytical results. The large excess of unreacted $AlCl_3$ in the reaction mixture supports these findings, since, with $AlCl_3$, even traces of Et_2AlCl would comproportionate immediately to $EtAlCl_2$ under the conditions of the Max Fischer patent according to the present state of knowledge.[15]

$$\text{Et}_2\text{AlCl} + \text{AlCl}_3 \longrightarrow 2\,\text{EtAlCl}_2 \quad (5)$$

Thus, the answer to the question asked at the beginning—whether Et_2AlCl could form from Al and $AlCl_3$ under conditions such as those described by *Fischer*[2]—is an unequivocal no.

The further investigation of the reaction mixture after reaction under comparably mild conditions (100–110 °C, 1 bar ethylene) led, however, to a surprising result. Upon treatment of both the separated undissolved part and the soluble part of the reaction mixture with D_2O, [D$_2$]ethane is found in the deuterolysis gas, namely, [1,2-D$_2$]ethane from the undissolved and [1,1-D$_2$]ethane from the dissolved part. The proportion of [D$_2$]ethane corresponds to ca. 26–30% of the maximal amount of $EtAlCl_2$ expected on the basis of Equation (4). Its origin can easily be explained by the formation of intermediates.

$$\gtrless\text{Al–CH}_2\text{CH}_2\text{–Al}\lessgtr + 2\,\text{D}_2\text{O} \longrightarrow 2\gtrless\text{AlOD} + \text{CH}_2\text{D–CH}_2\text{D} \quad (6)$$

$$\gtrless\text{Al–CH(CH}_3\text{)–Al}\lessgtr + 2\,\text{D}_2\text{O} \longrightarrow 2\gtrless\text{AlOD} + \text{CD}_2\text{H–CH}_3 \quad (7)$$

In the same way, we have prepared 1,2-ethanediyl bis(dichloroaluminum) **1** and the corresponding 1,1-ethanediyl compound **2**.[16]

$$2\,\text{Al} + 4\,\text{AlCl}_3 + 3\,\text{C}_2\text{H}_4 \longrightarrow \underset{\mathbf{1}}{3\,\text{Cl}_2\text{Al–C}_2\text{H}_4\text{–AlCl}_2} \quad (8)$$

The reactivity of the compounds **1** and **2**, which were hitherto unknown, towards $TiCl_4$ was compared with that of $EtAlCl_2$ (Table 1).

Table 1. Reduction of $TiCl_4$ at room temperature in heptane (10 mmol $TiCl_4$ + 10 mmol Al compound in 50 mL heptane).

Aluminum compound	t [min]	Ti$^{[11]}$ [%]
$Cl_2Al–C_2H_4–AlCl_2$ **1**	30	31.5
	60	34.5
$(Cl_2Al)_2CH–CH_3$ **2**	5	96
	15	100
$EtAlCl_2$	15	22.5
	60	42

Thus **2** exhibits comparatively exceptional reactivity. Although, under ethylene pressure at 150 °C, the external conditions as given in [2], the aluminum compound is no longer stable—it eliminates $EtAlCl_2$—it can be assumed that, in the presence of $TiCl_4$, it reacts immediately, without the formation of $EtAlCl_2$.

In the polymerization of ethylene at normal pressure using a catalyst prepared from **2** and $TiCl_4$, without addition of $AlCl_3$, a solid, high-molecular-weight, practically linear polyethylene is formed.

Even organoaluminum compounds containing more chlorine and appreciably fewer ethyl groups than Et_2AlCl are therefore suitable as cocatalysts, together with $TiCl_4$, for the conversion of ethylene into solid polymers. The structures of these polyethylenes, however, differ unequivocally from those that can be observed according to [12]. Such catalysts could not, therefore, result in the reactions described by *Fischer*.

Not only the examination of the stoichiometric ratios of catalyst components chosen by *Fischer*, but also of the mechanism of the reaction of Al and $AlCl_3$, indicates that the catalyst described by *Fischer* is of a different kind from that described by *Ziegler*.

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[16] 16 g Al powder, suspended in 500 mL *n*-heptane, was treated for 4 d with C_2H_4 (1 bar) after addition of 30 g $AlCl_3$ with stirring at 100°C. The mixture was filtered and the filtrate freed of solvent (maximum 50°C, 10^{-3} mbar). The oily residue (17.75 g) was treated with pentane. A colorless powder precipitated out (24.14% Al, 63.32% Cl, 12.32% ethane; deuterolysis: 95% [1,1-D_2]ethane, 5% [D_1]ethane). The structure of **2** shown here is in accord with the ^{1}H-NMR spectrum (230 K) ($\delta(C-H) = -1.20$, $\delta(CH_3) = 0.92$) as well as with the ^{13}C-NMR spectrum (210 K) ($\delta(C-H = 1.95$ (d), $\delta(CH_3) = 5.71$ (q)). The solid residue from the filtered reaction mixture contains undissolved **1** in addition to excess Al powder.

Nickel-Catalyzed Cyclodimerization of 2-*tert*-Butyl- and 2-Trimethylsilyl-1,3-butadiene**

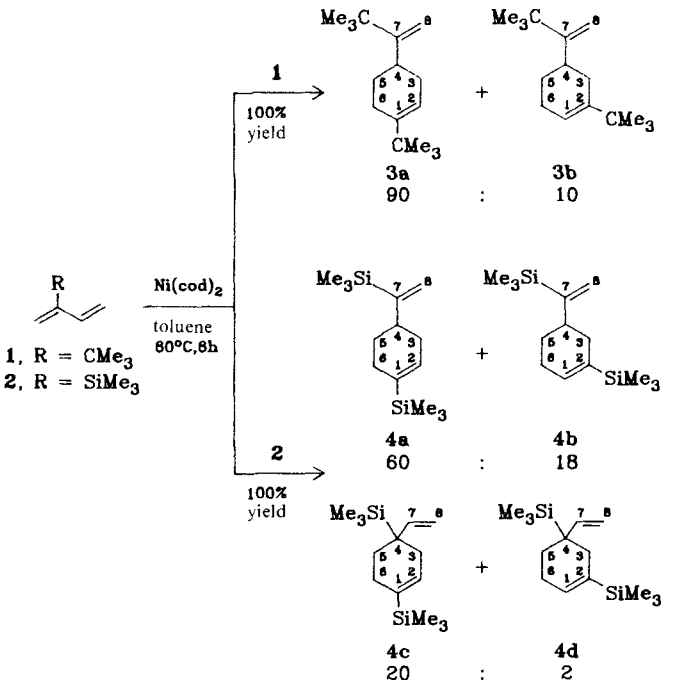
By *Tamas Bartik, Paul Heimbach,* Thomas Himmler,* and *Richard Mynott*

Dedicated to Professor Günther Wilke on the occasion of his 60th birthday

The oligomerization of 1,3-butadiene, first carried out by *H. W. B. Reed* on Reppe catalysts ($L_2Ni(CO)_2$),[1] only became a widely applicable synthetic method with the introduction of carbonyl-free Ni^0 catalysts by *G. Wilke* et al.[2] Butadiene is cyclotrimerized on "naked" nickel; in the presence of P ligands (phosphanes or phosphites), cyclodimerization takes place to give divinylcyclobutane, 4-vinylcyclohexene, and (*Z,Z*)-1,5-cyclooctadiene.[3] In order to use the Ni^0-catalyzed oligomerizations and co-oligomerizations better, the controlling factors, e.g., the conformation of the diene or the relative donor-acceptor behavior of the substituents (structural and electronic variables, "molecular order effectors")[4] must be understood. We show here how the substituents CMe_3 and $SiMe_3$ in the 2-position of 1,3-butadiene affect reactivity and selectivity in the Ni-catalyzed cyclodimerization.

Whereas the 2-alkyl-substituted 1,3-dienes that have been studied to date oligomerize more slowly than butadiene,[5] 2-*tert*-butyl- and 2-trimethylsilyl-1,3-butadiene, **1** and **2**, respectively, surprisingly react appreciably faster. Under conditions[6] that result in 30—40% cyclotrimerization of butadiene on the ligand-free nickel catalyst, the reaction of the dienes **1** and **2** is quantitative. In the case of both dienes, cyclodimerization occurs and only substituted vinylcyclohexenes are formed (Scheme 1).

The isomeric pairs **3a/3b** as well as **4a/4b** and **4c/4d** each differ only in the respective substitution of the double bond in the ring. It was not possible to assign the structures unequivocally from simple ^{1}H- and ^{13}C-NMR spectra. This was only achieved with the 2D-INADEQUATE technique, in which the $^1J(^{13}C\text{-}^{13}C)$ couplings are used to generate a carbon-carbon connectivity map[7] (see Table 1).



Scheme 1.

Table 1. ^{13}C-NMR data for **3a**, **3b**, and **4a**—**4d**. The signal assignments for **3a**, **3b** [12], **4a**, and **4c** were made unequivocally on the basis of the 2D-INADEQUATE ^{13}C-NMR spectra. δ-Values recorded relative to $CDCl_3$ and recalculated relative to TMS [$\delta(CDCl_3) = 77.0$] [a]. For numbering of the C atoms see Scheme 1.

C	3a	3b	4a	4b	4c	4d
1	145.0 (s)	116.7 (d)	138.2 (s)	135.0 (d)	138.3 (s)	135.4 (d)
2	118.1 (d)	146.4 (s)	135.5 (d)	138.7 (s)	133.8 (d)	136.8 (s)
3	35.5 (t)	34.4 (t)	34.1 (t)	33.9 (t)	30.3 (t)	29.6 (t)
4	35.9 (d)	36.5 (d)	38.9 (d)	39.3 (d)	29.6 (s)	30.0 (s)
5	32.5 (t)	31.5 (t)	29.5 (t)	28.8 (t)	26.7 (t)	26.1 (t)
6	26.0 (t)	26.8 (t)	27.7 (t)	27.8 (t)	22.8 (t)	23.2 (t)
7	164.3 (s)	164.6 (s)	157.5 (s)	157.6 (s)	142.5 (d)	142.4 (d)
8	105.1 (t)	105.1 (t)	122.5 (t)	122.4 (t)	110.9 (t)	110.9 (t)
CH_3	29.3/	29.0/	−0.9/	−1.0/	−2.2/	−2.4/
	28.9	28.8	−2.1	−2.2	−4.7	−4.7
$C(CH_3)_3$	36.9/	36.9/				
	35.2	35.2				

[a] The ^{13}C-NMR spectra were recorded in 10-mm tubes in $CDCl_3$ at 75.5 MHz on a Bruker WM-300 NMR spectrometer. Typical measurement conditions for the 2D-INADEQUATE spectra: data matrix $2K \times 256(t_2,t_1)$, 128 scans per t_2 increment; spectral width 11.9 kHz, τ-increment 5 ms (corresponding to average coupling $^1J_{CC} = 50$ Hz); cycle time 4.1 s.

The effect of the diene substituents (CMe_3, $SiMe_3$, and also CH_3[8]) on the relative proportions of head (H) and tail (T) coupling in the "diene" and "ene" parts for the reaction giving Diels-Alder products is shown in Table 2. The proportion of "symmetrically" coupled products (HH + TT) increases in the series $CMe_3 < SiMe_3 < CH_3$.

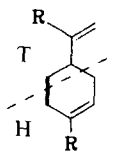
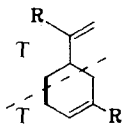
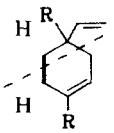
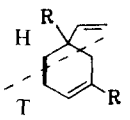
The rate of the Ni-catalyzed oligomerization is strongly affected by the addition of triphenylphosphane: the reaction of butadiene is accelerated, that of **1** and **2** inhibited (Fig. 1).

Using discontinuous inverse titration,[9] we were able to show that the Ni-catalyzed cyclodimerization of diene **2** to Diels-Alder products was practically fully suppressed upon addition of triphenylphosphane in the range $-1 < \lg[L]_0/[Ni]_0 < 0$, whereas, for the diene **1**, for ligand concentrations in the range $-1 < \lg[L]_0/[Ni]_0 < +1$, **3b** replaces **3a** as the main product in a very strongly inhibited

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Table 2. Proportions (%) of the four possible couplings to Diels-Alder products for the 1,3-dienes **1** and **2** and for 2-methylbutadiene [8].

Dimers	R = CMe_3	$SiMe_3$	CH_3
	90	60	40
	10	18	33
	0	20	27
	0	2	0

Sums of the proportions of the different coupling partners

	H	T	H	T	H	T
Ene part [a]	0	100	22	78	27	73
Diene part [b]	90	10	80	20	67	33
HH + TT [c]		10		38		60
HT + TH [d]		90		62		40

[a] Proportion of the dimers in which the ene was incorporated as head or tail. [b] Proportion of the dimers in which the head or tail of the diene was coupled with the terminal C atom of the ene components. [c] Sum of the HH- and TT-coupled dimers. [d] Sum of the HT- and TH-coupled dimers.

reaction (yield $< 15\%$ for $\lg[L]_0/[Ni]_0 > +0.5$). Nevertheless, this very retarded reaction is also clearly catalytic, since the diene **1** thermally dimerizes to only 0.2% under these reaction conditions in the absence of catalyst. For diene **2**, the slower uncatalyzed Diels-Alder reaction (yield ca. 20%), in which the isomers **4a**—**4d** are formed, is observed after "turning off" the catalysis by addition of triphenylphosphane ($\lg[L]_0/[Ni]_0 > 0$); comparison of the thermal with the catalytic dimerization shows that, catalytically, three isomers are formed: **4a** and **4b** in appreciably larger proportion than in the thermal dimerization, and **4c** in only slightly increased proportion. The isomer **4d**, on the other hand, is only formed thermally.

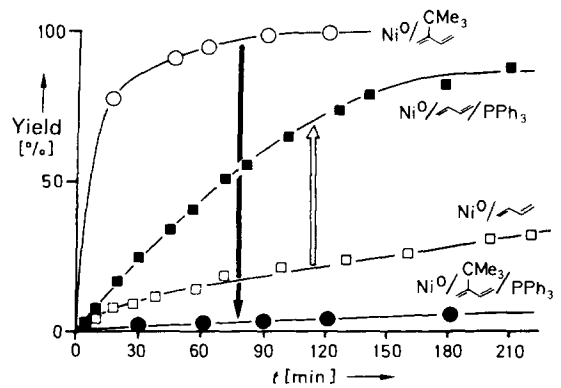


Fig. 1. Opposite effect of the addition of triphenylphosphane on the reaction rate (yield curves) in the Ni-catalyzed oligomerization of butadiene (activation) and 2-*tert*-butyl-1,3-butadiene **1** (inhibition); L : Ni = 10 : 1.

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[6] The series of experiments was carried out with a parent solution of bis(cyclooctadiene)nickel(0) in diene/toluene; *n*-hexane served in the GC analysis as internal standard for diene and catalyst. Triphenylphosphane was added in a benzene solution. After 6 h at 60°C in sealed glass ampules, the reaction mixtures were directly analyzed by gas chromatography (Perkin Elmer F20, 45m OV101 glass capillary column). The concentration of catalyst was 16 mmol/L, the ratio nickel : diene 1 : 160. All operations were carried out under argon. **1** was synthesized according to [10]; **2** by adaption of the procedure for 2-triethylsilyl-1,3-butadiene [11].
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[8] H. Krische, Dissertation, Universität Essen 1980.
[9] a) F. Brille, P. Heimbach, J. Kluth, H. Schenkluhn, *Angew. Chem. 91* (1979) 428; *Angew. Chem. Int. Ed. Engl. 18* (1979) 400; b) C. A. Tolman, J. W. Faller in L. H. Pignolet: *Homogeneous Catalysis with Metal Phosphine Complexes*. Plenum, New York 1983, p. 69ff.
[10] A. A. Korotkov, L. F. Roguleva, *Zh. Org. Khim. 1* (1965) 1180.
[11] M. Petrzilka, J. I. Grayson, *Synthesis 1981*, 753.
[12] Since the differences between the ^{13}C chemical shifts of **3a** and **3b** are unexpectedly small, we recorded the 2D-INADEQUATE spectrum of **3b** as a control. Especially noticeable are the similarities of the shifts of C-3 and C-6, respectively, in **3a** and **3b**. The signals of **4b** and **4d** were assigned by comparison with the other compounds.

Novel Trimerization of Cyclopentadiene with a Homogeneous, Bifunctional Palladium-Acid Catalyst System**

By *Arno Behr* and *Wilhelm Keim**

Dedicated to Professor Günther Wilke on the occasion of his 60th birthday

Although bifunctional catalysts have found wide application in heterogeneous catalysis,[1] there are still only very few corresponding examples of their use in homogeneous catalysis.[2] Herein, we describe the synthesis of two hitherto unknown cyclopentadiene trimers using a novel, bifunctional, mixed catalyst comprising a palladium complex and a carboxylic acid ("$Pd/H^{\oplus}$").

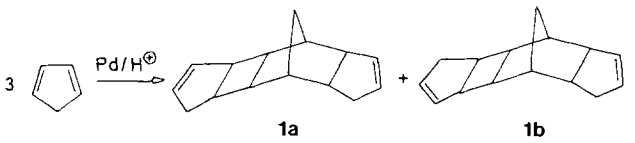
This preparative result indicates that bifunctional catalytic systems can also play an important part in homogeneous catalysis with transition-metals.

In the trimerization of cyclopentadiene two isomers are formed that can be preparatively separated[3] and fully

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characterized spectroscopically. On the basis of the 360-MHz H-NMR and 90-MHz ^{13}C-NMR spectra[4] and the result of decoupling experiments the trimers were assigned to the structures **1a** and **1b**. In both isomers the cyclopentene ring bound to the norbornane system is oriented in the *endo* position.



The 1:1 mixture of the pentacyclo[7.5.0.1^{2,8}.0^{3,7}.0^{10,14}]-pentadeca-4,12- **1a** and -4,11-diene **1b** forms white fibrous crystals (m.p. 49°C, b.p. 75°C/0.01 torr). No absorption maxima are observed in the UV spectrum above 200 nm; the IR spectrum[5] shows the typical C=C stretching band at 1608 cm^{-1} for the cyclopentene ring, while the stretching band of the norbornene ring at ca. 1570 cm^{-1} characteristic for Diels-Alder trimers is missing. The mass spectrum[6] is also consistent with the proposed structures.

In the catalytic hydrogenation of **1a** and **1b**, 2 moles of hydrogen are taken up per mole, in each case with formation of the same pentacyclopentadecane.

In the synthesis of **1a,b** palladium bis(acetylacetonate) Pd(acac)$_2$ or palladium bis(dibenzylideneacetone) Pd(dba)$_2$ is favored as palladium component of the catalyst. Both phosphanes (PEt_3, $PiPr_3$, PPh_3) as well as phosphites (triisopropyl phosphite, tris(*o*-tolyl) phosphite) are suitable as phosphorus ligands. As third component a carboxylic acid is required whose pK_a value lies between 3 and 5. This carboxylic acid must be present in at least the same molar amount as the starting cyclopentadiene; catalytic amounts of carboxylic acid are not sufficient for the formation of the trimers **1a**, **b**. The carboxylic acids employed were, e.g., acetic acid, monochloroacetic acid, benzoic acid, and pivalic acid. Too strongly acidic acids, e.g. trichloroacetic acid, lead to the formation of polycyclopentadiene. Remarkably, the catalyst system presented here is capable of almost completely suppressing formation of the Diels-Alder byproduct, dicyclopentadiene, even at reaction temperatures of 100 to 130°C.

The mechanism of the reaction is so far unclear. The reaction strongly depends on the solvent used, thus pointing to an ionic mechanism. A simple thermal [2+2]-cycloaddition can be ruled out, since comparative experiments without the bifunctional catalyst led only to the known Diels-Alder products. Also, when either the palladium complex or the acid alone is used as catalyst no trimer **1a**, **b** is formed.

Experimental:

In a typical reaction 0.65 mmol Pd(acac)$_2$ and 1.95 mmol PPh_3 were dissolved in 25 mL acetonitrile and treated with 9.9 g (0.15 mol) cyclopentadiene and 18 g (0.3 mol) acetic acid. Yield after 4 h at 100°C and subsequent work-up 7 g (70%) **1a**, **b**.

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1a, 95313-58-9; **1b**, 95313-59-0; Pd(acac)$_2$, 14024-61-4; PPh_3, 603-35-0; cyclopentadiene, 542-92-7; acetic acid, 64-19-7.

[1] a) J. Falbe, U. Hasserodt: *Katalysatoren, Tenside und Mineralöladditive*, Thieme, Stuttgart 1978; b) J. R. Anderson, M. Boudart: *Catalysis—Science and Technology, Vol. I—VI*, Springer, Berlin 1981–1984.
[2] G. C. A. Schuit, B. C. Gates, *CHEMTECH 1983*, 556, 693.
[3] Column with $AgNO_3$-impregnated SiO_2, hexane/ether 99:1 (cf. Woelm Information No. 49).
[4] ^{1}H-NMR, **1a**: δ = 1.45 (1), 1.70 (1), 1.95 (1), 2.02 (1), 2.11 (3), 2.20 (3), 2.58 (2), 2.65 (1), 2.97 (1), 5.43 (1), 5.53 (1), 5.68 (1), 5.72 (1); **1b**: δ = 1.46 (1), 1.83 (2), 2.03 (1), 2.13 (3), 2.24 (3), 2.52 (1), 2.62 (1), 2.76 (1), 2.98 (1), 5.41 (1), 5.55 (1), 5.67 (1), 5.72 (1); ^{13}C-NMR, **1a**: δ = 133.4 (d), 131.4 (d), 130.7 (d), 130.6 (d), 52.0 (d), 48.7 (d), 45.6 (d), 44.4 (d), 43.1 (d), 42.0 (d), 41.7 (d), 40.9 (t), 37.7 (d), 36.4 (t), 31.8 (t); **1b**: δ = 133.5 (d), 131.4 (d), 130.7 (d), 130.5 (d), 52.3 (d), 48.5 (d), 47.3 (d), 44.1 (d), 42.7 (d), 41.2 (d), 41.0 (t+d), 38.0 (d), 36.5 (t), 31.7 (t).
[5] IR, **1a**, **b** [cm^{-1}]: ν = 3040 s, 2930 s, 2840 m, 1640 sh, 1608 m, 1470 m, 1438 m, 712 s, 725 sh, 698 sh.
[6] MS, **1a**, **b** (*m/z*, rel. int. [%]): 198 (10), 183 (1), 169 (1), 157 (1), 132 (20), 131 (8), 117 (6), 91 (10), 66 (100).

A New Method for Determining Enantiomeric Excess, where the Sample Serves as its Own Reference**

By *Maurice L. Pasquier* and *Werner Marty**

The determination of the enantiomeric excess (*ee*) of a new, chiral substance is usually based on diastereomeric interactions between molecules of this substance and molecules of a different substance of known *ee*.[1,2] However, measurable diastereomeric interactions between *enantiomers* (i.e., molecules having the *same* constitution) in a sample are sufficient for determining the *ee*,[2–6] even in the *absence of an enantiomerically pure standard*. Procedures for determining the *ee* based on this principle appear attractive, but have not to our knowledge been developed so far. We discuss here one possible way of determining the *ee* by the use of this principle, which may be applied to a wide variety of compounds.

When a mixture of enantiomeric molecules C(abcd) (containing, e.g., only one stereogenic atom) in an unknown ratio $[R]_0/[S]_0$ is reacted with a bifunctional, achiral reagent F, diastereomers are expected, viz., an achiral *meso* species **m** and an *enantiomeric pair* of chiral species **e**. The species **m** and **e** may be distinguishable, e.g., by NMR spectroscopy,[7] and from the ratio r = [**m**]/[**e**], $[R]_0/[S]_0$ can be worked out in principle.[4] However, r may be affected appreciably by *diastereoselectivity* in the formation of **m** and **e**. This diastereoselectivity may be kinetic or thermodynamic in origin; the experimental distinction between these two contributions is laborious.[5]

If **m** and **e** are formed *reversibly*, then only thermodynamic diastereoselectivity is possible, and its extent is easily determined by analysis of the diastereomer ratio arising in the reaction of *racemic* C(abcd) with F. The thermodynamic diastereoselectivity is defined by $d = ([\mathbf{m}]/[\mathbf{e}])_{racemate}$.

The condition of reversibility is met if F is a kinetically *labile metal ion* M^{n+}[8] or a metal complex with at least two labile ligands. Metal ions can serve as templates to hold coordinating substrates at a close distance and, at the same time, as transmitters for electronic effects, as required for diastereomeric interaction. If r is to be determined by NMR, then the use of diamagnetic metal ions is indicated.[9]

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Complex formation may not be quantitative, or an *excess* of C(abcd) may be desirable to transform any $M[C(abcd)]^{m+}$ into $M[C(abcd)]_2^{g+}$. The *relative* amount of free substrate is defined by the ratio

$$h = [C(abcd)]_{free}/([\mathbf{m}]+[\mathbf{e}])$$

and may be determined, e.g., spectroscopically. It should be noted that the ratio of enantiomers in the excess substrate ($[R]/[S]$) may differ from that in the total substrate ($[R]_0/[S]_0$). This holds for any non-racemic mixture (where $r \neq d$) if $d \neq 1$.

For a system containing M^{n+}, C(abcd), $M[C(abcd)]^{m+}$, and $M[C(abcd)]_2^{g+}$ at equilibrium, the following equation is obtained, in which the experimental parameters r, d, and h are used:

$$\frac{[R]_0}{[S]_0} = \frac{\alpha^3(hr+h+2r+1)+\alpha^2(2r+1)+\alpha(1+hr+h)+1}{\alpha^3+\alpha^2(h+hr+1)+\alpha(2r+1)+2r+1+hr+h} \quad (1)$$

where α is the enantiomer ratio in the excess substrate;

$$\alpha = [R]/[S] = (r+\sqrt{r^2-d^2})/d.$$

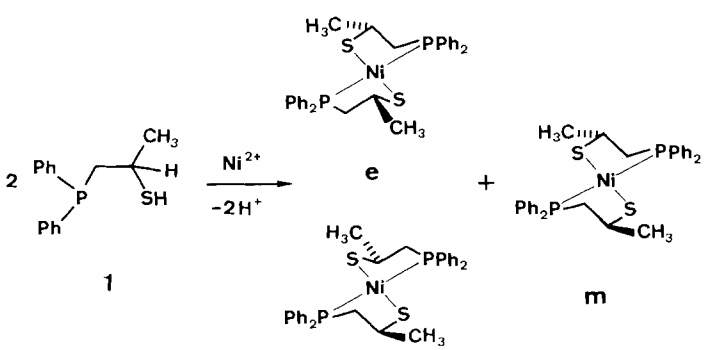
From equation (1), the *ee* is obtained using the familiar expression (2).

$$ee[\%] = [([R]_0/[S]_0-1)/([R]_0/[S]_0+1)] \times 100 \quad (2)$$

If $h \approx 0$, Equation (1) takes a simpler form and *ee* is given by Equation (3).

$$ee[\%] \approx \sqrt{r^2-d^2}/(r+1) \times 100 \quad (3)$$

This procedure may, in principle, be applied to any bidentate or unidentate coordinating molecule by proper choice of a metal ion or of a complex containing additional, non-labile ligands.[10] The procedure is very sensitive at high enantiomeric purities, and is rewarded by economy of enantiomerically highly enriched derivatizing reagents, shift reagents, or solvents. The metal complexes are best prepared in situ, and in completely homogeneous solution, in order to avoid fractionation of diastereomers.



In one example of application, the *ee* of 1-diphenylphosphino-2-propanethiol **1**[11] was determined. Both racemic and enantiomerically enriched **1** were treated in situ with a less than stoichiometric amount of $Ni(NO_3)_2 \cdot 6H_2O$ in CH_2Cl_2/MeOH (10:1) to form **m** and **e** diastereomers of *trans*-$Ni(\mathbf{1})_2$.[12] The ^{31}P-NMR spectra showed singlets at (a) $\delta = 52.65$ and (b) $\delta = 53.55$ (CH_2Cl_2/MeOH (10:1), relative to ext. H_3PO_4 in CD_2Cl_2) with intensity ratios of $d = (a)/(b) = 2.0$[13] and $r = 27$ for the racemate and the enantiomerically enriched sample, respectively. The excess of free ligand gave a singlet at $\delta = -18.92$, the intensity of which gave $h = 0.12$. From these data, $ee = 96.0\%$.[14] This result was confirmed by ^{1}H-NMR spectroscopy ($CDCl_3$, int. TMS, CH_3: $\delta = 1.41$ in **m** and 1.31 in **e**, $J_{HH} = 6.3$ Hz; *o*-phenyl H: 8.12 in **m** and 8.00 in **e**).[15] Equilibrium was shown to be attained by mixing known amounts of enantiomerically enriched (known *ee*) and racemic **1**; calculated and experimental r values agreed shortly after mixing.

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[1] The present discussion focuses on techniques that do not involve the resolution of enantiomers, e.g., by chromatography or isotope dilution. For a recent review on these two methods, see: J. D. Morrison: *Asymmetric Synthesis, Vol. 1*, Academic Press, New York 1983.

[2] A. Jacques, H. Collot, S. H. Wilen: *Enantiomers, Racemates and Resolutions*, Wiley-Interscience, New York 1981.

[3] Cf. [2], chap. 7.5.2., p. 410. These authors consider this possibility as an exception.

[4] J. P. Vigneron, M. Dhaenens, A. Horeau, *Tetrahedron 29* (1973) 1055.

[5] J. Leitich, *Tetrahedron Lett. 1978*, 3589.

[6] J. Reuben, *J. Am. Chem. Soc. 102* (1980) 2232.

[7] In some instances, the substrate molecules can *self-associate* (e.g., through hydrogen bonding in apolar solvents) to form diastereomeric aggregates with *anisochronous NMR signals:* (a) T. Williams, R. G. Pitcher, P. Bommer, J. Gutzwiller, M. Uskoković, *J. Am. Chem. Soc. 91* (1969) 1871; (b) M. I. Kabachnik, T. A. Mastryukova, E. I. Fedin, M. S. Vaisberg, L. L. Morozov, P. V. Petrovskii, A. E. Shipov, *Russ. Chem. Rev. 47* (1978) 821; (c) M. J. P. Harger, *J. Chem. Soc. Perkin 2 1977*, 188.

[8] If the diastereomers are to be analyzed by NMR, then the equilibration should be sufficiently slow such as to avoid exchange broadening of the lines. This may be ensured by proper choice of M^{n+}.

[9] However, lanthanide ions may serve as achiral shift reagents, increasing in some cases the chemical shift difference between the diastereomers [6].

[10] Proper choice of solvent may frequently prevent formation of significant amounts of undesired isomers with different coordination geometry, e.g., a *cis* or a *trans* square planar complex. Occasionally, the formation of such geometric isomers cannot be prevented, and then Equation (1) has to be modified, allowing for different diastereoselectivities of the individual geometric forms.

[11] a) Compound **1** (both racemic and enantiomerically enriched) was prepared in analogy to [11b] and [11c] from (±)-methylthiiran (Fluka) and (*R*)-methylthiiran, respectively. The products were foul-smelling, air-sensitive oils (b.p. 115–120°C, 0.02 torr; 87% yield); b) J. Chatt, J. R. Dilworth, J. A. Schmutz, J. A. Zubieta, *J. Chem. Soc. Dalton Trans. 1979*, 1595; c) T. Tsunetsugu, J. Furukawa, T. Fueno, *J. Polym. Sci. Part A1 9* (1971) 3529.

[12] E. Pfeiffer, M. L. Pasquier, W. Marty, *Helv. Chim. Acta 67* (1984) 654.

[13] For thermodynamically controlled reactions, this value corresponds to the absence of diastereoselectivity (no deviation from the statistical ratio of species concentrations).

[14] The peak areas of well-separated signals were determined with ±1% precision. If the accuracy of peak ratios is estimated as ±2% (W. H. Pirkle, S. D. Beare, *J. Am. Chem. Soc. 91* (1969) 5150; W. H. Pirkle, P. L. Rinaldi, *J. Org. Chem. 42* (1977) 3217), a value of 96.0±0.1% is obtained for the *ee* of the present example.

[15] The integrals of the ^{31}P-NMR signals were measured with due care, and interference from relaxation and nuclear Overhauser effects was eliminated.

4-Methylene-1-cyclopentenes from Methylenecyclopropanes and Alkynyltrimethylsilanes

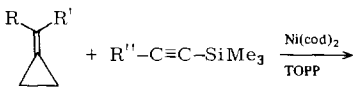
By *Paul Binger,* Qui-Hao Lü,* and *Petra Wedemann*

Dedicated to Professor Günther Wilke on the occasion of his 60th birthday

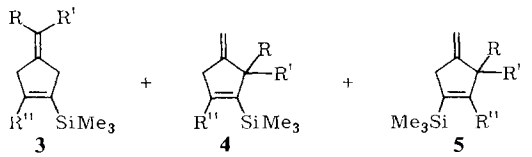
[3+2]-Cycloadditions have found increasing use in recent years for the direct entry to cyclopentanes.[1] Espe-

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cially suitable as a source for the C_3-unit required in such reactions are the methylenecyclopropanes **1**, which are also readily accessible in large amounts.[2] Thus, for example, 2,3- and 3,4-disubstituted methylenecyclopentanes can be obtained regioselectively from **1** and electron-deficient olefins, depending on the Ni^0- or Pd^0-catalysts used.[3,4].



1 **2**



3 **4** **5**

a, R=R'=H; **b**, R=H, R'=n-C_5H_{11}; **c**, R=H, R'=Ph; **d**, R=R'=CH_3; **e**, R=R'=Ph

Using triorganyl phosphite-containing Ni^0-catalysts, we have now also been able to carry out such additions of **1** to alkynes to give 4-methylene-1-cyclopentenes **3**—**5**; alkynylsilanes such as **2** (Table 1) are particularly suitable for these codimerizations.

Table 1. Ni(cod)$_2$/tris(*o*-phenylphenyl)phosphite (TOPP)-catalyzed addition of **1** to **2** [a].

No.	1	2 R''	Yield [b] [%]	3 [c]	4 [c]	5 [c]
1	c	$SiMe_3$	41 [62]	—	100%	
2	d	$SiMe_3$	50 [62]	—	100%	
3	e	$SiMe_3$	71 [84]	48%	52%	
4	b	CH_3	82 [89]	12% [d]	63%	25%
5	a	C_2H_5	48 [75]			
6	d	C_2H_5	88 [88]	—	85%	15%
7	e	C_2H_5	92 [92]	60%	24%	16%
8	a	CH_2OSiMe_3	59 [74]			
9	d	CH_2OSiMe_3	82 [82]	6%	60%	34%
10	e	CH_2OSiMe_3	90 [90]	53%	2%	45%
11	a	CO_2CH_3	72 [72]			
12	b	CO_2CH_3	65 [95]	25% [d]	22%	53%
13	c	CO_2CH_3	60 [85]	31%	28%	41%
14	d	CO_2CH_3	64 [75]	41%	21%	38%
15	e	CO_2CH_3	63 [79]	100%	—	—

[a] 1 mmol Ni(cod)$_2$, 1 mmol TOPP, 50 mmol **1**, 50 mmol **2**; 5—8 h, 80°C; the experiment with **1a** was carried out in a V4A steel autoclave, the experiments with **1b**—**1e** in a glass tube. [b] Calculated w.r.t. alkyne (consumed). In addition, non-distillable oligomers having unknown composition are formed. [c] All compounds were characterized by elemental analysis and ^{1}H-NMR, ^{13}C-NMR, and mass spectra. [d] Two isomers.

Corresponding reactions can also be carried out with 1-alkynes or dialkylacetylenes; so far, however, side reactions such as oligomerization in the case of 1-alkynes and cotrimerization and cotetramerization in the case of dialkylacetylenes could not be avoided. In contrast, alkynes with electron-attracting moieties, such as propiolates or acetylenedicarboxylates, cyclotrimerize so rapidly that an addition to **1** no longer occurs.

The cycloadditions of **1** to **2** outlined here show some remarkable differences compared to analogous reactions of **1** with alkenes on the same or similar Ni^0 catalysts. Thus, all the methylenecyclopropanes so far employed codimerize with alkynylsilanes with opening of the distal three-membered ring bond, irrespective of the number or type of substituents in the two reactants. In the cycloadditions of **1a** with electron-deficient olefins, on the other hand, it depends on the substituents in the olefin as to whether the σ-bond adjacent to the C=C bond or the distal σ-bond of **1a** is opened[3b]; in contrast, the methylenecyclopropanes **1b**—**1e** with substituents on the C=C double bond always react with opening of the distal three-membered ring bond.[5]

The tendency for the formation of methylenecyclopentanes in which the groups R and R' are bound to the five-membered ring at the α-position to the methylene group is distinctly higher in the cycloadditions described here than in the corresponding reactions with olefins. With **1d**, for example, over 90% **4d** and **5d** is obtained; an exception is found only on codimerization with the methoxycarbonylalkynyltrimethylsilane (Table 1, Entry 14). In contrast, the methyl groups largely remain bonded to the methylene group in the Ni^0-catalyzed cycloadditions of **1** with electron-deficient olefins.[5] The phenyl-substituted compound **1e** behaves differently. In the cycloadditions of **1e** with electron-deficient olefins the phenyl groups remain attached to the methylene group,[5] whereas with alkynes, **3e** and **4e**/**5e** are generally formed in about equal amounts. Here too, an exception is the methoxycarbonylalkyne derivative, which affords only the methylenecyclopentene of type **3e**.

The regioselectivity of the addition is generally low. Consequently, additions with **1b**—**1e** lead to two isomers, **4** and **5**. The regioselectivity can, however, be influenced by changes in the electronic properties of the substituents on the alkyne (cf. Table 1, e.g. Entries 6, 9 and 14 or 4 and 12). The trimethylsilyl group can be regarded as a weakly negative substituent, obviously because of the interaction with the π-electrons of the triple- and double-bond.[7]

No detailed information can, as yet, be given about the mechanism of these cycloadditions. In particular, the structure of the organonickel intermediates (formulated, e.g., as "η^4-trimethylenemethane"-nickel complex or polar "η^3-trimethylenemethane" complex, as in the case of palladium[6]) is still unknown.

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1a, 6142-73-0; **1b**, 91509-06-7; **1c**, 7555-67-1; **1d**, 4741-86-0; **1e**, 7632-57-7; **2** (R''=$SiMe_3$), 14630-40-1; **2** (R''=CH_3), 6224-91-5; **2** (R''=C_2H_5), 62108-37-6; **2** (R''=CH_2OSiMe_3), 50965-66-7; **2** (R''=CO_2CH_3), 42201-71-8; (*E*)-**3b** (R''=CH_3), 95797-91-4; (*Z*)-**3b** (R''=CH_3), 95797-92-5; (*E*)-**3b** (R''=CO_2CH_3), 95797-96-9; (*Z*)-**3b** (R''=CO_2CH_3), 95797-97-0; **3c** (R''=C_2H_5), 95797-93-6; **3c** (R''=CO_2CH_3), 95797-98-1; **3d** (R''=CH_2OSiMe_3), 95797-94-7; **3d** (R''=CO_2CH_3), 95797-99-2; **3e** (R''=$SiMe_3$), 95797-90-3; **3e** (R''=CH_2OSiMe_3), 95797-95-8; **3e** (R''=CO_2CH_3), 95798-00-8; **4b** (R''=CH_3), 95798-04-2; **4b** (R''=CO_2CH_3), 95798-09-7; **4c** (R''=$SiMe_3$), 95798-01-9; **4c** (R''=CO_2CH_3), 95798-10-0; **4d** (R''=$SiMe_3$), 95798-02-0; **4d** (R''=C_2H_5), 95798-05-3; **4d** (R''=CH_2OSiMe_3), 95798-07-5; **4d** (R''=CO_2CH_3), 95798-11-1; **4e** (R''=$SiMe_3$), 95798-03-1; **4e** (R''=C_2H_5), 95798-06-4; **4e** (R''=CH_2OSiMe_3), 95798-08-6; **5b** (R''=CH_3), 95798-12-2; **5b** (R''=CO_2CH_3), 95798-17-7; **5c** (R''=CO_2CH_3), 95798-18-8; **5d** (R''=C_2H_5), 95798-13-3; **5d** (R''=CH_2OSiMe_3), 95798-15-5; **5d** (R''=CO_2CH_3), 95798-19-9; **5e** (R''=C_2H_5), 95798-14-4; **5e** (R''=CH_2OSiMe_3), 95798-16-6; Ni(cod)$_2$, 1295-35-8; TOPP, 13885-11-5.

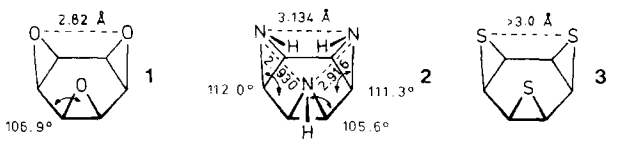
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[2] a) R. Köster, S. Arora, P. Binger, *Justus Liebigs Ann. Chem. 1973*, 1219; b) S. Arora, P. Binger, *Synthesis 1974*, 801; c) K. Utimoto, M. Tamura, K. Sisido, *Tetrahedron 29* (1973) 1169.
[3] a) P. Binger, A. Brinkmann, P. Wedemann, *Chem. Ber. 116* (1983) 2920; b) P. Binger, P. Wedemann, *Tetrahedron Lett. 26* (1985) 1045.
[4] a) P. Binger, U. Schuchardt, *Chem. Ber. 114* (1981) 3313; b) P. Binger, P. Bantz, *Angew. Chem. 94* (1982) 66; *Angew. Chem. Int. Ed. Engl. 21* (1982) 62; *Angew. Chem. Suppl. 1982*, 153.
[5] P. Binger, P. Wedemann, *Tetrahedron Lett. 24* (1983) 5847.
[6] B. M. Trost, D. M. T. Chan, *J. Am. Chem. Soc. 105* (1983) 2326.
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cis-Triaza-tris-σ-homobenzene as Tridentate Ligand $[La(C_6H_9N_3)_4 \cdot CH_3CN \cdot (ClO_4)_3]$: LaN_{12} Complex with Icosahedral Coordination**

By *Reinhard Schwesinger, Klaus Piontek, Walter Littke,* and *Horst Prinzbach**

Originally, the readiness of the *cis*-trihetero-tris-σ-homobenzenes **1**–**3** to complex metal ions was studied merely from the analytical or preparative viewpoint.[1] But severe limits are set on such applications because the interactions in solution are usually very weak. The complexes gained importance, however, through the fact that unusual coordination behavior ought to be realizable with the potentially tridentate ligands, because of their special geometric and electronic properties.[2,3] For example, in [Ca $\mathbf{1}_3 \cdot H_2O \cdot (ClO_4)_2$],[3] [Sr $\mathbf{1}_4 \cdot (ClO_4)_2$], and [Ba $\mathbf{1}_4 \cdot (ClO_4)_2$][4] **1** does in fact function as a tridentate ligand, whereby unusually high coordination numbers of 10 and 12 are realizable (CaO_{10}: tetracapped trigonal prism; SrO_{12}, BaO_{12}: icosahedron).



As with **1**, numerous, generally microcrystalline compounds of the cation composition $M\mathbf{2}_2$ ($M = Li^+$, Na^+, Ca^{2+}, Sr^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+}, Cd^{2+}, Co^{3+}), $M\mathbf{2}_3$ ($M = Ba^{2+}$, Sc^{3+}, Y^{3+}), and $M\mathbf{2}_4$ ($M = La^{3+}$, Lu^{3+}) (elemental analysis) were also isolated with **2**.[4,5] In the case of $[Co\mathbf{2}_2 \cdot H_2O \cdot (NO_3)_3]$ an X-ray structure analysis confirmed that **2** was present as tridentate ligand.[4] Single crystals of the higher coordinated compounds could only be obtained in the case of $La\mathbf{2}_4^{3+}$. In acetonitrile, leaflet-shaped prisms of **4** were formed, which, unlike the microcrystalline, colorless material, are pale yellow. Presumably, they decompose slightly during the course of (several weeks) crystallization (**2** is sensitive towards O_2 and CO_2[1]). This might also be responsible for the rather large deviations in some of the data obtained from the X-ray structure analysis (Fig. 1, 2)[6] (particularly regarding the C–C bond lengths).

$[La(C_6H_9N_3)_4 \cdot CH_3CN \cdot (ClO_4)_3]$ **4**

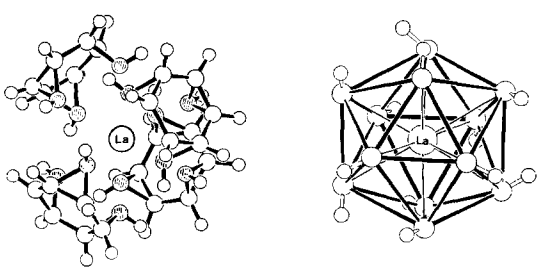


Fig. 1. Left: Structure of **4** in the crystal (N: hatched); right: LaN_{12} coordination polyhedron.

The central La^{3+} ion is complexed by four tridentate ligands **2**, the imino hydrogen atoms are oriented outwards, CH_3CN and counterions do not participate in the coordination. The coordination sphere corresponds to a slightly distorted icosahedron.[6] The mean N–N distance in **4** is smaller than that in the free H-bridged trisimine **2**; the interplanar angles in **4** are of the order of magnitude of the smallest in **2**; the C_6 rings in **4** are almost planar—consistent with the absence of the H-bridges and as a normal[4] consequence of complexation. The average H–N–La angle is 117°, which enables the imino hydrogen atoms to approach to within 2.7 Å of the adjacent N-atom of a neighboring molecule. Interactions between the imino protons and the perchlorate ions and CH_3CN molecules lead to a closest packing of the molecules.

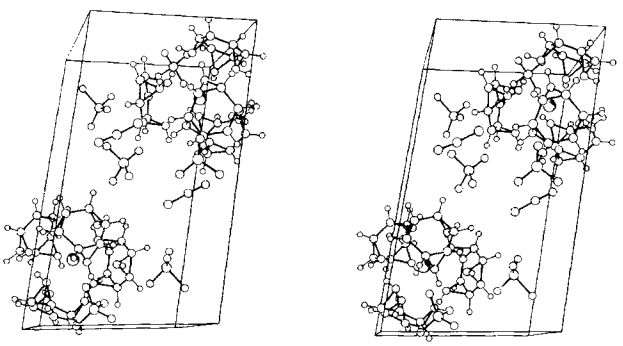


Fig. 2. Stereograph of the packing in the unit cell of **4**.

The MN_{12} coordination realized here is unusual;[7] in the case of $[Pr(Napy)_6 \cdot (ClO_4)_3]$[8] with the bidentate 1,8-naphthyridine (Napy) ligands, the deviations of the PrN_{12} polyhedron from the ideal geometry of the icosahedron are much greater. The stability of the 1:4 complex of **2** with $La(ClO_4)_3$ is due to a high lattice energy: In CD_3OD, no 1:4 complex is detectable (^{1}H-NMR); **2** ($\delta = 2.37$) forms the following complexes with $La(n\text{-}C_4F_9SO_3)_3$ **5** (depending on the stoichiometry, either as a single substance or as a mixture): $\mathbf{5} \cdot \mathbf{2}_3$ ($\delta = 2.73$, br. s, cf. the CaO_{10}-complex of **1**[3]); $\mathbf{5} \cdot \mathbf{2}_2$ ($\delta = 2.86$, br. s), $\mathbf{5} \cdot \mathbf{2}$ ($\delta = 2.91$, br. s) as well as a species of the (apparent) composition $\mathbf{5}_3 \cdot \mathbf{2}_2$ ($\delta = 2.95$, br. s). On addition of D_2O, lanthanum compounds precipitate out.

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4, 95529-58-1.

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[2] W. Littke, U. Drück, *Angew. Chem. 86* (1974) 557; *Angew. Chem. Int. Ed. Engl. 13* (1974) 539; W. Littke, U. Drück, *Acta Crystallogr. B35* (1979) 1905. The trisulfide **3** and the sole complex isolated, $[Ni\mathbf{3}_2 \cdot (ClO_4)_2]$—the PF_6^--salt has also been prepared by *G. J. Grant*, University of Tennessee, USA—are unstable towards X-rays.

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[4] R. Schwesinger, K. Piontek, W. Littke, O. Schweikert, H. Prinzbach, C. Krüger, Y.-H. Tsay, *Tetrahedron Lett. 1982*, 2427.

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[6] Cell data: $a = 10.040$, $b = 10.206$, $c = 18.090$ Å, $\beta = 99.17°$; $Z = 2$; $\rho_{calc} = 1.76$, $\rho_{obs} = 1.78$ g/cm^3; $P2_1$, determination of absolute configuration; $Mo_{K\alpha}$; $T = 20°C$; $\mu = 14.89$ cm^{-1}; 2706 independent structure am-

plitudes [$I > 2\sigma(I)$] together with Friedel reflections; $R = 0.066$. N–La–N angles of the diagonals 175.0–178.5°; La–N 2.734–2.831 Å (mean value 2.770 Å); intra-**2** N–N 2.772–2.976 Å (mean value 2.917 Å); inter-**2**-N–N 2.816–3.097 Å (mean value 2.976 Å); interplanar angle aziridine/basal six-membered ring 103.4–106.7°. Further details of the crystal structure investigation are available on request from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2, on quoting the depository number CSD 51209, the names of the authors, and full citation of the journal.

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$I(py)_2BF_4$, a New Reagent in Organic Synthesis: General Method for the 1,2-Iodofunctionalization of Olefins**

By *Jose Barluenga,* Jose M. González, Pedro J. Campos,* and *Gregorio Asensio*

Dedicated to Professor Günther Wilke on the occasion of his 60th birthday

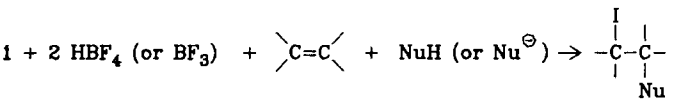
The functionalization of olefins is an important process in organic synthesis. A common strategy is the use of iodine and a silver salt as reaction promoter to allow the iodofunctionalization by subsequent addition of a nucleophile. However, only strong nucleophiles or reagents giving stable I–Nu compounds can be added in this way to olefins.[1] A different approach, suggested by *Diner* and *Lown*,[2] is the use of bis(pyridine)iodine(I) nitrate. The scope of this method is, however, severely limited by the presence in the reaction medium of pyridine and the nitrate anion, which can act as nucleophiles.

In the course of our study on the mercury(II) oxide–tetrafluoroboric acid system as promotor in the iodination of arenes,[3] we found that this system, supported on silica gel, reacts with pyridine in the presence of iodine to afford a stable white solid, **1**.[4]

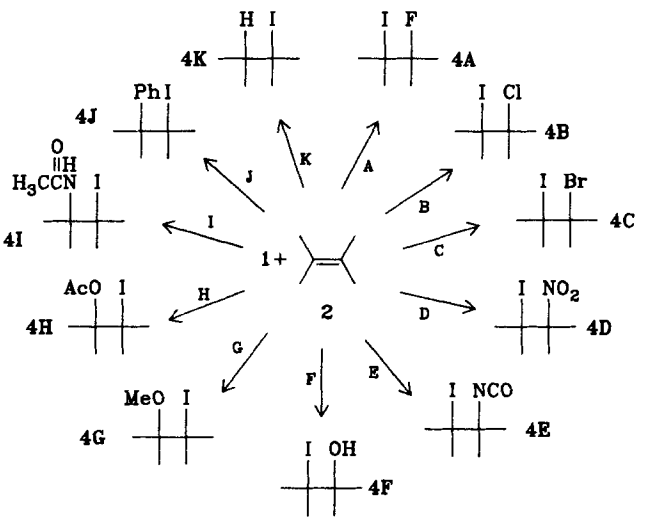
$$HgO \cdot HBF_4 \cdot \text{silica gel} + I_2 \xrightarrow[CH_2Cl_2]{\text{pyridine}} \underset{\mathbf{1}}{I(py)_2BF_4}$$

When compound **1** is allowed to react with olefins in the presence of a nucleophile and, if necessary, the stoichiometric amount of tetrafluoroboric acid or boron trifluoride to neutralize the pyridine, the corresponding 1,2-iodofunctionalized compounds **4** are obtained.

The low nucleophilicity of the $BF_4^{\ominus}$ anion allows a wide variety of charged as well as uncharged nucleophiles **3** to be added to the olefin **2**. Only in the absence of **3** does 1,2-iodofluorination take place.



The versatility of the bis(pyridine)iodine(I) tetrafluoroborate in the iodofunctionalization of olefins is illustrated in Scheme 1. Ethylene **2a**, cyclohexene **2b**,[5] and styrene **2c**[6] have been used as olefins; examples are given in Table 1. The products **4** showed elemental analyses and ^{1}H-NMR, ^{13}C-NMR, and IR spectra in good agreement with the proposed structures.



Scheme 1.

Table 1. 1,2-Iodofunctionalization of olefins **2** with $I(py)_2BF_4$ **1** and nucleophiles **3**. Olefins: ethylene **2a**, cyclohexene **2b**, styrene **2c**.

Olefin 2	Nucleophile 3	T [°C]	t [h]	Solvent for 2	Acid (in Et_2O)	Product	Yield [%] [a]
2b	**3A** $F^{\ominus}$ [b]	−30	3	CH_2Cl_2	HBF_4	**4Ab**	67
2b	**3B** $Cl^{\ominus}$ [c]	20	0.5	dioxane/H_2O (10:1)	—	**4Bb**	70
2b	**3C** $Br^{\ominus}$ [c]	20	0.5	dioxane/H_2O (10:1)	—	**4Cb**	64
2b	**3D** $NO_2^{\ominus}$ [c]	20	0.5	dioxane/H_2O (10:1)	—	**4Db**	42
2b	**3E** $OCN^{\ominus}$ [c]	20	3	dioxane/H_2O (10:1)	—	**4Eb**	51
2b	**3F** H_2O	20	0.5	dioxane/H_2O (10:1)	—	**4Fb**	76
2c	**3F** H_2O	20	0.5	tetrahydrofuran/H_2O	HBF_4	**4Fc**	48
2c	**3G** CH_3OH	0	0.5	CH_3OH	HBF_4	**4Gc**	80
2a	**3H** CH_3COOH	0	2	CH_3COOH/CH_2Cl_2	HBF_4	**4Ha**	58
2b	**3I** CH_3CN	−30	2	CH_3CN	HBF_4	**4Ib**	49
2b	**3J** benzene	20	2	benzene	HBF_4	**4Jb**	41
2b	**3K** Et_3SiH	20	1	CH_2Cl_2 [d]	HBF_4	**4Kb**	50

[a] Relative to **1**, not optimized. [b] From $BF_4^{\ominus}$. [c] As sodium or lithium salt in a mole ratio **1** : **3** = 1 : 5. [d] **1** in CH_2Cl_2 is treated with a solution of HBF_4 in Et_2O and then with a mixture of **2b** and Et_3SiH.

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Among the merits of the method it should be noted that a great variety of iodofunctionalized compounds are easily available from a single reagent, **1**, which is readily prepared from common chemicals. In this way, for instance,

the formal addition of H–I, Ph–I, and F–I to olefins is possible. The resulting 1,2-iodofunctionalized compounds can be converted into other synthetically useful compounds by transformation of the iodo functionality. The yields of compounds **4** and the reaction conditions have not yet been optimized.

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1, 15656-28-7; **2a**, 74-85-1; **2b**, 110-83-8; **2c**, 100-42-5; **3A**, 16984-48-8; **3B**, 16887-00-6; **3C**, 24959-67-9; **3D**, 14797-65-0; **3E**, 71000-82-3; **3F**, 7732-18-5; **3G**, 67-56-1; **3H**, 64-19-7; **3I**, 75-05-8; **3J**, 71-43-2; **3K**, 617-86-7; **4Ab**, 6906-08-7; **4Bb**, 33427-17-7; **4Cb**, 34701-03-6; **4Db**, 95617-18-8; **4Eb**, 89877-27-0; **4Fb**, 10039-14-2; **4Fc**, 54766-50-6; **4Gc**, 13684-98-5; **4Ha**, 627-10-1; **4Ib**, 7707-58-6; **4Jb**, 95617-19-9; **4Kb**, 626-62-0; $HgO \cdot HBF_4$, 95646-77-8; I_2, 7553-56-2; pyridine, 110-86-1.

[1] Selected examples: H. O. House: *Modern Synthetic Reactions*, W. A. Benjamin, Menlo Park, CA, 1972. A. Hassner, M. E. Lorber, C. Heathcock, *J. Org. Chem. 32* (1967) 540; E. J. Corey, N. M. Weinshenker, T. K. Schaaf, *J. Am. Chem. Soc. 91* (1969) 5675; G. L'abbé, A. Hassner, *Angew. Chem. 83* (1971) 103; *Angew. Chem. Int. Ed. Engl. 10* (1971) 98; K. Dehnicke, *ibid. 91* (1979) 527 and *18* (1979) 507, respectively.

[2] U. E. Diner, J. W. Lown, *Chem. Commun. 1970*, 333; *Can. J. Chem. 49* (1971) 403.

[3] J. Barluenga, P. J. Campos, J. M. González, G. Asensio, *J. Chem. Soc. Perkin Trans. 1 1984*, 2623.

[4] M.p. = 149–151 °C (decomp.) (recrystallized from dichloromethane). IR (Nujol): ν = 690, 760, 1610 cm^{-1} (pyridine) and 1040 cm^{-1} ($BF_4^{\ominus}$). ^1H-NMR ($CDCl_3$–CH_2Cl_2, 80 MHz): δ = 7.63 (m, 2H), 8.33 (br. t, 1H), 8.87 (br. d, 2H). ^{13}C-NMR (CH_2Cl_2, 20 MHz): δ = 127.76, 141.97, 149.27.

[5] A single stereoisomer, tentatively assigned the *trans* configuration, is formed.

[6] Only the regioisomer PhCHNu–CH_2I is formed.

Catalytic Transformations of Sesquiterpene Hydrocarbons on Alkali Metal/Aluminum Oxide

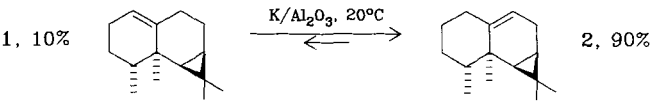
By *Roland Rienäcker** and *Jürgen Graefe*

Dedicated to Professor Günther Wilke on the occasion of his 60th birthday

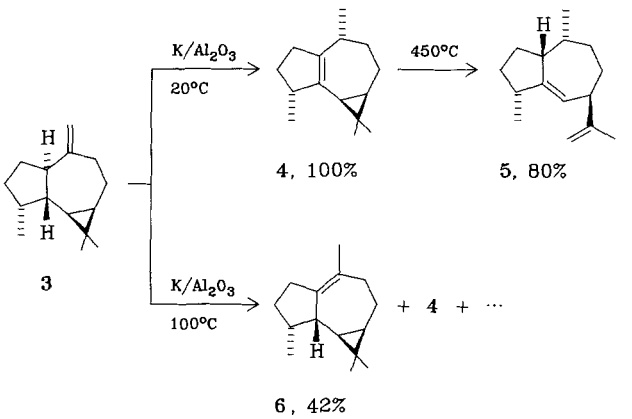
Of the variety of media used for the base-catalyzed isomerization of olefins,[1] alkali metal/aluminum oxide catalysts are especially noteworthy; according to our studies, they are able to effect new, selective transformations of cyclic sesquiterpene hydrocarbons. C=C bond shifts, dehydrogenations, and skeletal rearrangements can take place, depending on the structure of the substrate, the type of catalyst, and the reaction conditions. In some cases, compounds that were unknown up to now are formed.

Of the numerous sesquiterpene hydrocarbons studied by us, (+)-calarene **1**, (+)-aromadendrene **3**, (+)-δ-cadinene **7**, and (+)-longifolene **11** are presented here as examples of the possibilities of such catalytic transformations.

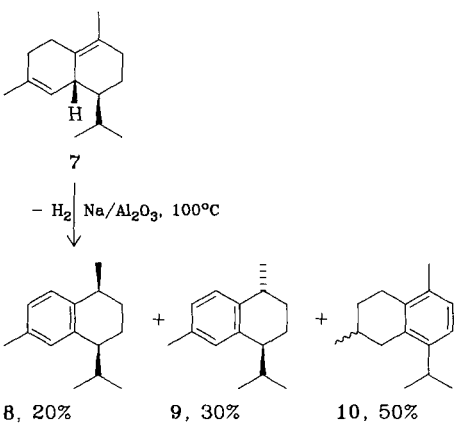
For instance, in the presence of K/Al_2O_3, **1** undergoes an extensive isomerization already at 20 °C to (–)-aristolene **2**, which is thus easily accessible for the first time.



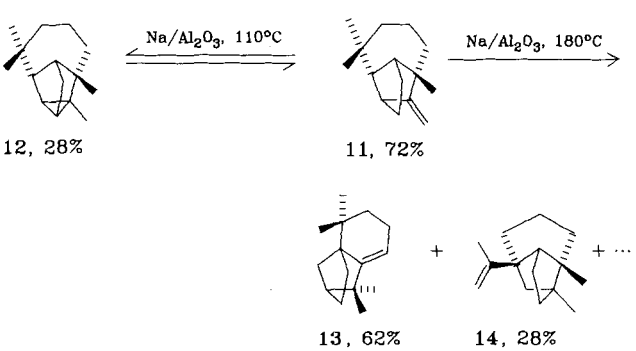
The hydrocarbon (–)-**4**, unreported up to now, is obtained quantitatively from **3** with K/Al_2O_3 at room temperature; **4** can be transformed thermally to (+)-γ-gurjunene **5**.[5] When the isomerization of **3** with K/Al_2O_3 is carried out at 100 °C, 42% (+)-ledene **6** is obtained along with **4** and other isomers.



Upon treatment of **7** with Na/Al_2O_3, the isomerization is followed by a dehydrogenation with formation of (+)-*cis*-calamenene **8**, (–)-*trans*-calamenene **9**, and the hydrocarbon (+)-**10**.



When **11** is heated with Na/Al_2O_3, an equilibrium is established below 140 °C with (+)-longicyclene **12**. At higher temperatures, a skeletal rearrangement to (–)-isolongifolene **13**,[2] (–)-alloisolongifolene **14**,[3,4] and other



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hydrocarbons takes place. Thus, e.g., a mixture containing 62% **13** and 28% **14** is obtained from **11** at 180°C.

The products were obtained in a purity of over 99% by vacuum fractional distillation on 1m-Spaltrohr® columns and identified on the basis of ^{1}H-NMR, ^{13}C-NMR, and mass spectroscopy, as well as on the basis of the physical data given in Table 1.

Table 1. Physical data of **1**—**14**.

	n_D^{20}	α_D^{20} Measured values [c]	Reported values	
1	1.5050	+ 70.9	+ 69.1	[6]
2	1.5028	− 91.7	− 90.0	[6]
3	1.4965	+ 10.9	+ 10.7	[7]
4	1.4939	− 51.2	—	
5	1.5022	+ 142.0	+ 133.8	[8]
6	1.5050	+ 64.1	+ 48.4 [a]	[9]
7	1.5096	+ 99.2	+ 86.2	[10]
8	1.5228	+ 3.7	+ 41.3 [a]	[11]
9	1.5230	− 65.1	− 96.0 [a]	[12]
10	1.5285	+ 39.2	—	
11	1.5049	+ 44.2	+ 43.1	[13]
12	1.4931	+ 27.7	+ 31.3	[14]
13	1.4992	− 124.7	− 125.0 [b]	[15]
14	1.5009	− 34.4	− 40.6 [a]	[3]

[a] Specific rotation $[\alpha]_D^{20}$. [b] Calculated for optically pure **13**. [c] Neat.

Experimental Procedure

All work was carried out under argon with oxygen- and water-free solvents and with substrates that had been distilled from $NaAlEt_4$.

In order to prepare the catalysts, basic Al_2O_3 (Alumina Woelm® B-Super I) is dried in vacuum (1 torr) at 200°C and then vigorously stirred with 2 to 10 wt.-% sodium or potassium until the mixture cools. Uniformly colored, free-flowing powders are obtained which are not pyrophoric, but which, on exposure to air or water, immediately discolor and lose their activity. Na/Al_2O_3 is bright to dark grey, K/Al_2O_3 is bright to deep blue; the color intensity markedly increases with increasing alkali-metal content.

For isomerization or dehydrogenation, 5 to 10 wt.-% catalyst is added to the sesquiterpene hydrocarbons and the suspension is vigorously stirred for several hours under the conditions given. The course of the reaction is followed to completion by gas chromatography. Subsequently, the reaction products are distilled from the catalyst in an oil-pump vacuum.

Alternatively, in the conversion of **3** to **4**, 200 mL *n*-hexane and 400 g K/Al_2O_3 (10% K) are added per mole of **3**; at the end of the reaction, the catalyst is filtered off and the residue washed twice with *n*-hexane.

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[1] Review cf. H. Pines, W. M. Stalick: *Base-Catalyzed Reactions of Hydrocarbons and Related Compounds*, Academic Press, New York 1977.
[2] In contrast to the acid-catalyzed isomerization of **11** (for a review see S. Dev, *Fortschr. Chem. Org. Naturst. 40* (1981) 49), **13** ($[\alpha]_D^{20}$ − 134.3), prepared in the presence of Na/Al_2O_3, exhibits a significantly higher enantiomeric purity. As we were able to show, enantiomerically pure **13** has a specific rotation of $[\alpha]_D^{20}$ − 159.9.
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[4] H. R. Shitole, V. S. Dalavoy, V. B. Deodhar, U. R. Nayak, K. R. Acharya, S. S. Tavale, T. N. Guru Row, V. P. Kamat, S. K. Paknikar, *Tetrahedron Lett. 1983*, 4739.
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[15] R. Ranganathan, S. Dev, *Tetrahedron 26* (1970) 621.

Torsional Isomerism in Metallocenes: Hindered Cp-Rotation in (*s-cis*-η-Butadiene)-bis(η-*tert*-butylcyclopentadienyl)zirconium**

By *Gerhard Erker,** Thomas Mühlenbernd, Reinhard Benn, Anna Rufińska, Yi-Hung Tsay,* and *Carl Krüger*

Dedicated to Professor Günther Wilke on the occasion of his 60th birthday

The cyclopentadienyl(Cp)-metal torsional barrier in metallocenes is often very small. The activation energy for rotation about the Cp—M bond, e.g. in ferrocene, has been determined reliably by various methods to be 0.9 to 1.8 ± 0.3 kcal/mol.[1] Consequently, rotation about the Cp(centroid)-metal vector in (η-cyclopentadienyl)transition-metal complexes has been regarded as unhindered in solution. This assumption, however, does not generally hold in the case of metallocenes when bulky substituents are present on the Cp ligands.[2] Substituted bent metallocenes are finding increasing application in organometallic chemistry.[3] We present here to the best of our knowledge the first evidence for hindered Cp-M rotation in solution in such molecules together with the estimated activation energy for this process.

At high temperature, the NMR spectra of (*s-cis*-η-butadiene)bis(η-*tert*-butylcyclopentadienyl)zirconium **1**[4] appear consistent with the molecule having C_{2v} molecular symmetry. Lineshape analysis of the low-temperature ^{1}H- and ^{13}C-NMR spectra reveals that this apparent simplicity of the high-temperature spectra results from two separate dynamic processes. In the 100.6-MHz ^{13}C-NMR spectrum of **1** at 188 K all the diene- and Cp-carbon atoms are nonequivalent (cf. Fig. 1, Spectrum A). On raising the temperature, pairwise coalescence of signals is observed (Spectrum B). We interpret this as resulting from equilibration of two enantiomeric Cp-rotational isomers **1** ⇄ **1′** (for a schematic representation, cf. Fig. 1). All these coalescences are consistent with a Gibbs activation energy of $\Delta G^{\neq}(233\,K) = 9.8 \pm 0.2$ kcal/mol. On increasing the temperature further, only two signals are observed for the Cp-methine carbon atoms (Spectrum C). In addition to the equilibration of the *tert*-butyl signals, the ^{1}H-NMR spectrum indicates that the terminal diene protons undergo exchange. This second dynamic process is a typical ring inversion in a metallacyclic σ^2,π skeleton (**1′** ⇄ **1″**),[5] for which a barrier $\Delta G^{\neq}(265\,K) = 13.5 \pm 0.2$ kcal/mol was estimated from the coalescences of signals in the NMR spectra. The transformation from apparent C_{2v}- via C_s-molecular symmetry to a chiral complex geometry can also be monitored in the temperature dependence of the 400-MHz ^{1}H-NMR spectra of **1**.[6]

The X-ray structure analysis of **1** shows a molecular geometry in the solid state that exhibits the characteristics of the most stable conformation found in solution at low temperature. The (*s-cis*-η^4-butadiene)zirconium moiety in **1** has a pronounced σ-character. The Zr—C1/C4 bond lengths are short. The substantially greater Zr—C2/C3 distances indicate π-interaction of the metal with the internal

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[+] NMR analysis.

[+ +] X-ray structure analysis.

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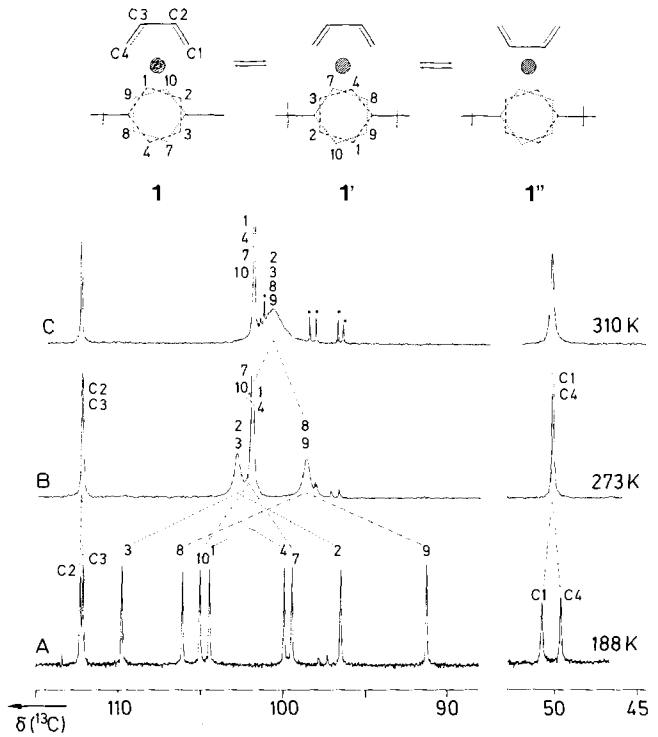


Fig. 1. Sections from the $^{13}C\{^1H\}$-NMR spectra (100.6 MHz, [D$_8$]toluene) of **1** at 188 K, 273 K, and 310 K. The signals marked with an asterisk do not belong to **1**.

diene positions.[7] Like the observed C–C bond length sequence (long/short/long) of the butadiene ligand, this is typical for diene-metallocene complexes of the group 4 transition metals.[5a,b] The most remarkable feature of the molecular structure of **1** is the arrangement of the substituted Cp-ligands; they are arranged in a staggered conformation, the *tert*-butyl substituents are located in the lateral sectors of the bent metallocene unit (Fig. 2). The C5–Cp5 and C9–Cp6 vectors are oriented at an angle of ca. 11° to the Cp planes pointing away from the metal. This, together with the small bending angle of the metallocene unit ($\theta = 122.5°$) compared to that in other Cp_2Zr complexes,[8] is probably due to steric interactions of the *tert*-butyl groups with the diene ligand.

It can be assumed that the preferred conformation of bis(*tert*-butylcyclopentadienyl)zirconium chloride **2**[9] has *trans* Cp substituents analogous to **1**. However, we found

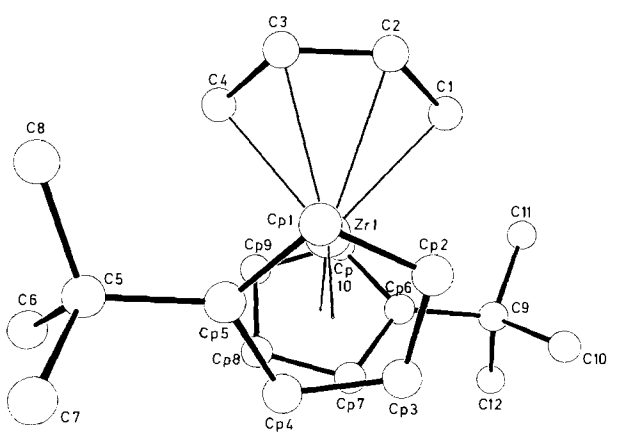


Fig. 2. Molecular structure of **1** in the crystal.

no indication of line broadening in the ^{13}C-NMR spectra of **2** down to −100°C that could be due to this rotamer (C_2 symmetry) freezing out in solution.[10] Therefore, the magnitude of the barrier to Cp-rotation in **1** appears to be determined by interaction between the diene ligand and the Cp substituents.

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1, 95464-95-2; **2**, 32876-92-9; **3**, 95464-96-3; $(\eta\text{-}C_5H_4tBu)_2HfCl_2$, 33010-55-8.

[1] K. Schlögl, *Top. Stereochem. 1* (1967) 39; a number of recent papers are cited in [2]; b) similarly small values are also found for the Cp-rotation in bent metallocenes: D. F. R. Gilson, G. Gomez, *J. Organomet. Chem. 240* (1982) 41.

[2] a) 1,1',4,4'-Tetra-*tert*-butyluranocene: $\Delta G^{\neq}_{rot}(-70°C) = 8.3$ kcal/mol; 1,1',3,3'-tetra-*tert*-butylferrocene: $\Delta G^{\neq}_{rot}(-27.5°C) = 13.1$ kcal/mol: W. D. Luke, A. Streitwieser, Jr., *J. Am. Chem. Soc. 103* (1981) 3241; b) cf. also: W. Hofmann, W. Buchner, H. Werner, *Angew. Chem. 89* (1977) 836; *Angew. Chem. Int. Ed. Engl. 16* (1977) 795; J. L. Davidson, *J. Chem. Soc. Chem. Commun. 1980*, 113.

[3] P. Renaut, G. Tainturier, B. Gautheron, *J. Organomet. Chem. 148* (1978) 35, 43; see also: P. T. Wolczanski, J. E. Bercaw, *Acc. Chem. Res. 13* (1980) 121; G. Erker, *ibid. 17* (1984) 103.

[4] **1** was prepared by reaction of **2** [3] with "butadiene-magnesium" (92% yield, m.p. 93°C, correct elemental analysis). Details of the synthesis and of the chemical properties of **1** will be reported separately. ^1H-NMR ([D$_8$]toluene, −90°C, numbering scheme as in Fig. 1): butadiene: $\delta = -0.72$ (H1a), −0.39 (H4a), 3.38 (H1s), 3.15 (H4s), 4.95 (H2), 4.68 (H3); Cp–R (H at Cp1–4, 7–10): 5.46, 5.58, 5.72, 3.84, 4.75, 5.28, 4.42, 4.50; (*t*Bu): 1.07, 1.29. ^{13}C-NMR ([D$_8$]toluene, −85°C, ^1J(CH) [Hz] in brackets); butadiene (C1–C4): $\delta = 50.8$ (130, 153), 112.32 (157), 112.15 (156), 49.6 (131, 155); Cp–R (Cp1–10): 104.5 (167), 96.5 (168), 109.8 (171), 99.9 (167), 132.8 (–), 125.9 (–), 99.5 (168), 106.1 (166), 91.3 (170), 105.1 (171); (*t*Bu): 32.5 (–), 32.2 (125); 31.5 (–), 31.9 (126). A complete assignment of the resonances was not attempted. The assignment of the signals 1–4 to one Cp ring and 7–10 to the second is based on information from the ^1H-NMR spectrum together with a 2D-^{13}C-^1H correlated spectrum. X-ray structure analysis of **1**: $P2_1/n$, $a = 18.412(3)$, $b = 9.448(2)$, $c = 23.751(3)$ Å, $\beta = 106.141(9)°$, $V = 3968.59$ Å^3, $\rho_{calc} = 1.30$ g cm^{-3}, $\mu = 5.43$ cm^{-1}, $Z = 8$. Total number of reflections 8952, observed reflections 5869, 415 refined parameters, $R = 0.0471$, $R_w = 0.0412$. Selected bond lengths and angles (mean values for both crystallographically independent molecules): Zr–C1 2.335(4), Zr–C2 2.525(8), Zr–C3 2.524(15), Zr–C4 2.332(9), C1–C2 1.425(7), C2–C3 1.385(7), C3–C4 1.423(6) Å; C1–C2–C3 126.0(6), C2–C3–C4 127.0(5), Zr–C1–C2 80.5(3), C3–C4–Zr 80.5(8)°. Folding angle of the diene-zirconium skeleton (C1, Zr, Ce/C1, C2, C3, C4) = 68°. Further details of the crystal structure analysis are available on request from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2, on quoting the depository number CSD 51 122, the names of the authors, and full citation of the journal.

[5] a) G. Erker, J. Wicher, K. Engel, C. Krüger, A.-P. Chiang, *Chem. Ber. 115* (1982) 3300, 3311; R. Benn, G. Schroth, *J. Organomet. Chem. 228* (1982) 71; b) G. Erker, K. Engel, C. Krüger, G. Müller, *Organometallics 3* (1984) 128; G. Erker, C. Krüger, G. Müller, *Adv. Organomet. Chem. 24* (1985), in press; C. Krüger, G. Müller, G. Erker, U. Dorf, K. Engel, *Organometallics 4* (1985) 215; c) see also: B. Gautheron, G. Tainturier, *J. Organomet. Chem. 262* (1984) C30.

[6] (*s-cis*-η^4-Butadiene)bis(η-*tert*-butylcyclopentadienyl)hafnium **3** behaves analogously. ^1H-NMR ([D$_8$]toluene, −95°C); butadiene: $\delta = -0.87$ (H1a), −0.54 (H4a), 3.14 (H1s), 2.92 (H4s), 5.20 (H2), 4.95 (H3); Cp–R (H at Cp1–4, 7–10): 5.23, 5.44, 5.78, 4.06, 4.62, 5.28, 4.48, 4.72, (*t*Bu): 1.12, 1.30. ^{13}C-NMR ([D$_8$]toluene, −85°C, ^1J(CH) [Hz] in brackets); butadiene (C1–C4): $\delta = 46.4$ (140), 114.66 (152), 114.19 (152), 45.7 (139); Cp–R (Cp1–10): 102.7 (165), 95.2 (168), 111.7 (168), 100.4 (166), 133.1 (–), Cp6 masked by solvent signals, 99.7 (168), 106.6 (168), 90.5 (170), 104.1 (170), (*t*Bu): 32.6 (–), 31.6 (126), 31.8 (–). The crystalline metallocene complexes **3** and **1** are isomorphic.

[7] G. Erker, K. Kropp, J. L. Atwood, W. E. Hunter, *Organometallics 2* (1983) 1555.

[8] a) E. D. Jemmis, S. Alexandratos, P. von R. Schleyer, A. Streitwieser, Jr., H. F. Schaefer, III, *J. Am. Chem. Soc. 100* (1978) 5695; regarding the problem of the bending of the substituents in π-ligands see also: R. Goddard, C. Krüger, F. Mark, R. Stansfield, X. Zhang, *Organometallics*, in press, and references cited therein, as well as [5b]; b) typical values of 128 to 135° were found for θ in the case of Cp_2ZrX_2 complexes with less

bulky ligands: J. W. Lauher, R. Hoffmann, *J. Am. Chem. Soc. 98* (1976) 1729; P. C. Wailes, R. S. P. Coutts, H. Weigold: *Organometallic Chemistry of Titanium, Zirconium, and Hafnium*, Academic Press, New York 1974, p. 122, and references cited therein.

[9] This has recently been demonstrated by an X-ray structure analysis in the case of $(\eta\text{-}C_5H_4tBu)_2TiCl_2$: R. A. Howie, G. P. McQuillan, D. W. Thompson, *J. Organomet. Chem. 268* (1984) 149; see however: J. L. Petersen, L. F. Dahl, *J. Am. Chem. Soc. 97* (1975) 6422.

[10] This is true for $(\eta\text{-}C_5H_4tBu)_2HfCl_2$.

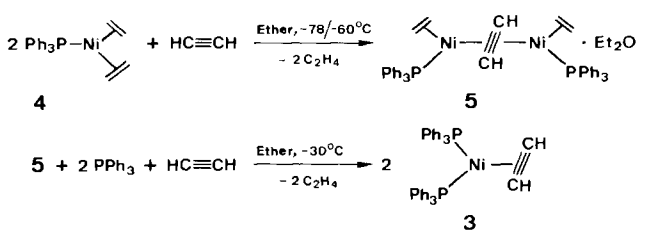
Ethynebis(triphenylphosphane)nickel(0)

By *Klaus R. Pörschke,* Yi-Hung Tsay,* and *Carl Krüger*

Dedicated to Professor Günther Wilke on the occasion of his 60th birthday

According to *Reppe* and *Schweckendiek*,[1] a contact catalyst developed from $(Ph_3P)_2Ni(CO)_2$ **1** and ethyne at 100–120°C catalyzes the cyclooligomerization of ethyne at 60–70°C/15 atm to give a benzene/styrene mixture (7 : 1); it is assumed that ethynenickel complexes are involved in the catalytic cycle. Starting from $(Ph_3P)_2Ni(C_2H_4)$ **2**, *Wilke* and *Herrmann*[2] have obtained alkyne complexes $(Ph_3P)_2Ni(C_2R_2)$ with disubstituted acetylenes but not the ethyne complex. **2** does not react with ethyne in the cold; above −10°C, polyacetylene is formed.[2a] We have now succeeded in preparing via a modified reaction path the first ethyne complex of nickel(0)[3] **3** that is stable at room temperature.

When yellow **4**[4] is allowed to react with ethyne in ether at −78/−60°C, partial replacement of ethene occurs and a red-brown solution of the dinuclear complex **5**[5] is formed. This reacts at −30°C with further ethyne and a stoichiometric amount of triphenylphosphane to give **3**.



3 (yield 80%) crystallizes as yellow needles[6] which are stable towards air at room temperature (m.p. ca. 160°C, decomp.). In solution (tetrahydrofuran, toluene, CH_3CN) it slowly decomposes at 0°C with the formation of a brown flocculent precipitate ("niprene"). Reaction of **3** with $P(OPh)_3$ leads to liberation of ethyne; reaction with CO affords **1**. The CO-free complexes **2** and **3** catalyze the trimerization of ethyne without pretreatment ("Kontaktentwicklung"[11]) at 40°C/10 atm ethyne to give almost pure benzene (2% styrene). Like **3**, the complexes $(Ph_3P)_2Ni(C_2(H)CH_3)$ **6** (80%, yellow cubes) and $(Ph_3P)_2Ni(C_2(H)Ph)$ **7** (85%, fine rods) can be prepared in analytically pure form.

The ethyne ligand in **3** was characterized by an intense IR band ($\nu_{C\equiv C}$ = 1630 cm^{-1}) and by its ^{1}H- and ^{13}C-resonances (δ_H = 6.41 (m); δ_C = 122.1 (m)).[7] The coupling between the acetylenic H- and C-atoms is for **3** (J_{CH} = 212 Hz) less reduced compared to free ethyne (J_{CH} = 249 Hz) than for the corresponding trialkylphosphane complexes (J_{CH} = 201 Hz[3]). The ^{31}P-resonance of **3** (δ = 39.0) is shifted downfield considerably compared to that of **1** (δ_P = 32.6) and **2** (δ_P = 33.3; free PPh_3: δ_P = −5.5).

The X-ray structure analysis of **3**[8] revealed a structure comparable to the ethylene complex **2**[9] with trigonal-planar coordinated nickel atom (Fig. 1). The Ni–C bonds of **3** (1.873(3) and 1.882(3) Å) both lie below the P,P,Ni plane (angle to plane about 5.2°); the ethyne H-atoms even lie below the Ni,C,C plane and are turned away from the central atom (H–C–C 148(±2)°; H–C–C–H torsion angle 1°). The C–C distance of 1.239(4) Å in the ethyne ligand[10] is relatively short and lies between that in ethynecopper (1.19 Å[11]) and ethynemolybdenum or ethynetungsten complexes (1.29 Å[12, 13]). The propeller-shaped triphenylphosphane groups (Ni–P 2.153(1) and 2.166(1) Å) are oriented so as to minimize their steric hindrance.

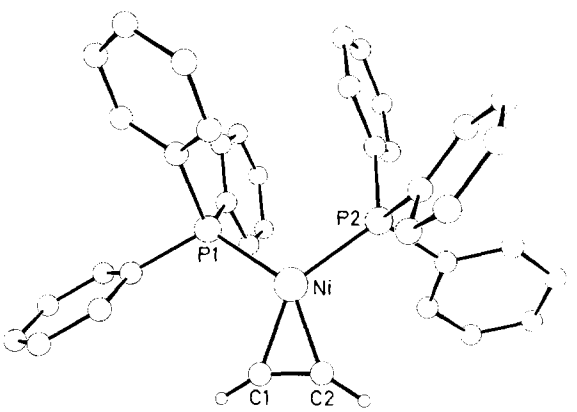


Fig. 1. Molecular structure of **3** in the crystal.

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CAS Registry numbers:
1, 13007-90-4; **2**, 23777-40-4; **3**, 95465-19-3; **4**, 33042-32-9; **5**, 95465-20-6; **6**, 95482-73-8; **7**, 95482-74-9; benzene, 71-43-2; ethyne, 74-86-2.

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Kaiser-Wilhelm-Platz 1, D-4330 Mülheim a. d. Ruhr 1 (FRG)

[+] X-Ray structure analysis.

[1] W. Reppe, W. J. Schweckendiek, *Justus Liebigs Ann. Chem. 560* (1948) 104.

[2] a) G. Herrmann, Dissertation, Technische Hochschule Aachen 1963; b) G. Wilke, G. Herrmann, *Angew. Chem. 74* (1962) 693; *Angew. Chem. Int. Ed. Engl. 1* (1962) 549.

[3] See also K. R. Pörschke, R. Mynott, K. Angermund, C. Krüger, *Z. Naturforsch. B 40* (1985) 199.

[4] a) P. W. Jolly, I. Tkatchenko, G. Wilke, *Angew. Chem. 83* (1971) 328; *Angew. Chem. Int. Ed. Engl. 10* (1971) 328; b) B. Büssemeier, Dissertation, Universität Bochum 1973.

[5] K. R. Pörschke, unpublished. **5** is isolable in the form of yellow, temperature-sensitive needles. These and other bridged ethynenickel complexes will be reported on in more detail in a later publication.

[6] Procedure for **3** (with exclusion of oxygen and water): Ethyne (ca. 150 mL) was allowed to diffuse, without stirring, into a clear yellow solution of **4** [4] (1.88 g, 5.0 mmol) in ether (50 mL) at −60°C. The resulting reddish-brown solution was then treated with a solution of Ph_3P (1.31 g, 5.0 mmol) in ether (30 mL). On raising the temperature to −30°C, yellow crystals began to form. These were separated from the mother-liquor, washed twice with cold ether, and dried in an oil-pump vacuum. Yield of **3** 2.44 g (80%) (correct elemental analyses). (We thank *Petra Feldmann* for assistance with the preparative work.)

[7] IR (KBr): ν = 1630 cm^{-1} (HC≡CH); ^{1}H-NMR ([D$_8$]THF, relative to TMS, −40°C): δ = 7.35–7.10 (m, PPh_3), 6.41 (m, C_2H_2); ^{13}C-NMR ([D$_8$]THF, relative to TMS, −40°C): δ = 135.67, 134.50, 129.52, 128.58 (PPh_3), 122.08 (m, J(CH) = 212 Hz, J(PC) = ±32.8 Hz, J(P'C) = ∓8.7 Hz, C_2H_2); ^{31}P-NMR ([D$_8$]THF, relative to 85% H_3PO_4, −40°C): δ = 39.0 (PPh_3), J(PP) = 25.0 Hz (from analysis of ^{13}C-NMR spectra).

[8] Unit cell: a = 10.0640(9), b = 33.803(4), c = 10.5110(6) Å, β = 117.865(6)°, V = 3161.22 Å^3, ρ_c = 1.28 g cm^{-3}, μ = 7.39 cm^{-1}, Z = 4, $P2_1/c$, 8457 mea-

sured reflections, weighted to 7884, 5624 observed reflections, 498 refined parameters, $R = 0.0423$, $R_w = 0.0407$. Further details of the crystal structure analysis are available on request from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2, on quoting the depository number CSD 51 143, the names of the authors, and full citation of the journal.

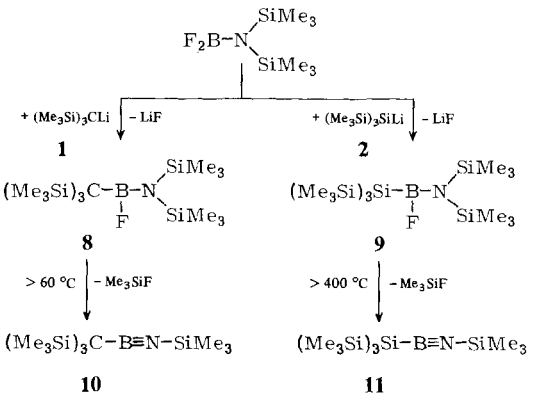
[9] W. Dreissig, H. Dietrich, *Acta Crystallogr. B37* (1981) 931, and references cited therein.

[10] In $(\eta^5\text{-}C_5H_5Ni)_2(C_2H_2)$, in which ethyne as a 4e-ligand bridges two metal centers, the C–C distance is 1.34 Å; Y. Wang, P. Coppens, *Inorg. Chem. 15* (1976) 1122.

[11] J. S. Thompson, J. F. Whitney, *J. Am. Chem. Soc. 105* (1983) 5488.

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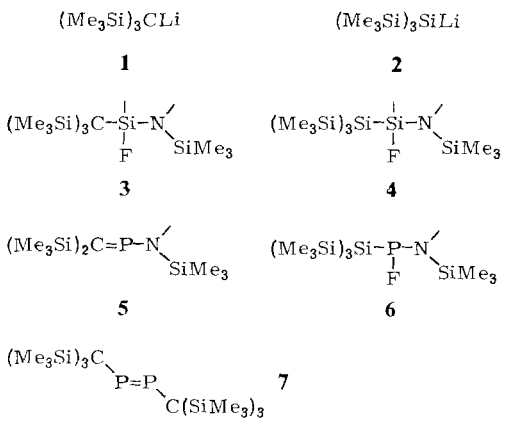
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Simple Synthesis of Stable Iminoboranes**

By *Martin Haase* and *Uwe Klingebiel**

Tris(trimethylsilyl)methyllithium **1** and tris(trimethylsilyl)silyllithium **2** react with fluoro(trimethylsilylamino)silanes to give thermally stable silicon compounds of the type **3** and **4**, respectively.[1,2] Reaction of **1** and **2** with fluoro(trimethylsilylamino)phosphanes furnished the phos-



phaethenes **5** and stable silylated fluorophoshanes **6**, respectively.[2] The reaction of **2** with $(Me_3Si)_3C-PCl_2$, on the other hand, led to formation of the diphosphene **7**[3] via cleavage of $(Me_3Si)_3SiCl$.

We have now examined the reaction of **1** and **2** with difluorobis(trimethylsilyl)aminoborane. In tetrahydrofuran (THF), cleavage of LiF takes place in an exothermic reaction with formation of the substitution products **8** and **9**, respectively.[4] Compound **8** [$\delta(^{19}F) = 52$] steadily loses Me_3SiF on attempted distillation above ca. 60°C and could not be obtained in pure form; from **8**, the iminoborane **10** is obtained.[5] Compound **9** is stable up to 400°C and only thereafter loses Me_3SiF, with formation of the iminoborane **11**.[6]

Trimethylsilylimino[tris(trimethylsilyl)methyl]borane **10** and trimethylsilylimino[tris(trimethylsilyl)silyl]borane **11** are thermally unexpectedly stable iminoboranes;[7] e.g., no decomposition is observed up to 300°C during gas-chromatographic analysis. To our knowledge **10** and **11** are the first iminoboranes that can be stored for months at room temperature. Chemically, **10** and **11** are remarkably inert; e.g., **10** does not react with $AlCl_3$, $SiCl_4$, benzaldehyde, or methacrolein.

The structures of the substitution product **9** and of the iminoboranes **10** and **11** were elucidated by their NMR, IR, and mass spectra and by C,H elemental analyses. In the ^{29}Si-NMR spectrum of **10**, a coupling – $^1J_{SiN} = 15$ Hz – is observed, thus indicating the polar character of the iminoboranes.

Experimental:

A solution of **1** or **2** (0.05 mol) in THF (100 mL) was treated at room temperature with a solution of $F_2BN(SiMe_3)_2$ (0.05 mol) in THF (50 mL). In each case, the mixture was then heated under reflux for 1 h and the solution separated from LiF by filtration. **9** was recovered in pure form by distillation. **8** steadily loses Me_3SiF with formation of **10** on distillation at 60°C/0.01 torr. For recovery of **11** from **9** by cleavage of Me_3SiF, **9** was passed through a 30-cm furnace heated at 400°C at 6 torr. **10** and **11** were purified by distillation.

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1, 28830-22-0; **2**, 4110-02-5; **8**, 95464-57-6; **9**, 95464-54-3; **10**, 95464-55-4; **11**, 95464-56-5; $F_2BN(SiMe_3)_2$, 2251-46-9.

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[**] This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.

[1] M. Haase, U. Klingebiel, *Z. Anorg. Allg. Chem.*, in press.

[2] M. Haase, U. Klingebiel, L. Skoda, *Z. Naturforsch. B39* (1984) 1500.

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[4] **9**: colorless solid; yield: 11.1 g (51%); m.p. 41°C; MS (70 eV): *m/z* 422 (3) ($M^+ - CH_3$), 345 (100) ($M^+ - Me_3SiF$); ^{1}H-NMR (CH_2Cl_2, TMS int.): $\delta = 0.25$ ($NSiMe_3$, $J(HF) = 1.05$ Hz), 0.27 ($SiSiMe_3$, $J(HF) = 0.5$ Hz); ^{11}B-NMR ($CH_2Cl_2/CDCl_3$, $BF_3 \cdot OEt_2$ ext.): $\delta = 44.6$; ^{13}C-NMR ($CDCl_3$, TMS int.): $\delta = 3.18$ ($SiSiC_3$, $J(CF) = 1.04$ Hz), 4.38 ($NSiC_3$, $J(CF) = 2.1$ Hz); ^{19}F-NMR (CH_2Cl_2, C_6F_6 int.): $\delta = 156.3$; ^{29}Si-NMR ($CDCl_3$, TMS int.): $\delta = -121.5$ (SiBF), -10.22 (Si_3, $J(SiF) = 8.52$ Hz), 4.69 (NSi_2, $J(SiF) = 15.2$ Hz).

[5] **10**: colorless liquid; yield: 7.4 g (45%); b.p. 47°C/0.01 torr; m.p. 15°C; FI-MS: *m/z* 329 (M^+); IR (pure, [cm^{-1}]): 1940 (^{10}B≡N), 1885 (^{11}B≡N); ^{1}H-NMR (CH_2Cl_2, TMS int.): $\delta = 0.10$ ($NSiMe_3$), 0.23 ($CSiMe_3$); ^{11}B-NMR (CH_2Cl_2/C_6D_6, $BF_3 \cdot OEt_2$ ext.): $\delta = 21.0$; ^{13}C-NMR (CH_2Cl_2/C_6D_6, TMS int.): $\delta = 2.55$ ($NSiC_3$), 3.15 ($CSiC_3$); ^{14}N-NMR ($CDCl_3$, TMS, $MeNO_2$ ext.): $\delta = -262.4$; ^{29}Si-NMR (CH_2Cl_2/C_6D_6, TMS int.): $\delta = -12.21$ (NSi, $J(SiN) = 15$ Hz), 0.12 (CSi_3).

[6] **11**: colorless liquid; yield: 9.8 g (57%); b.p. 50°C/0.01 torr; FI-MS: *m/z* 345 (M^+); IR (pure, [cm^{-1}]): 1925 (^{10}B≡N), 1875 (^{11}B≡N); ^{1}H-NMR (CH_2Cl_2, TMS int.): $\delta = 0.08$ ($NSiMe_3$), 0.24 ($SiSiMe_3$); ^{11}B-NMR (CH_2Cl_2/C_6D_6, $BF_3 \cdot OEt_2$ ext.): $\delta = 21.9$; ^{13}C-NMR ($CDCl_3$, TMS int.): $\delta = 1.82$ ($SiSiC_3$), 2.32 ($NSiC_3$); ^{14}N-NMR ($CDCl_3$, TMS, $MeNO_2$ ext.): $\delta = -218.3$; ^{29}Si-NMR ($CDCl_3$, TMS int.): $\delta = -143.5$ (BSi), -11.1 (NSi), -9.46 ($SiSi_3$, $J(SiSi) = 57.4$ Hz).

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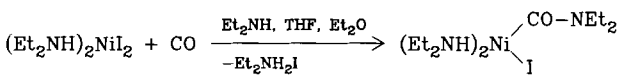
The First Isolated Carbonylation-Active σ-Carbamoylnickel Complex

By *Heinz Hoberg** and *F. Javier Fañanás*

Dedicated to Professor Günther Wilke on the occasion of his 60th birthday

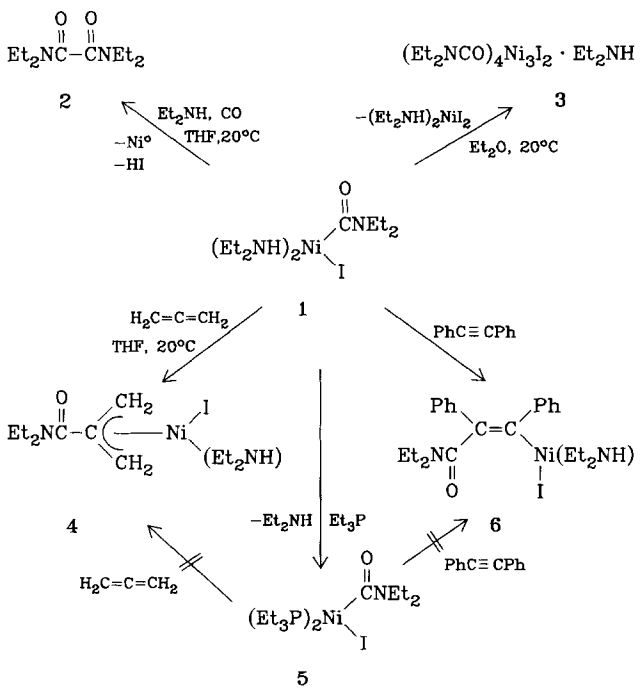
Recently, we introduced a novel method for CC bond formation between CO and unsaturated substrates; it occurs under basic conditions, e.g., in the presence of secondary amines, with nickel(II) halides.[1] As intermediates, we postulated σ-carbamoylnickel complexes,[2] which, however, it has not yet been possible to isolate.

We have now succeeded in preparing the first reactive compound of this class of substances, the σ-carbamoylnickel iodide **1**. The compound, stable as a solid, is suitable for a variety of CC bond formations.



1

When a suspension of $(Et_2NH)_2NiI_2$ in Et_2NH/tetrahydrofuran (THF)/Et_2O (2/1/1) is treated with *one* mole equivalent CO (1 bar) at 20°C, the nickel salt dissolves, accompanied by a color change from green to dark red, and the ammonium salt Et_2NH_2I precipitates out almost quantitatively. The analytically pure σ-complex **1** can be isolated in 92% yield from the filtrate. The brown, microcrystalline solid **1** [m.p. = 82°C (decomp.)] exhibits characteristic bands in the IR spectrum (KBr) at 1480 [ν(C=O)] and 3120 cm^{-1} [ν(N−H)]. The mass spectrum contains peaks only for the ion fragments *m/z* 73 (Et_2NH) and 200 ($Et_2NCO-CONEt_2$, **2**); **2** is presumably formed by coupling of two Et_2NCO moieties. The carbamoyl complex **1** is diamagnetic, indicating a square-planar coordination in the *trans* configuration.



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The complex **1** is unstable in solution (Et_2O) in the absence of Et_2NH and already disproportionates at 20°C into $(Et_2NH)NiI_2$ and the carbamoylnickel cluster **3**,[3] which is inactive for CC bond formation. The superb carbonylating activity of **1** is evident upon treatment with additional CO (1 bar) and Et_2NH in THF. Already at 20°C, the oxalic acid derivative **2**[1a,2a] is formed in 82% yield via intramolecular CC bond formation in a bis(carbamoyl)nickel complex which has not yet been isolated.

The ability of the Ni−C σ-bond in **1** to undergo addition to multiple bond systems is also very pronounced already at 20°C. Thus, upon addition of allene to a solution of **1** in THF, the η^3-allyl complex **4** [95%, m.p. = 82°C (decomp.); IR (KBr): ν = 1635 (C=O), 3130 cm^{-1} (N−H)] is formed via insertion. **4** can be protonated to give *N,N*-diethylmethacrylamide (67%) and, after addition of Et_2NH and CO (1 bar), yields the aminoamide $Et_2NCO-C(=CH_2)-CH_2NEt_2$ (69%), which is also obtained by the direct reaction of NiI_2 with allene, Et_2NH, and more than two mole equivalents of CO.[4]

1 reacts with diphenylacetylene via 1,2-addition to form the ocher-colored vinyl complex **6** [75%; m.p. = 102°C (decomp.); IR (KBr): ν = 1560 (C=O), 3160 cm^{-1} (N−H)]. **6** affords *cis-N,N*-diethyl-2-phenylcinnamamide (62%) upon protonolysis and the *N,N,N',N'*-tetraethyldiphenylmaleamide (68%)[5] after addition of Et_2NH with CO (1 bar, 20°C).

1 reacts quickly with a monodentate phosphane, such as Et_3P, via ligand exchange to form the inactive carbamoylnickel complex **5** (96%).[3]

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1, 95532-36-8; **2**, 14288-05-2; **4**, 95532-37-9; **6**, 95532-38-0; $(Et_2NH)_2NiI_2$, 14896-98-1; $Et_2NCO-C(=CH_2)-CH_2NEt_2$, 94123-17-8; NiI_2, 13462-90-3; *N,N*-diethylmethacrylamide, 5441-99-6; *cis-N,N*-diethyl-2-phenylcinnamamide, 78956-17-9; *N,N,N',N'*-tetraethyldiphenylmaleamide, 95503-08-5; allene, 463-49-0; diphenylacetylene, 501-65-5.

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[2] a) H. Hoberg, F. J. Fañanás, H. J. Riegel, *J. Organomet. Chem. 254* (1983) 267; b) H. J. Riegel, H. Hoberg, *ibid. 260* (1984) 121.
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[4] F. J. Fañanás, H. Hoberg, *J. Organomet. Chem. 275* (1984) 249.
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CC Bond Formation of Alkenes with Isocyanates on Ni^0 Complexes—a New Synthesis of Acrylamides

By *Heinz Hoberg,** *Klaus Sümmermann*, and *Armin Milchereit*

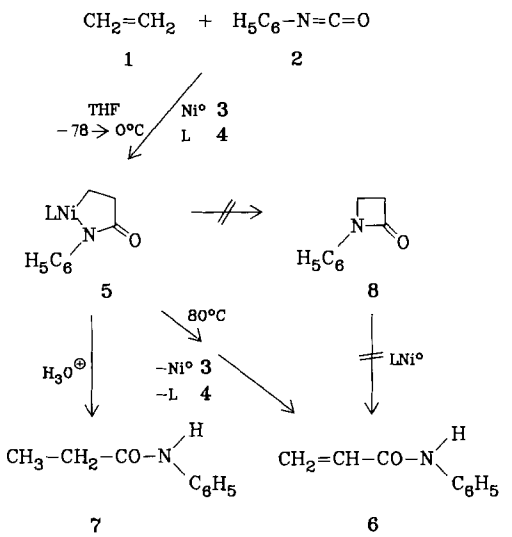
Dedicated to Professor Günther Wilke on the occasion of his 60th birthday

Acrylic acid derivatives are prepared by Ni-catalyzed reaction of ethyne with carbon monoxide and water, alcohols, or amines.[1] Reactive alkenes, such as enamines, can also react with isocyanates, the double bond being retained.[2] We report here the synthesis of acrylanilide from ethene and phenyl isocyanate on Ni(0) complexes.

Isocyanates react with multiple bond systems such as C≡C,[3] C=C,[4] C=N,[5] and C=O[6] on nickel(0) com-

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plexes via 1 : 1-coupling to give five-membered nickelacycles, which are intermediates in catalytic cycles.[7] The reaction of ethene **1** with phenyl isocyanate **2** on Ni^0 complexes **3**,[8] in the presence of basic, sterically demanding monodentate ligands, such as (*cyclo*-$C_6H_{11})_3P$ **4**, leads to CC bond formation. When **2**, **3**, and **4** (mole ratio 5 : 1 : 1) are mixed in tetrahydrofuran (THF) at −78 °C in an autoclave in the presence of **1** (1 bar) and warmed to 0 °C over 20 h, then subsequently heated to 80 °C for 2 h, the acrylanilide **6** can be isolated in 90% yield (based on **3**) after hydrolytic workup.



The acrylanilide **6** is released already upon heating, and not only upon hydrolysis, thereby providing the basis for a catalytic reaction. The IR spectrum of the heated reaction solution already shows the typical bands of **6**, and, after removal of the volatile components, sublimation of the viscous reaction product at 60 °C and 10^{-6} bar also affords **6** (45%). **6** is presumably formed via an azanickelacyclopentanone, **5**,[9] which can be precipitated in 92% yield by the addition of *n*-pentane to the cold (−10 °C) reaction solution before it is heated to 80 °C.[10] As expected, the hydrolysis of **5** gives propionanilide **7** (83%).

We propose, therefore, the following reaction pathway for the formation of **6**: first, at low temperature, **1** couples with **2** on LNi^0 to form **5**. Upon heating, β-H cleavage and reductive elimination occur to give **6**. A route via the β-lactam **8** (**5**→**8**→**6**) can be ruled out, since independently synthesized **8** does not isomerize to **6** in the presence of LNi^0.

The formal addition of a vinylic C–H bond of ethene to the CN double bond of the isocyanate is the first metal-induced synthesis of an acrylic acid derivative from a non-activated alkene and an isocyanate.

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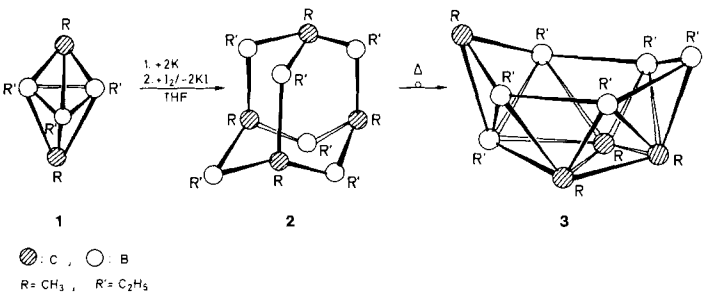
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[5] H. Hoberg, K. Sümmermann, *J. Organomet. Chem. 253* (1983) 383.
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[7] H. Hoberg, K. Sümmermann, *Z. Naturforsch. B39* (1984) 1032.
[8] Ni^0: e.g., (cdt)Ni where cdt = 1,5,9-cyclododecatriene or $(cod)_2Ni$ where cod = 1,5-cyclooctadiene.
[9] Metallacycles of type **5** are also available via oxidative addition of acrylamides on LNi^0: T. Yamamoto, K. Igarashi, S. Komiya, A. Yamamoto, *J. Am. Chem. Soc. 102* (1980) 7448.
[10] A correct elemental analysis (C, H, N, Ni, P) was obtained: m.p. = 170 °C (decomp.); IR (KBr): ν = 1510 cm^{-1} (C=O); MS: no molecular peak, only fragment ions.

Dimerization of a C_2B_3-*closo*-Carbaborane(5) to the C_4B_6-Adamantane and its 2z/3z Valence Isomerization to the C_4B_6-*nido*-Carbaborane(10)**

By *Roland Köster,* Günter Seidel,* and *Bernd Wrackmeyer*

Dedicated to Professor Günther Wilke on the occasion of his 60th birthday

Recently, we reported that pentaethyl-1,5-dicarba-*closo*-pentaborane(5) is dimerized in tetrahydrofuran (THF) by potassium metal and iodine to give decaethyltetracarbadecaborane(10).[1] Under the same conditions, we have now obtained **2**,[4a,5] which is also a crystalline dimer (MS),[3] from 2,3,4-triethyl-1,5-dimethyl-1,5-dicarba-*closo*-pentaborane(5) **1**;[2] **2**, however, undergoes autooxidation at room temperature. In the ^{11}B-NMR spectrum, **2** shows only one signal ($\delta = +65$) and is therefore not a C_4B_6-carbaborane,[1] but rather an organoborane with a C_4B_6-adamantane skeleton.[6,7] The X-ray structure analysis[8] confirms this and shows that, within the standard deviations, essentially all interatomic distances and bond angles of the C_4B_6 skeleton of **2** are in accord with those of the skeleton of the known $H_4C_4B_6(CH_3)_6$-adamantane.[9] Only the CC distances in the C_4B_6 skeleton of **2** are markedly longer by ≈0.07 Å.



With metallic potassium, a different type of product is slowly formed from **1** than from pentaethyl-C_2B_3-carbaborane(5). Upon treatment of **1** with potassium in a mole ratio of 1 : 1, the signal ($\delta = +13.5$)[6] of **1** vanishes completely in the ^{11}B-NMR spectrum of the diamagnetic solution. In addition to the resonances of small amounts of dicarba-*nido*-pentaborate(2−) 1^{2-}[1] ($\delta = -10, -24, -37$), an intense, broad signal ($\delta = +6.5$, $h_{1/2} \approx 900$ Hz) is observed. The oxidation of the equimolar K-**1** solution with iodine at 20 °C occurs rapidly with formation of **2**;[4a] **1** reacts with cesium in THF markedly faster than with potassium. Up to two moles of cesium are consumed per

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[**] Boron compounds, Part 65. – Part 64: [1].

mole of **1**. **2** is obtained from the equimolar Cs-**1** solution with iodine; however, **1** is recovered from the 2Cs-**1** solution with iodine. The degree of metalation of **1** thus plays an important part in the C_2B_3 dimerization. **2** consumes potassium up to a mole ratio $\approx 1:2$ in THF at 0°C. Pure **2** can be recovered from the yellow-brown solution ($\delta^{11}B = +5.1$, $h_{1/2} \approx 1600$ Hz) with iodine at 0°C. From **1**, we have thus far only obtained a peralkylated C_4B_6-adamantane.[4b]

When **2** is heated in solution (e.g., mesitylene) or as a solid to ≈160°C, the isomer **3**[4c] with a C_4B_6-carbaborane structure[1] is obtained rapidly and quantitatively. The organoborane/carbaborane isomerization can be followed well by ^{11}B-NMR spectroscopy (cf. Fig. 1). **2**[10] thus differs clearly from the thermally highly stable $H_4C_4B_6(CH_3)_6$-adamantane.[7]

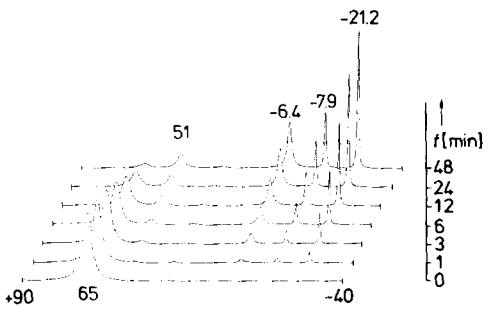


Fig. 1. ^{11}B-NMR spectra (96.3 MHz, [D_8]toluene, 25°C) [12] of the irreversible 2z/3z valence isomerization of **2** to **3**; recorded, in each case, after heating at ≈80°C.

The new carbaborane **3** has a dynamic structure. For the three ^{11}B-NMR high-field resonances of **3**,[11] an average signal ($\delta = -7.6$) is found above 100°C, while the ^{11}B-NMR signal at higher frequency ($\delta = +51$) becomes very broad.

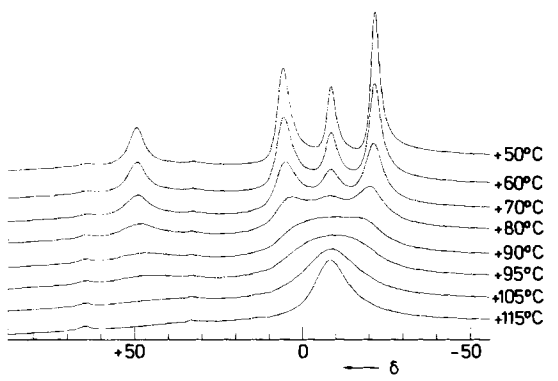


Fig. 2. Temperature-dependent ^{11}B-NMR spectra (64.21 MHz) of **3** in [D_8]toluene between 50 and 115°C.

The ^{13}C-NMR signals of the $CH_3(C)$ and $CH_3(CH_2B)$ groups are also broadened already at ≈20°C.[11] On the basis of the ^{11}B- and ^{13}C-NMR data, we suggest the same *nido*-C_4B_6 structure[13] for **3** as for the decaethyl derivative.[1]

In the dimerization of an equimolar mixture of 2,3,4-triethyl-1,5-dimethyl- and pentaethyl-1,5-dicarba-*closo*-pentaborane(5) using the potassium/iodine procedure, three C_4B_6-carbaboranes are obtained, which are separable by gas chromatography:[14] MS:[3] **3** (M^+, 348); $(H_3C)_2(H_5C_2)_2C_4B_6(C_2H_5)_6$ (376); $(H_5C_2)_4C_4B_6(C_2H_5)_6$ (404).[1] In the gas chromatographic separation,[14] owing to thermal equilibrium of the four skeletal C atoms, only one "mixed" dimer appears. An alkyl-methanetriyl exchange on the boron atoms can be ruled out by the results of the mixed dimerization.

3, like the decaethyl derivative,[1] is stable to ≈300°C. In contrast to **2**, **3** does not react at ≈20°C with oxygen. **3** is decomposed at ≈80°C by ethanol to ethyl-ethoxy boranes ($\delta^{11}B = 53.7, 31.1$). At 20°C in THF, **3** reacts with potassium metal; with cesium, it reacts markedly faster ($\delta^{11}B = -15.2$, $h_{1/2} \approx 100$ Hz). With iodine, **3** is quantitatively recovered from the yellowish brown solutions.

The formation of **3** from **2** is the first 2z/3z valence isomerization of an organoborane with $CN_B = 3$ to a carbaborane with $CN_B \geq 4$ to be followed by NMR spectroscopy (cf. Fig. 1). Apparently, the tendency to form carbaboranes depends, even for different alkyl substituents on the boron atoms, on the C substituents of the C_4B_6 skeleton. Thus, experimental evidence[15] is now available for the first time for the competition between classical and nonclassical structures in carbon-rich carbaboranes of the type $C_4B_nR_{n+4}$.

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[2] R. Köster, G. W. Rotermund, *Tetrahedron Lett. 1964*, 1667.
[3] D. Henneberg, Max-Planck-Institut für Kohlenforschung, Mülheim a. d. Ruhr 1984.—The mass spectra of **2** and **3** are identical: *m/z* 348 (B_6, 100%): **2** could only be introduced into the ion source at ≈60°C due to its low vapor pressure.
[4] a) **2**: 1.95 g (11.2 mmol) **1** in 15 mL THF is stirred with 0.77 g (19.7 mmol) potassium at ≈20°C. After 4 d, the dark reddish brown solution is separated from unreacted potassium (0.32 g, 8.2 mmol) and filtered; a dark THF solution is obtained [$\delta^{11}B$: +6.4 (br.); small: −10.2, −23.9, −37.2].—1.36 g (5.4 mmol) iodine in 10 mL THF is added in 30 min to 20 mL THF solution (≈10.7 mmol K) (discoloration). After 2 h stirring at 20°C, the solution is filtered off from 1.68 g KI, the THF evaporated (14 torr), and the residue recrystallized from $(C_2H_5)_2O$ (−20 to −78°C). After washing with cold $(C_2H_5)_2O$ and drying in vacuum, 0.51 g (27%), ≈99 percent (GC) **2** is obtained: m.p. = 285—286°C. (b) The compound $(H_5C_2)_4C_4B_6(C_3H_7)_6$ (MS [3]: *m/z* 488) with C_4B_6-carbaborane structure (^{11}B-NMR) is obtained, in analogy to the pentaethyl C_2B_3 compound [1], from 1,5-diethyl-2,3,4-tripropyl-1,5-dicarba-*closo*-pentaborane(5) [6] with potassium/iodine in THF. c) **3** from solid **2**: **2** is heated ≈10 min to ≈160°C (partial sublimation). The initially yellow compound affords colorless **3** upon cooling; m.p. = 285—286°C.—**3** from **2** in solution: **2** is heated for 10 min in mesitylene to 160°C; the solvent is removed in vacuum and **3** is obtained (cf. Fig. 1).
[5] The elemental analyses of **2** and **3** correspond to the molecular formula $C_{20}H_{42}B_6$ (cf. [3]).
[6] R. Köster, H.-J. Horstschäfer, P. Binger, P. K. Mattschei, *Justus Liebigs Ann. Chem. 1975*, 1339.—2,4,6,8,9,10-Hexaethyl-2,4,6,8,9,10-hexaboraadamantane: m.p. = 51°C; $\delta^{11}B = +67$.
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[8] C. Krüger, Max-Planck-Institut für Kohlenforschung, Mülheim a. d. Ruhr 1984. For **2**, the following values were found for the C_4B_6 skeleton: CC 2.729(4)—2.748(4) Å; CB 1.575(5)—1.586(4) Å.
[9] I. Rayment, H. M. M. Shearer, *J. Chem. Soc. Dalton Trans. 1977*, 136. The following values were found for the C_4B_6 skeleton: CC 2.660(5)—2.676(5) Å and CB 1.557(8)—1.571(5) Å.
[10] DSC measurements showed that, in the solid phase at 49.3°C, **2** is initially transformed endothermally (−19 kJ/mol) and reversibly, and that the compound is then converted at ≈120°C into **3** exothermally (+14.9 kJ/mol) and irreversibly. In solution, this isomerization of **2** to **3** can already be observed at ≥40°C.—DSC (*D*ifferential *S*canning *C*alorimetry) measurements by *W. R. Scheidt*, Max-Planck-Institut für Kohlenforschung, Mülheim a. d. Ruhr 1984.
[11] NMR data of **2** and **3**: **2**: ^1H-NMR (400 MHz, $CDCl_3$) [12]: $\delta^1H = 1.54$ (s, 12H); 0.95 (q, 12H); 0.62 (t, 18H).—^{11}B-NMR (32.1 MHz, $CHCl_3$): $\delta^{11}B = 65.0$.—^{13}C-NMR (50.3 MHz, [D_8]toluene): $\delta^{13}C = 75.1$ (s); 16.5

(q, CCH_3); 11.7 (t, BCH_2); 6.2 (q, BCH_2CH_3). **3**: ^{1}H-NMR (200 MHz, [D$_8$]toluene, −40°C) [12]: In the range of $\delta^1H = 1.2-0.7$ are several overlapping groups of signals (5 singlets?), which were not assigned; at −80°C, signal broadening.—^{11}B-NMR (64.2 MHz, [D$_8$]toluene): $\delta^{11}B = +51, +6.4, -7.9, -21.2$ in the ratio 1:2:1:2.—^{13}C-NMR (50.3 MHz, [D$_8$]toluene, −50°C): $\delta^{13}C = 28.2, 22.6, -10.5$ (s, br., BC in the ratio 1:2:1), 12.3, 11.5, 10.7 (q, CCH_3, 2:1:1), 10.4, 10.1, 9.8, 8.6 (q, BCH_2CH_3, 1:2:2:1), 7.0–7.5 and −3.5 to −4.0 (BCH_2, br.).—Assignment of the ^{11}B and ^{13}C signals of the C_4B_6 skeleton, cf. [1].

[12] R. Benn, R. Mynott, Max-Planck-Institut für Kohlenforschung, Mülheim a. d. Ruhr.

[13] The X-ray structure analysis of 2-[η^6-$H_3CC_6H_5$]Fe-[6,7,9,10-$(H_3C)_4C_4B_5H_5$], whose structure is derived from decaborane(14), has since been reported: R. P. Micciche, J. J. Briguglio, L. G. Sneddon, *Organometallics 3* (1984) 1396.

[14] G. Schomburg, F. Sagheb, Max-Planck-Institut für Kohlenforschung, Mülheim a. d. Ruhr 1984; Measurement conditions: 34-m capillary column, Dexsil OV-1, injection-block temperature 250°C; column temperature 100–300°C.

[15] MO calculations for $C_4B_2H_6$ predict a small energy difference between 1,4-dibora-2,5-cyclohexadiene and 2,3,4,5-tetracarba-*nido*-hexaborane(6): R. N. Camp, D. S. Marynick, G. D. Graham, W. N. Lipscomb, *J. Am. Chem. Soc. 100* (1978) 6781.

Crystal and Solution Structures of $[t\mathrm{Bu_2C{=}NLi\cdot O{=}P(NMe_2)_3}]_n$**

By *Donald Barr, William Clegg, Robert E. Mulvey, David Reed,* and *Ronald Snaith**

All previously known lithium methyleneamides have been clusters with the μ_3-amido ligands usually found over Li_3 triangular faces. Several lithium methyleneamides, such as **1a**, **1b**[1a], and **1c**,[1b] have solid-state hexameric structures (n = 6) based on slightly folded chair-shaped Li_6 rings with μ_3-N=CRR′ ligands over the six smaller of the eight triangular Li_3 faces. In contrast to these crystalline, soluble materials, lithium diarylmethyleneamides such as $(Ph_2C{=}NLi)_n$ are polymeric powders, though complexing agents can convert them into oligomers, e.g., the pseudo-cubane tetramer **2**[2a] and the pentanuclear lithiate **3**[2b]. **2**, like **1**, contains exclusively μ_3-N–Li linkages, though the latter additionally has amido ligands spanning Li_2 edges. Such μ_2-N–Li bonding is found in the compounds $[RR'NLi(donor)]_n$, n = 4, 3, 2, which always exist as $(NLi)_n$ rings, rather than as clusters. Examples are the tetramer **4**[3], the trimer **5**[4], and the dimer **6**[4].

$[RR'C{=}NLi]_n$ **1**

a, R = R′ = *t*Bu; **b**, R = R′ = Me_2N; **c**, R = Ph, R′ = *t*Bu, Me_2N

$[PhC{=}NLi\cdot pyridine]_4$ **2**

$[Li(hmpa)_4]^+[Li_5(N{=}CPh_2)_6(hmpa)]^-$ **3** hmpa: $O{=}P(NMe_2)_3$

$[Me_2C(CH_2)_3CMe_2NLi]_4$ **4** $[(PhCH_2)_2NLi]_3$ **5**

$[(PhCH_2)_2NLi(hmpa)]_2$ **6** $[t\mathrm{Bu_2C{=}NLi(hmpa)}]_n$ **7**

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The 1:1 complex **7** was obtained by reaction of HMPA with a solution of **1a** (see Experimental Procedure). Subsequent X-ray diffraction studies showed that complexation had in fact converted the hexameric cluster **1a** into the dimeric (n = 2) ring **7** (Fig. 1); **7** thus represents the first example of a lithium methyleneamide ring species in which the ligand exclusively engages in μ_2-bridging between two lithium atoms, as in **4**, **5**, and **6**.

The core of the solid-state structure of **7** is a strictly planar Li_2N_2 ring, the $C_2C{=}N$ plane being inclined at 58.6° to this ring. The Li–N bond lengths in **7** (1.923 and 1.948 Å)

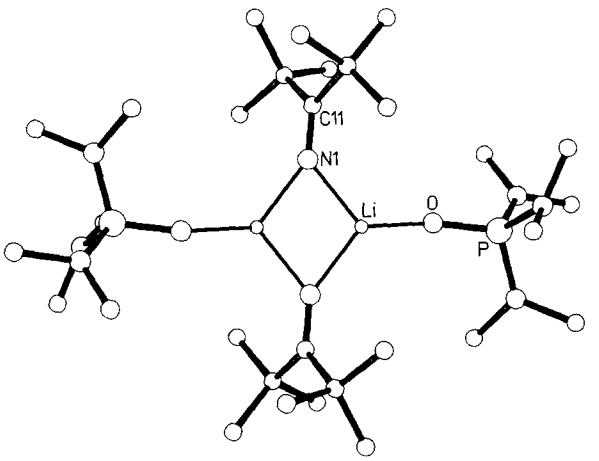


Fig. 1. Molecular crystal structure of **7**, n = 2. P$\bar{1}$, $a = 9.505(1)$, $b = 11.128(2)$, $c = 12.015(3)$ Å, $\alpha = 115.95(1)$, $\beta = 101.91(1)$, $\gamma = 98.22(2)°$, $Z = 1$, $R = 0.070$ for 2719 reflections with $F > 4\sigma(F)$. Further details on the crystal structure analysis can be obtained from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2 (FRG), by quoting the depository number CSD 51234, the names of the authors, and the journal citation.

are the shortest yet found in any organonitrogen-lithium ring compound, and can be compared with those in **6** (mean 2.007 Å)[4]. The ring angle at Li in **7** (104.6°) is slightly expanded compared to that in **6** (102.7°) and this, together with the shorter Li–N bonds, brings the lithium atoms much closer (Li···Li 2.368 Å in **7**, 2.505 Å in **6**); indeed the Li···Li distance in **7** is remarkably similar to the shortest ones found in the Li_3 triangles of **1** (2.395 Å).

Cryoscopic measurements at −108°C in tetrahydrofuran (THF) of (3,6-diethoxy-1-lithio-2,5-dimethyldihydropyrazine·1.5 thf)$_n$ which, like **7**, exists in the solid state as a dimeric $(NLi)_2$ ring[5], gave a value of n = 1.15, indicating a 5:1 ratio of monomer to dimer. Earlier isopiestic studies of the compound $[LiN(SiMe_3)_2]_3$[6] supported the existence of a monomer/dimer mixture in diethyl ether, whereas ^{7}Li-NMR spectra in THF at −40°C showed just one Li resonance at low concentration (assigned to the monomer); at higher concentrations, a second (dimer) resonance appeared[7]. Subsequently, a solid dimeric complex, $[(Me_3Si)_2NLi\cdot OEt_2]_2$, has been isolated from ether solution[3,8].

Molecular weight measurements show that in a dilute benzene solution (*ca.* 0.02 M) **7** has an average degree of aggregation of n = 1.12, indicating a roughly 6:1 preponderance of monomer over dimer, but that on concentration (to *ca.* 0.04 M), n increases to 1.33 (a 2:1 ratio).

In the high-field ^{7}Li-NMR spectra at room temperature (Fig. 2a), on dilution, the lower field resonance substantially grows (from 1:2.85 (n = 1.59) to 1:1.35 (n = 1.40)),

implying that it is due to Li nuclei within monomeric **7**. The corresponding ^{1}H-NMR spectra (Fig. 2b) support this conclusion: the two distinct *t*Bu group resonances have near-identical relative integration values to those of lithium (changing from 1 : 3.03 (n = 1.60) to 1 : 1.36 (n = 1.40) on dilution), though now the *t*Bu proton signals of the monomer are those at higher field. Therefore, on dilution, the $(NLi)_2$ ring, which is also present in the solid state, is cleaved. Amido-ligand exchange between the monomeric and dimeric species, if it occurs at all, is slow on the NMR time-scale.

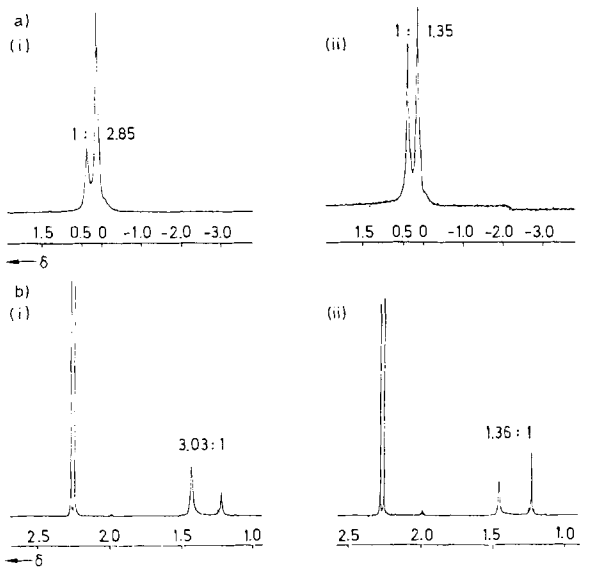


Fig. 2. High-field NMR spectra of **7** in [D_8]toluene at 33°C: a) ^{7}Li, 139.96 MHz; b) ^{1}H, 360 MHz; (i) relatively concentrated solution; (ii) dilute solution.

Experimental Procedure

Reaction of *t*BuCN (0.83 g, 10 mmol) in hexane (5 mL) with a chilled solution of *t*BuLi (5.0 mL of a 2.0 M solution in pentane, 10 mmol), gave a pale yellow solution of **1a**, n = 2. Addition of an equivalent of HMPA (1.79 g, 10 mmol) caused a deepening of the color, and cooling at −10°C afforded highly air-sensitive yellow crystals of **7**, m.p. = 128–130°C, yield 82%.

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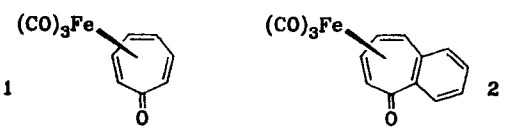
CAS Registry numbers:
1a, 95218-73-8; **7** (n = 1), 95218-71-6; **7** (n = 2), 95218-70-5.

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Activation Energy of the Racemization of Optically Active Tricarbonyl(tropone)iron Complexes**

By *Akio Tajiri,* Noboru Morita, Toyonobu Asao,* and *Masahiro Hatano*

The possible existence of tricarbonyl(tropone)iron **1**[1] in two enantiomeric forms, which was first noted by *Weiss* and *Hübel*,[2] prompted *Goldschmidt* et al.[3] to enrich a given isomer by selective destruction of the other with circularly polarized light. The recent interest shown in thermal rearrangements of polyene-transition-metal complexes motivated *Eisenstadt*[5] and *Hunt*[1c] to determine, by ^{1}H-NMR measurements, the activation energy of the 1,3 iron shift[4] which would racemize the complex **1**.



Herein we report on the resolution of **1** and 2,3-benzotropone(tricarbonyl)iron **2**[6] by high-performance liquid chromatography (HPLC) and on the determination of the kinetic parameters of the racemization by circular dichroism (CD) measurements on the optically active compounds **1** and **2** in solution.

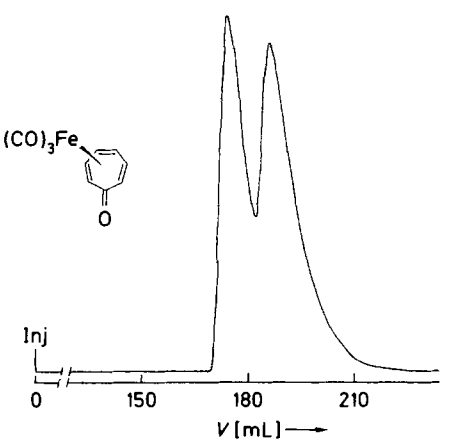


Fig. 1. Resolution of (±)-**1** at room temperature. Eluent: hexane/2-propanol (97 : 3); flow rate: 3 mL/min; column packing: CHIRALPAK OT(+); internal diameter of column 1.67 cm. *V* = elution volume.

Racemic complex **1** was resolved into the enantiomers at room temperature on a column packed with DAICEL CHIRALPAK OT(+), using hexane/2-propanol (97 : 3) as eluent (Fig. 1). Absorption and CD spectra of the first frac-

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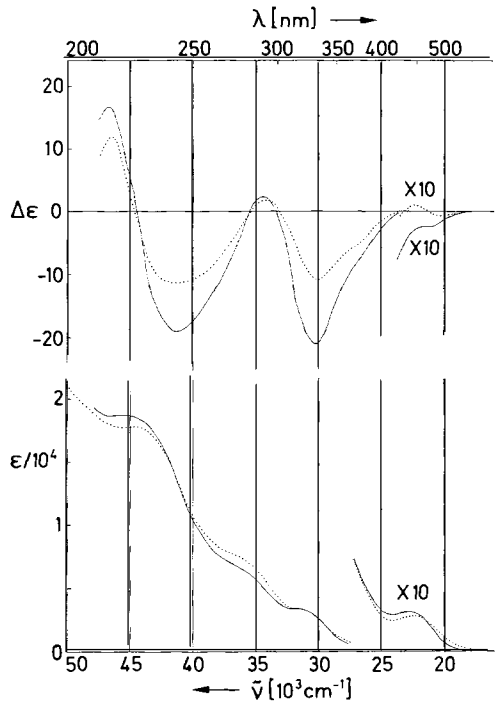


Fig. 2. Absorption (bottom) and CD (top) spectra of (−)-**1** in isooctane (—) and acetonitrile (·····) at room temperature.

tion, which is levorotatory, are illustrated in Figure 2.[7] $\Delta\varepsilon$ is 20—30, and, thus, only one tenth of the value found for biaryls[8] and helicenes.[9] The CD measurement in polar solvents indicates that the lowest wave number absorption shoulder, which occurs only in complexes, comprises two electronic transitions, one of which may be a charge-transfer (CT) transition.[10] A strong negative CD band at 30500 cm^{-1} could, in view of its position and its intensity, arise from a $\pi^* \leftarrow \pi$ transition of the distorted tropone ligand.

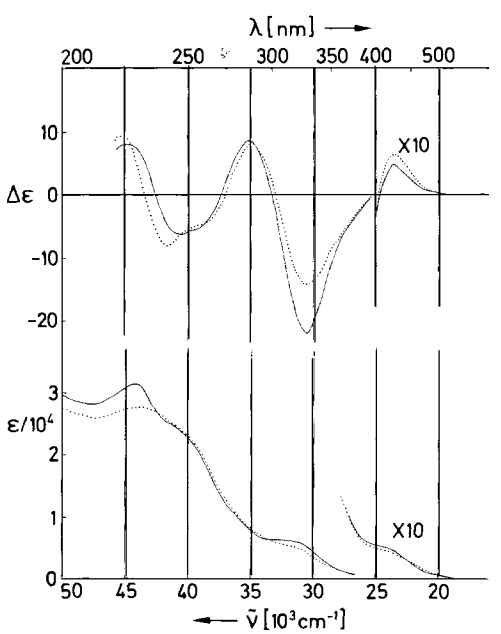


Fig. 3. Absorption (bottom) and CD (top) spectra of (−)-**2** in hexane (—) and acetonitrile (·····) at room temperature.

Absorption and CD spectra of the first fraction of **2**, which is likewise levorotatory, are shown in Figure 3. The spectra of (−)-**1** and (−)-**2** are similar in their profile. The second fraction in the resolution of both **1** and **2** is dextrorotatory and gives a mirror image of the CD spectrum of the first fraction.

The pure fractions racemize slowly within a week when stored in the dark at room temperature. Using the isooctane solution of (−)-**1**, the racemization in the temperature range 25—65 °C was monitored CD-spectroscopically by way of the band at $\tilde{\nu}_{max} = 30500\ cm^{-1}$. On plotting $\log K$ against $1/T$, a linear relationship is obtained, thus indicating that the racemization is a first order reaction. The activation energy for this process was found to be 25.8 kcal/mol^{-1} (108 kJ mol^{-1}). Experimental thermodynamic parameters at 65 °C are $\Delta G^{\neq} = 25.5$ kcal mol^{-1} (107 kJ mol^{-1}), $\Delta H^{\neq} = 25.1$ kcal mol^{-1} (105 kJ mol^{-1}), $\Delta S^{\neq} = -1.2$ kcal mol^{-1} (-5.0 J mol^{-1}) and $k = 2.7 \times 10^{-4}$ s^{-1}. Thus, the observed free energy of racemization is in agreement with the lower limit, 25 kcal mol^{-1} estimated by *Karel* et al.[4]

From a consideration analogous to that for the exchange process in tricarbonyl(cycloheptatriene)iron, a likely mechanism for the racemization of **1** involves a 1,3 iron shift by way of an η^2-intermediate. The activation energy of the racemization of **1** is substantially higher and the rate constant considerably smaller than in the isomerization of tricarbonyl(cycloheptatriene)iron and its derivatives; this is attributed to the strong interaction of the $2e_u$-MOs of $(CO)_3Fe$ with the HOMO of tropone.

Isooctane solutions of **2**, in which racemization is possible only through an intermolecular exchange process, exhibit no CD spectral change under the conditions of the racemization of **1**.[11]

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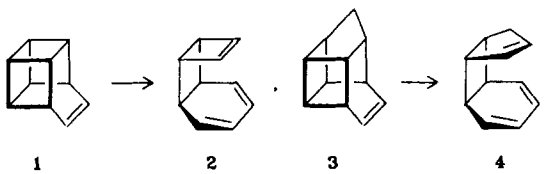
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[6] **2** was obtained in 49% yields by reaction of 2,3-benzotropone with $Fe_2(CO)_9$ in ether under reflux. M.p. 135—136 °C; IR (KBr): $\nu = 2050$, 2040, 1990, 1635, 1630 cm^{-1}; ^{1}H-NMR ($CDCl_3$): $\delta = 3.43$ (m, 1H), 3.47 (m, 1H), 6.13 (m, 1H), 6.20 (m, 1H), 7.0—7.3 (m, 3H), 7.71 (m, 1H); ^{13}C-NMR ($CDCl_3$): $\delta = 54.8$, 61.4, 91.3, 92.3, 126.8, 129.1 (3C), 132.4, 141.3, 197.0, 208.9.
[7] The optical purity of (−)-**1** and (−)-**2** (>98%) was determined by HPLC. Absorption and CD were recorded with a JASCO UVIDEC 510 spectrophotometer and a JASCO J500C circular dichrometer, respectively. The concentration of (−)-**1** and (−)-**2** in solution was 4—5×10^{-4} mol/L. A quarz cell with 1 mm light-pass length was employed for measurements in the wave-number region higher than 30000 cm^{-1}.
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[10] The authors are very grateful for a personal communication from Prof. T. A. Albright, Houston, TX, USA, providing them with the results of extended Hückel MO calculations.
[11] Both (−)-**1** and (−)-**2** in solution exhibit distinctly different absorption spectra from that of **1** and **2** on prolonged heating (1 h) at temperatures over 50 °C, when decomposition seems to set in.

Intramolecular [4+2]-Cycloreversion of the Two Symmetrical Homobasketenes

By *Wolfram Grimme,* Wolfgang Mauer,* and *Christian Sarter*

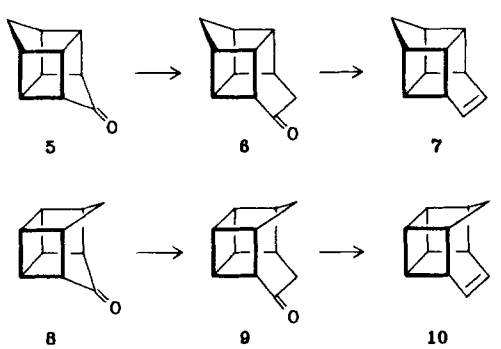
Dedicated to Professor Günther Wilke on the occasion of his 60th birthday

The reverse of the Diels-Alder reaction proceeds exothermally only in those cases when the fragments gain in aromatic resonance or when strain energy in the reactant is relieved. The latter-mentioned driving force is responsible for the intramolecular [4+2]-cycloreversion of basketene **1**[1] to give the *syn*-tricyclo[4.4.0.0^{2,5}]deca-3,7,9-triene **2** and of the asymmetric homobasketene **3**[2] to give the *syn*-tricyclo[5.4.0.0^{2,6}]undeca-3,8,10-triene **4**; both cage-openings are followed by further rearrangements.



1 **2** **3** **4**

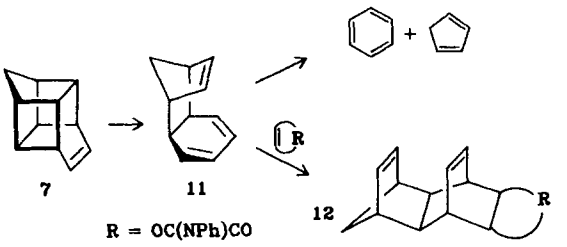
The same mode of stabilization is open to the highly strained homobasketenes **7** (Table 1) and **10**; since we are interested in the relationship between structure and reactivity in cycloreversions, we have investigated the thermal behavior of the two cage compounds. The homobasketenes were obtained, using a standard method, from the bishomocubanones **5**[3] and **8**,[4] respectively, in which the symmetry of the target compounds is already present: Ring expansion with diazomethane in methanol/ether in the presence of lithium bromide affords the homologous ketones **6**[5] and **9**[6], respectively, which are converted with lithium diisopropylamide and diethyl chlorophosphate in tetrahydrofuran into the enol phosphates. Reduction of the enol esters with lithium in liquid ammonia/tetrahydrofuran/*tert*-butyl alcohol furnishes the homobasketenes **7** and **10**.[6]



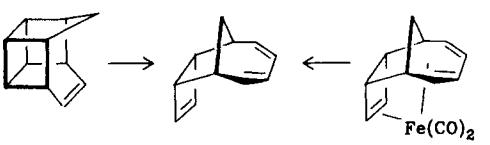
5 **6** **7**

8 **9** **10**

The C_{2v}-homobasketene **7** decomposes to benzene and cyclopentadiene already at 80°C. This cleavage results from two consecutive [4+2]-cycloreversions, the first of which converts the homobasketene into the *endo*-tricyclo[6.2.1.0^{2,7}]undeca-3,5,9-triene **11**. This tricycle has already been obtained via an alternative route; its cleavage at 40°C to give benzene and cyclopentadiene is known.[7] The intermediate **11** can be trapped as the cycloadduct **12** (Table 1) if a mixture of **7** and *N*-phenylmaleimide (molar ratio 1:5) in dichloroethane is heated to boiling for 7.5 h; small amounts of the cycloadduct of cyclopentadiene are formed at the same time.



The C_s-homobasketene **10** undergoes cycloreversion at 150°C to give the tricyclo[4.4.1.0^{2,5}]undeca-3,7,9-triene **13**. The structure of **13** was established by independent synthesis from the dicarbonyliron complex **14**,[8] which is formed by photoaddition of cycloheptatriene to tricarbonyl(cyclobutadiene)iron. Oxidation with cerium ammonium nitrate in aqueous acetone leads to liberation of the organic ligand **13** from **14** (Table 1).



10 **13** **14**

Table 1. Some physical data of the compounds **7**, **12**, and **13**. The ^{1}H-NMR spectra were recorded at 90 MHz in $CDCl_3$ (that of **7** at 0°C in $CFCl_3$).

7, ^{1}H-NMR: δ=6.06 (AA'XX' half-spectrum, 2H), 3.32 (AA'XX' half-spectrum, 2H), 2.9 (m, 2H), 2.0 (m, 4H), 1.16 (t, 2H, CH_2); MS: *m/z* 141 (M^+), 78 ($C_6H_6^+$, 36%), 66 ($C_5H_6^+$, 100%)

12, m.p. 217–219°C (decomp.); ^{1}H-NMR: δ=7.5–7.0 (m, 5H), 5.64 (dd, 2H), 5.47 (t, 2H), 3.17 (m, 2H), 2.98 (t, 2H), 2.78 (m, 2H), 2.41 (m, 2H), 1.32 (AB, J=8 Hz, 2H, CH_2)

13, m.p. 86°C; ^{1}H-NMR: δ=6.10 (s, 2H), 5.7 (m, 4H), 3.45 (d, J=8 Hz, 2H), 2.6 (m, 3H), 2.23 (AB half-spectrum, J=11 Hz, 1H, CH_2); UV (hexane): λ_{max}=252 (ε=3800) sh, 257 (4200), 268 (3900), 279 (2100); MS: *m/z* 144 (M^+), 129 ($M^+ - CH_3$, 100%), 91 ($C_7H_7^+$, 36%)

In order to determine the kinetic parameters for the cleavage of **7** in dodecane solution between 81 and 85°C, the increasing extinction at 264 nm (cyclopentadiene absorption) was monitored until a constant value was observed. The kinetics of the isomerization of **10** were determined in heptane solution between 150 and 164°C by the ampule technique, the reactant/product ratio being measured by gas chromatography.

The activation parameters for the intramolecular [4+2]-cycloreversion of basketene **1** and its three homologues **3**, **7**, and **10** are listed in Table 2. Also listed is the strain re-

Table 2. Activation parameters and strain release for the intramolecular [4+2]-cycloreversion of basketene and its homologues.

Cpd.	log$A$ [a]	E_a [a] [kcal/mol]	ΔG^+(130°C) [kcal/mol] [a]	ΔE_{st} [kcal/mol]
1	13.2 [1]	29.7 [1]	29.8 [b]	113−(30+26+5)=52
3	12.8±0.5 [2]	35.3±1.0 [2]	35.6±0.1	74−(26+5+6) =37
7	12.0±0.6	25.9±0.4	28.2±0.1 [b]	81−(20+5) =56
10	12.5±0.7	33.2±1.2	34.0±0.2	87−(30+16) =41

[a] The error limits are the standard deviation from the linearly adjusted Arrhenius equation. [b] Because of twofold degeneracy of the reaction, $RT\ln 2$ was added.

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lease that occurs on opening of the cage compounds. Force field calculations are already available for the strain energy of the saturated educts;[9] the additional strain energy due to the double bond is almost the same in all four compounds and has been neglected. The strain in the products is made up additively from the contributions of the individual rings.[10]

There is a linear relationship [Eq. (1)] between the loss in strain energy ΔE_{st} and the free enthalpy of activation ΔG^{+} at 130°C; the correlation coefficient is 0.9999, at a confidence level of more than 99.5%.

$$\Delta G^{+} = 49.9 - 0.39\Delta E_{st} \qquad (1)$$

Equation (1) indicates that in the transition state for the opening of each of the structurally related cage compounds 39% of the strain release has occurred and that this alone determines the stability of the compounds. The extrapolation of Equation (1) to a [4+2]-cycloreversion without any loss of strain, which is not realizable in cage compounds, leads to $\Delta G^{+} = 50 \pm 0.6$ kcal/mol. For the cycloreversion of cyclohexene to ethene and butadiene, which proceeds without loss of strain, a free enthalpy of activation of 57 ± 1 kcal/mol at 130°C is obtained from the activation parameters;[11] the agreement is satisfactory, considering the extent of extrapolation.

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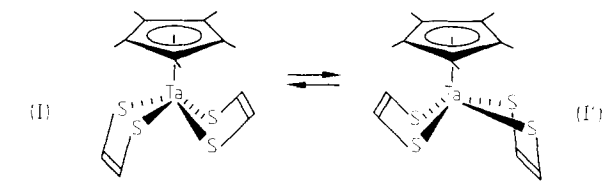
A New Class of Tantalum(v) Dithiolate Complexes: Synthesis and Characterization of $[Ta(\eta^5\text{-}C_5Me_4R)(SCH{=}CHS)_2]$ (R = Me, Et) and $[Ta(\eta^5\text{-}C_5Me_5)(SCH_2CH_2S)_2]$

By *Kazuyuki Tatsumi, Junko Takeda, Yoitsu Sekiguchi, Masaki Kohsaka,* and *Akira Nakamura**

There is obvious fundamental and practical interest in understanding the chemistry of transition metal thiolate complexes because of their biological and catalytic implications.[1] In contrast to the ubiquitous *S*-coordinated chelate complexes of group 6, 7, and 8 transition metals, such complexes of group 5 metals, particularly of Nb and Ta, are scarce.[2-4] Herein we report the preparation[5a] and characterization[5b-d] of $[Ta(\eta^5\text{-}C_5Me_4R)(SCH{=}CHS)_2]$ **1a**, R = CH_3 and **1b**, R = C_2H_5 and $[Ta(\eta^5\text{-}C_5Me_5)(SCH_2CH_2S)_2]$ **2**.

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The ^{1}H-NMR spectrum of **1a** measured at 36°C shows a broad singlet at $\delta = 7.5$ for the SCH=CHS. At temperatures above 40°C, the broad peak begins to sharpen, while at low temperature (−50°C) it appears as two sharp singlets ($\delta = 7.14$, 7.84) of equal intensity. The spectral changes were found to be reversible and independent of concentration. On the other hand, the singlet of η^5-C_5Me_5 at $\delta = 2.25$ remained unchanged in the temperature range studied. These observations indicate the presence of two identical conformers in equilibrium, each of which contains orientationally nonequivalent dithiolate ligands.



Given the stoichiometry, $Ta(\eta^5\text{-}C_5Me_5)(SCH{=}CHS)_2$, the spectral data described above are consistent with the structure (I) in which two SCH=CHS ligands are folded around the SS axis, one with the open side pointing toward the η^5-C_5Me_5 group and the other with the opposite orientation. The conformation appears to be fluxional, and the mutual interconversion (I)⇄(I') occurs at a detectable rate ($\Delta G^{\ddagger}_{50°C} = 14.9$ kcal/mol, $\Delta H^{\ddagger}_{50°C} = 14.7$ kcal/mol, $\Delta S = -0.6$ cal mol^{-1} K^{-1}, $T_c = 34$°C),[6] probably by an inversion process of the five-membered TaS_2C_2 chelate rings. A similar temperature dependence of the SCH=CHS proton resonance was observed for **1b**, where the activation parameters were practically the same as those of **1a**. Nonplanarity of the TaS_2C_2 ring is not surprising, but is common to SCH=CHS complexes with d^0 transition metals, a typical example of which is the well-established structure of $[Ti(\eta^5\text{-}C_5H_5)_2(SCH{=}CHS)]$.[7] The folding in the Ti complex was attributed to the bonding interaction occurring between a vacant Ti d orbital and the occupied C=C π orbital of SCH=CHS.[8]

The interesting structure (I) can be explained with the aid of molecular orbital considerations. **1a** and **1b** contain four basal Ta–S σ bonds, forming a so-called four-legged piano stool skeleton. The d^0 "piano stool" molecule carries two low-lying vacant d orbitals[9, 10] (x^2-y^2 and z^2), which act as potential acceptors of electrons from the C=C π-donor orbital of SCH=CHS (Fig. 1); stabilization of **1** is maximal when both d orbitals are fully utilized in such a way that one C=C π orbital interacts with x^2-y^2 at the lateral side and the other π orbital with z^2 at the bottom. Conformation (I) fulfills this requirement.

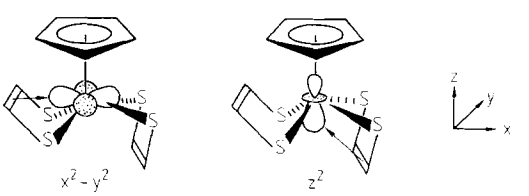
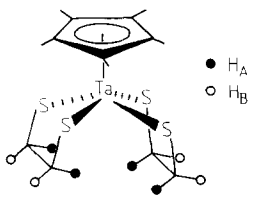


Fig. 1. Stabilization of the structure of **1a** and **1b**.

Lack of the additional donor interactions in **2** may be relevant to the experimental fact that **2** is much less stable than **1a** and **1b** under aerated conditions and/or in donor solvents, e.g., THF. The ^{1}H-NMR spectrum of **2** exhibits a symmetric A_2B_2 pattern for the SCH_2CH_2S protons, consisting of two multiplets at $\delta = 4.02$ and 4.64, and a singlet at 2.12 for the η^5-C_5Me_5 protons. This data is consistent with the structure (II). The spectrum is temperature independent between -70 °C and $+70$ °C, indicating that conformers arising from the possible ring puckering of the ethane portion are in labile equilibrium.

(II)



Noteworthy here is a contrast between fragmentation patterns observed in the EI mass spectra of **1a** (or **1b**) and **2**. In addition to the parent ion isotopic cluster, the mass spectrum for **2** exhibits two sets of peaks in close to theoretical isotopic abundances, which we assign as signals derived from $[Ta(\eta^5\text{-}C_5Me_5)(SCH_2CH_2S)(S_2)]^{\oplus}$ and $[Ta(\eta^5\text{-}C_5Me_5)(S_2)_2]^{\oplus}$. These ions are probably formed by a loss of one or two ethylene moieties from the parent ion. Fragmentation of **1a** (or **1b**), on the other hand, gave $[Ta(\eta^5\text{-}C_5Me_4R)(SCH{=}CHS)(SC_2H)]^{\oplus}$ and $[Ta(\eta^5\text{-}C_5Me_4R)(S_2)(SC_2H)]^{\oplus}$, R = Me or Et. The first step of fragmentation involves liberation of "SH" instead of C_2H_2. Although the mechanism of these fragmentations still needs to be elucidated, the unexpected behavior of **1a** and **1b** is compatible with the presence of bonding interactions between Ta and the olefinic carbons.

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CAS Registry numbers:
1a, 95740-37-7; **1b**, 95740-38-8; **2**, 95740-39-9; $[(\eta^5\text{-}C_5Me_5)TaCl_4]$, 71414-47-6; $[(\eta^5\text{-}C_5Me_4Et)TaCl_4]$, 95740-40-2; $Na_2S_2C_2H_2$, 3353-90-0; $Na_2S_2C_2H_4$, 23851-16-3.

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[5] a) *Procedure:* A THF solution of $[Ta(\eta^5\text{-}C_5Me_5)Cl_4]$ was added slowly to a vigorously stirred suspension of two equivalents of $Na_2S_2C_2H_2$ in THF at -10 °C; an immediate color change from orange to dark green was observed. Rapid removal of THF followed by extraction with ether afforded a yellowish green powder. Recrystallization of the crude product from benzene and *n*-hexane afforded **1a** in 28% yield as analytically pure deep-green crystals [5b]. **1b** was synthesized in an analogous way from $[Ta(\eta^5\text{-}C_5Me_4Et)Cl_4]$ and $Na_2S_2C_2H_2$ [5b]. Treatment of $[Ta(\eta^5\text{-}C_5Me_5)Cl_4]$ with two equivalents of $Na_2S_2C_2H_4$ in CH_2Cl_2 at room temperature yielded **2** (23%) as a carmine-red crystalline powder [5c]. While **1a** and **1b** are relatively air-stable as solids, **2** is sensitive to air. All operations were carried out under an argon atmosphere, using degassed solvents.—**1a**, **1b**, and **2** gave satisfactory elemental analyses.—b) **1a**: m.p. 186—187 °C; ^{1}H-NMR (100 MHz, $CDCl_3$, room temperature) $\delta = 2.25$ (s, 15H, CH_3), $\delta = 7.5$ (br. s, 4H, SCH=CHS); MS (EI, 75 eV) *m/z* (rel. intensity) 499 (2), 498 (14), 497 (16), 496 (100, $C_{14}H_{19}S_4Ta$), 465 (2), 464 (3), 463 (40, $C_{14}H_{18}S_3Ta$), 439 (4), 438 (9), 437 (36, $C_{12}H_{16}S_3Ta$).—c) **1b**: m.p. 137—139 °C; ^{1}H-NMR ($CDCl_3$, room temperature) $\delta = 1.07$ (t, $J = 7$ Hz, 3H, CH_2CH_3), $\delta = 2.24$ (s, 12H, CH_3), $\delta = 2.56$ (q, 2H, CH_2CH_3), $\delta = 7.5$ (br. s, 4H, SCH=CHS); MS (EI, 75 eV) *m/z* (rel. intensity) 513 (4), 512 (20), 510 (100, $C_{15}H_{21}S_4Ta$), 479 (5), 478 (6), 477 (32, $C_{15}H_{26}S_3Ta$), 453 (6), 452 (8), 451 (34, $C_{13}H_{18}S_3Ta$).—d) **2**: m.p. 135—137 °C; ^{1}H-NMR (C_6D_6 or $C_6D_5CD_3$, room temperature) $\delta = 2.12$ (s, 15H, CH_3), $\delta = 4.02$, 4.64 (m, $J_{gem} = -11.5$ Hz, $J_{vic}(cis) = 3.5$ Hz, $J_{vic}(trans) = 7.4$ Hz, 8H, SCH_2CH_2S); MS (EI, 75 eV) *m/z* (rel. intensity) 503 (0.4), 502 (1.7), 501 (1.5), 500 (7.8, $C_{14}H_{23}S_4Ta$), 475 (3), 474 (17), 473 (15), 472 (88, $C_{12}H_{19}S_4Ta$), 447 (3), 446 (20), 445 (15), 444 (100, $C_{10}H_{15}S_4Ta$).

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Complete Signal Assignment of the ^{13}C-NMR Spectra and Structure Determination of Corrinoids by 2D-INADEQUATE and 2D ^{13}C,^{1}H-NMR Chemical Shift Correlation Using ^nJ(C,H)

By *Reinhard Benn** and *Richard Mynott*

Dedicated to Professor Günther Wilke on the occasion of his 60th birthday

The structural analysis of corrinoids[1,2] has relied upon X-ray crystallography, chemical synthesis, and reaction studies and upon spectroscopic investigations. However, although the ^{1}H- and ^{13}C-NMR spectra of corrinoids are potentially very informative, the presence of several similar structural subunits makes it difficult to assign all the resonances unambiguously. As a result, a large variety of substances for comparison and the use of a number of special NMR techniques have usually been required.[3] We report here the application of 2D-NMR techniques to such compounds and show that 2D-INADEQUATE[4] or 2D ^{13}C,^{1}H-NMR[4] chemical shift correlation diagrams using ^nJ(C,H) are most powerful methods for making the assignments quickly and reliably and for determining the structure of corrins.

Heptamethyl cobyrinate **1**,[5] in which the cobalt has the formal oxidation state +1, is very soluble in benzene; it was therefore possible to obtain a 2D-INADEQUATE ^{13}C-NMR spectrum of a saturated solution at 100.6 MHz. Although the resonances of the 52 nonequivalent carbon atoms in **1** are found over a range of more than 17 kHz and the ^1J(C,C) coupling constants lie between 30 and 80 Hz,[6] all the carbon signals, with the exception of those from the methoxy groups, could be identified and assigned, starting with the trivial assignment of C1, C10, and C19 (Fig. 1).

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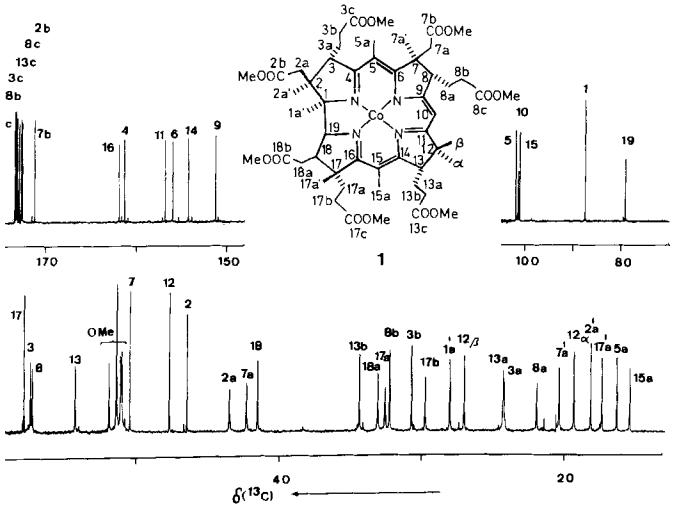


Fig. 1. Structure and ^{13}C-{^1H}-NMR spectrum of **1** recorded at 100.6 MHz (ca. 40 wt.-% in [D_6]benzene, sample volume ca. 3 mL).

Using the ^{13}C satellites of the olefinic carbon atoms 16, 4, 11, 6, 14, and 9 (Fig. 2), the resonances of their nearest neighbors were identified (i.e., 15 and 17; 3 and 5; 10 and 12; 5 and 7; 13 and 15; and 8 and 10, respectively).

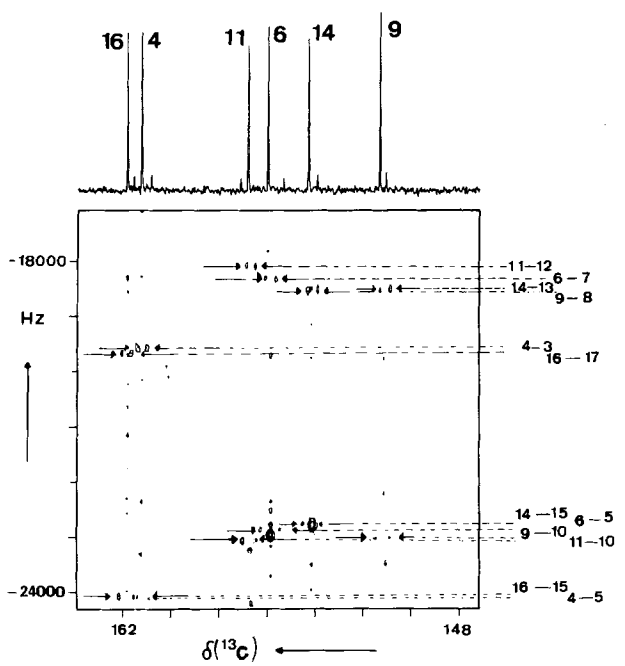


Fig. 2. Expansion of part of the low-field region of the 100.6-MHz ^{13}C-{^1H}-NMR spectrum of **1** (top) and of the 100.6-MHz 2D-INADEQUATE spectrum of the same sample (data matrix 4 K × 256, optimized for $^1J(C,C) = 54$ Hz, relaxation delay 1 s, 768 scans per increment, total measurement time 60 h) (bottom).

The ^{13}C satellites of these signals then revealed the connectivities of the skeletal carbon atoms 1—19. This in turn allowed the signals of all the other carbon atoms to be assigned, with the exception of the methoxy carbons. The latter, however, could be assigned from the 2D ^{13}C,^1H-NMR correlation diagram using the $^3J(C,H)$ coupling constants to identify the signals of the carbonyl carbon atoms to which the methoxy groups are bound (see Fig. 3).

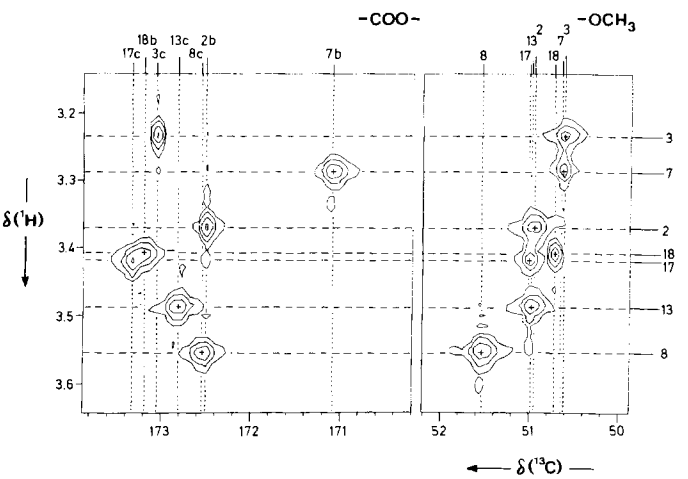


Fig. 3. Expansion of part of the 75.5-MHz ^{13}C,^1H-NMR chemical shift correlated spectrum of **1** ($\delta(^{13}C)$ along the x axis, $\delta(^1H)$ along the y axis, data matrix 4 K × 512, optimized for $^nJ(C,H) = 12$ Hz) showing the cross peaks of the carbonyl and O—CH_3 groups which stem from coupling to identical methoxy protons.

The proton signals of the remaining eight methyl groups are all singlets. The carbon atoms two and three bonds removed from these protons can also be identified via the $^nJ(C,H)$ couplings, since the signal assignment and the location of a given carbon in the skeleton can be derived by examining the cross peaks arising from the coupling with different protons. The assignments (Table 1) using the two techniques, which did not require prior assignment of the proton NMR spectrum, were made independently and are consistent with one another.

These results show that it is possible to determine the structure of corrinoids and to assign all the ^{13}C-NMR signals by 2D-NMR techniques. While the 2D-INADEQUATE method is more direct and does not require additional information, it needs more material in solution and a longer measurement time. The analysis can also be carried out using the 2D ^{13}C,^1H-NMR chemical shift correlation technique. The more methyl signals in the proton spectrum that are present as sharp singlets, the more effective the method. The cross peaks then undergo little modu-

Table 1. ^{13}C-NMR chemical shifts of **1** ([D_6]benzene, relative to internal TMS, 310 K). The numbering of the carbon atoms is given in Fig. 1.

C Atom	δ	C Atom	δ	C Atom	δ
1	87.46	1a′	27.96	2b	172.61
2	46.29	2a′	18.16	2OMe	51.12
3	57.20	2a	43.33	3c	173.15
4	161.33	3a	24.21	3OMe	50.76
5	101.87	3b	30.65	7b	171.22
6	155.98	5a	16.34	7OMe	50.81
7	50.27	7a′	20.33	8c	172.72
8	57.08	7a	42.15	8OMe	51.66
9	151.24	8a	21.91	13c	172.94
10	101.34	8b	32.17	13OMe	51.12
11	156.82	12α	19.32	17c	173.42
12	47.52	12β	26.97	17OMe	51.16
13	54.08	13a	24.27	18b	173.29
14	154.27	13b	34.30	18OMe	50.88
15	101.04	15a	15.45		
16	161.93	17a′	17.37		
17	57.63	17a	32.48		
18	41.38	17b	29.70		
19	79.14	18a	32.99		

lation due to $^1H,^1H$ coupling and the loss of magnetization occurring during the longer intervals in the pulse sequence for small $^nJ(C,H)$ couplings is not critical, even when the standard pulse sequence is employed.[7]

There are large differences between the chemical shifts of **1** and those of the corresponding dicyano Co(III) corrin **2**.[8] The same is found when the corrin skeleton is modified—even the signals of carbon atoms well removed from the site of alteration can be shifted considerably.[9] In some cases this can be interpreted as being due in part to changes in the conformation of the skeleton. It thus follows that conventional methods of assignment, such as comparison with related systems (as, for example, so successfully applied to steroids) are not only much more time consuming but can in addition lead to errors in interpretation.

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CAS Registry numbers:
1, 84062-90-8; **2**, 95464-52-1.

[1] D. Dolphin: *B_{12}, Vol. 1, 2*, Wiley Interscience, Chichester 1982.
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[3] a) For a comprehensive ^{13}C-NMR study of corrinoids, see L. Ernst, habilitation thesis, Technische Universität Braunschweig 1980; b) *Liebigs Ann. Chem. 1981*, 376; c) *J. Chem. Soc. Perkin Trans. 1 1984*, 2267.
[4] For 2D-INADEQUATE, see A. Bax, R. Freeman, T. A. Frenkiel, M. H. Levitt, *J. Magn. Reson. 43* (1981) 478; for 2D $^{13}C,^1H$-NMR correlation, see A. A. Maudsley, R. R. Ernst, *Chem. Phys. Lett. 50* (1977) 368; for a review of 2D NMR, see R. Benn, H. Günther, *Angew. Chem. 95* (1983) 381; *Angew. Chem. Int. Ed. Engl. 22* (1983) 350.
[5] **1** was prepared by the reduction of heptamethyl dicyanocobyrinate **2**. H. H. Inhoffen, G. Wilke, unpublished.
[6] P. E. Hansen, *Annu. Rep. NMR Spectrosc. A 11* (1981) 66; V. Wray, P. E. Hansen, *ibid. A 11* (1981) 99.
[7] H. Kessler, C. Griesinger, J. Lautz, *Angew. Chem. 96* (1984) 434; *Angew. Chem. Int. Ed. Engl. 23* (1984) 444, have reported a modified pulse sequence for 2D $^{13}C,^1H$-correlated spectra using long-range couplings. The INADEQUATE pulse sequence can be employed when more concentrated samples are available. Since this pulse sequence is a priori shorter, the losses due to relaxation in the case of **1** were not significant.
[8] The assignment of the ^{13}C resonances of **2**, obtained from the 2D $^{13}C,^1H$-NMR chemical shift correlation using $^nJ(C,H)$ without assignment of the ^1H-NMR spectrum, is consistent with that given in [3]. The resonances of C1, C8, C10, and C19 in **2** are shifted by 5.0, 3.1, 10.3, and 4.5 ppm, respectively, relative to those of **1**. The signals of C4, C6, C9, C11, C14, and C16 are shifted by -10 to -20 ppm relative to those of **1**.
[9] Hexamethyl 7-decarboxymethyl-7,8-didehydrocobyrinate **3** can be prepared from **1** by thermolysis (compare with the thermolysis of **2**, L. Ernst, G. Holze, H. H. Inhoffen, *Liebigs Ann. Chem. 1981*, 198). In the ^{13}C-NMR spectrum of **3**, even the signals of C18, C19, and C1, which are well removed from the site of the elimination, are shifted by 2.0, 3.4, and 4.3 ppm, respectively, relative to those of **1**.

^{13}C-NMR Spectroscopy of Mixed Dialkylzinc Compounds with Prochiral Alkyl Residues

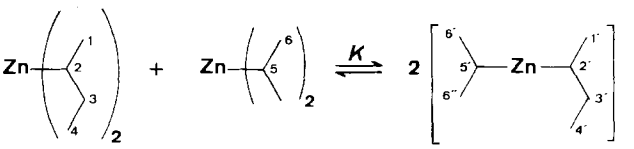
By *Richard Mynott,* Barbara Gabor, Herbert Lehmkuhl,* and *Ingo Döring*

Dedicated to Professor Günther Wilke on the occasion of his 60th birthday

The existence of mixed diorganozinc compounds of the type R^1R^2Zn is disputed. According to *Job* and *Reich*,[1] they readily undergo exchange to form the symmetrical compounds R^1_2Zn and R^2_2Zn. Other authors[2–5] have reported that mixed diorganozinc compounds are isolable species which form the symmetrical components only after standing for some time or on warming.[2] Recent mass spectroscopic and calorimetric investigations show that mixed diorganozinc compounds are present in equilibrium with the symmetrical compounds.[6]

$$2\,R^1R^2Zn \overset{K}{\rightleftharpoons} R^1_2Zn + R^2_2Zn$$

We have now been able to prove the existence of mixed diorganozinc compounds directly by ^{13}C-NMR spectroscopy.



1 **2** **3**

In the course of ^{13}C-NMR investigations on dialkylzinc compounds with chiral alkyl groups, we observed splitting of the ^{13}C signals that appeared to be due to the presence of diastereoisomers. In bis(*sec*-butyl)zinc **1**,[7] the *sec*-butyl residue contains a chiral carbon atom; therefore, two sets of signals are to be expected, corresponding to the diastereoisomers in which these carbon atoms have the same (*RR,SS*) or different (*RS,SR*) configurations. This splitting is observed for each carbon resonance in the ^{13}C-NMR spectrum of **1** at -30°C (Fig. 1a).

In order to establish the formation of mixed species that contain two structurally different alkyl groups rather than groups that differ only in configuration, bis(isopropyl)zinc **2** was selected as the second component. There is just one methyl resonance observed in the ^{13}C-NMR spectrum of pure **2**[7] in [D_8]tetrahydrofuran (THF) (Fig. 1b) because the methyl groups are enantiotopic. The methyl carbons should (with the possible exception of restricted rotation at very low temperatures) give different signals *only* if the isopropyl group is part of a chiral compound.

The ^{13}C-NMR spectrum (-30°C) of a 1:1 mixture of **1** and **2** prepared at room temperature in [D_8]THF is shown in Figure 1c. In addition to the signals of **1** and **2**, resonances of a third component are observed which are assigned to the mixed compound **3**. Particularly significant is the nonequivalence of the methyl carbons C6′ and C6″ (numbering given in the formula) of the isopropyl group ($\delta = 23.50$ and 23.44, respectively).[8] This proves conclusively that the isopropylzinc moiety is bound to a chiral residue. The signal intensities indicate that **1**, **2**, and **3** are present in the ratio 0.27:0.40:0.33, so that the equilibrium constant K for the formation of **3** is 1.0 within experimental error.

The 25.2-MHz ^{13}C-NMR spectra of pure **1** in [D_8]THF and in [D_8]toluene were recorded between -80°C and $+35$°C. Although the splittings of the signals become smaller at higher temperature, the signals from C2, C3, and C4 of the diastereoisomers could still be resolved even at $+35$°C in [D_8]THF.

It was not possible to carry out a lineshape analysis of the exchange-modified resonances to obtain the thermodynamic parameters because the separations of the respective signal pairs are strongly temperature dependent. Neverthe-

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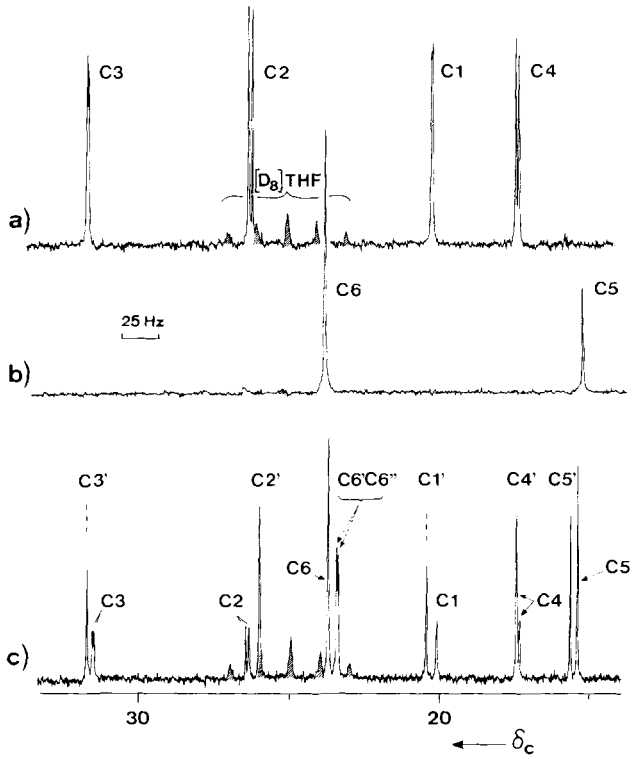


Fig. 1. $^{13}C\{^1H\}$-NMR spectra (20.1 MHz) of **1**–**3** (−30°C, [D$_8$]THF). a) Spectrum of **1**. b) Spectrum of **2**. c) Spectrum of a 1:1 mixture of **1** and **2**; the additional signals are due to **3**.

less, the observation of a splitting of just 0.8 Hz for C3 at 35°C places an upper limit on the exchange rate ($k < 4$ s^{-1})[9] at this temperature. In [D$_8$]toluene, the signal splittings were smaller ($\Delta\delta < 0.06$). They also become smaller at higher temperature and were not resolved above 20°C.

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CAS Registry numbers:
1 (isomer I), 95590-02-6; **1** (isomer II), 95590-03-7; **2**, 625-81-0; **3**, 95590-04-8.

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[6] H. Nehl, W. Scheidt, *J. Organomet. Chem.*, in press.
[7] **1** and **2** were prepared from the corresponding alkylmagnesium halides in ether and obtained, after vacuum distillation, in yields of 65% and 64%, respectively: see also K. Nützel in *Houben-Weyl-Müller, Methoden der Organischen Chemie, Vol. 13/2a*, Thieme, Stuttgart 1973, p. 592.
[8] ^{13}C-NMR spectra: Varian XL 100 15A or Bruker WP 80 FT (25.2 and 20.1 MHz, respectively). δ (20.1 MHz, [D$_8$]THF, −30°C) relative to int. TMS: **1**: δ = 31.68, 31.62 (C3); 26.54, 26.43 (C2); 20.12, 20.10 (C1); 17.40, 17.30 (C4).—**2**: δ = 23.79 (C6); 15.38 (C5).—**3**: δ = 31.87 (C3'), 26.08 (C2'), 23.50, 23.44 (C6', C6"); 20.47 (C1'); 17.43 (C4'); 15.62 (C5').
[9] The exchange process for the diastereoisomers in pure **1** is not a simple two-site exchange since not all transfer reactions lead to a change of environment for a given alkyl group. For example, exchange of alkyl groups between two molecules with *RR* configurations will not result in a change in environment for any alkyl group, while that between *RR* and *RS* molecules will change that of only two of the alkyl groups. Overall, the rate of exchange of alkyl groups in cases where the environment is changed (e.g., *RR* to *RS*, or vice versa) is exactly half the total rate of alkyl exchange. Since the two signals for C3 are resolved ($\Delta\nu = 0.8$ Hz), the apparent rate of exchange must be less than that at coalescence ($k = 2.22\,\Delta\nu$), so that the real exchange rate must be less than 4 s^{-1}. The activation energy for alkyl exchange is therefore greater than 72 KJ/mol.

Chiral Copper(II) Complexes for the Enantioselective Resolution of DL-Dansyl-Amino Acids by HPLC**

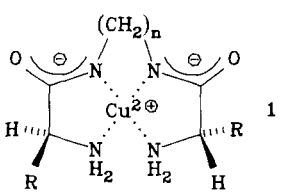
By *Rosangela Marchelli,* Arnaldo Dossena, Giuseppe Casnati, Francesco Dallavalle,* and *Shulamith Weinstein*

Separation of free or derivatized DL-amino acids by HPLC has mainly been achieved by using either chiral complexing stationary phases[1] or chiral metal complexes as additives to the mobile phase.[2] In both cases, the enantiomeric separation has been generally interpreted as being due to ligand exchange.

We report here the preliminary results obtained from a systematic study aimed at increasing the understanding of the molecular mechanism of chiral recognition. The present ligands were specifically designed to study the correlation of the structure and the stability of their copper(II) complexes with the ability of the complexes to separate DL-dansyl-amino acids, as well as to provide an insight into the nature of the interactions involved in the chiral recognition.

The main feature of the new ligands AA-NN-2 and AA-NN-3 is that two L-amino acid amides are joined via the amide nitrogen atoms by ethylene and trimethylene bridges, respectively, and endowed with varying degrees of lipophilicity and bulkiness according to the nature of the amino acid side chain (AA = alanine, valine, phenylalanine). They are easily synthesized as hydrochlorides in high yields (>90%) by condensation of the hydroxysuccinimidic esters of L-Z-amino acids (Z = benzyloxycarbonyl) with 1,2-ethane- and 1,3-propanediamine, respectively, followed by deprotection via hydrogenolysis and treatment with HCl in MeOH.

In agreement with the reported behavior of similar ligands,[3] AA-NN-3 forms only *one* complex with copper(II), $CuLH_{-2}$ **1**, in the pH range 7–8, whereas AA-NN-2 forms *two* Cu(II) complexes, $(Cu_2L_2H_{-2})^{2+}$ and $CuLH_{-2}$. However, since the best enantiomeric separation was obtained between pH 7.5 and 8, where the species $CuLH_{-2}$ is predominant, we assume that the latter is the species involved in the separation.



1

R = $C_6H_5CH_2$ (Phe)
R = $(CH_3)_2CH$ (Val)
R = CH_3 (Ala)
n = 2, AA–NN–2
n = 3, AA–NN–3

Chiral resolution of DL-dansyl-amino acids (dansyl = 5-dimethylamino-1-naphthylsulfonyl) was performed on a C_8 column (Perkin-Elmer) using water/acetonitrile solutions of the different ligands and copper acetate at various pHs. Quite high α values were achieved, as given in Table

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1. A typical separation of a racemic mixture containing a number of amino acids is shown in Fig. 1.

Table 1. Separation factors α of DL-dansyl-amino acids [a].

DL-dansyl-amino acid	L = Phe-NN-2 α	L = Phe-NN-3 α
glutamic acid	2.20	1.23
aspartic acid	2.48	1.36
serine	2.00	1.29
threonine	1.50	1.11
α-aminobutyric acid	1.23	1.00
valine	1.16	1.00
methionine	1.27	1.00
phenylalanine	1.47	1.10
tryptophan	2.01	1.20

[a] Column: 24 × 0.46 cm, C_8, 10 μm; eluent: H_2O: CH_3CN (67:27), $Cu(OAc)_2$ 2 mM, L 2 mM, NaOAc 0.3 M; pH = 7.5; flow rate 1.3 mL/min; room temperature; $\alpha = R_L/R_D$, where R_L and R_D are the adjusted retention times of the L and D enantiomers.

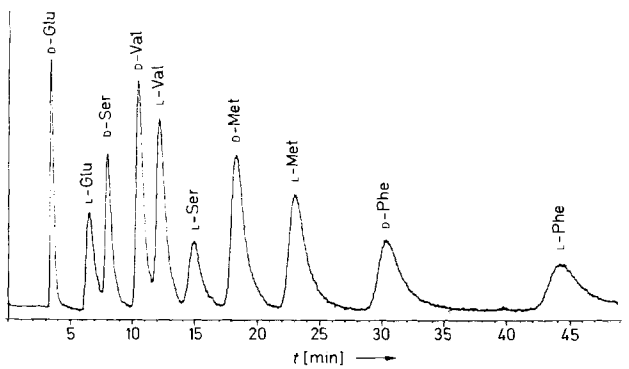


Fig. 1. HPLC separation of a DL-dansyl-amino acid mixture. Conditions as in Table 1; flow rate 1.2 mL/min.

In general, copper(II) complexes of ligands AA-NN-2 give better results than those of AA-NN-3. Phe-NN-2 and Val-NN-2 give comparatively good separations for most amino acids, whereas Ala-NN-2 gives no or poor resolution. The separation factors are pH-dependent; they increase as the pH is raised from pH 6.3 to pH 7.5—8, so that deprotonation of the dansyl-substituted amino group is also effective in the recognition process. For a given ligand, the order of elution of the enantiomers is constant: D-amino acids always elute before L-amino acids. As expected, the aromatic amino acids phenylalanine and tryptophan interact most strongly with the copper(II) complex and the column and therefore give higher retention times. However, enantiomer discrimination is more effective for the polar amino acids aspartic acid, glutamic acid, and serine, which give the best separation factors α.

CPK models of the $CuLH_{-2}$ complexes reveal structures with little conformational freedom. The AA-NN-2 ligands do not completely surround the copper ion, which is therefore more accessible to the amino acids to be separated; in contrast, the AA-NN-3 ligands circularly enclose the copper ion. It is to be noted that enantiomer discrimination is more effective with the weaker complex **1** ($\log\beta = -6.04(3)$ for L = Phe-NN-2) than with the stronger complex ($\log\beta = -2.73(2)$ for Phe-NN-3), which is presumably less able to interact further with the amino acid.

Moreover, the copper(II) complex **1** must be located at the interface between the mobile phase and the "organic" reversed phase; it must be at least partially embedded in the organic phase, thus exhibiting a specific diastereofacial selectivity.

In this context, it is difficult to assume that chiral discrimination takes place via ligand exchange between the tetradentate complex adsorbed on the organic phase and the enantiomer. It is more likely that the incoming dansyl-amino acid interacts initially (through the carboxylate) with the apical position of the copper complex, which is accessible to coordination, and eventually forms hydrogen bonds with the terminal NH_2 of the ligand or displaces it from the equatorial position. Although we do not have sufficient grounds on which to substantiate either mechanism, we think that the present model may allow further developments in this important area of research.

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On the Role of Radical Ion Pairs in [4 + 2] Cycloadditions**

By *Mechthild Dern, Hans-Gert Korth, Gebhard Kopp,* and *Reiner Sustmann**

Dedicated to Professor Dietrich Schulte-Frohlinde on the occasion of his 60th birthday

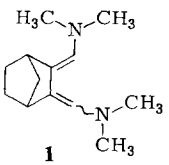
The mechanism of the Diels-Alder reaction has been extensively investigated.[1] Depending on the pattern of substitution and the reaction conditions, the reaction can take place in a concerted fashion or in two steps via biradicals[1] or zwitterions;[2] most reactions can be interpreted as being concerted in the sense of the Woodward-Hoffmann rules. Several years ago it was postulated on the basis of theoretical studies that radical ions, formed by electron transfer from the electron-rich to the electron-poor reaction partner, could also be intermediates in the cycloaddition.[3] The observation of transient charge-transfer (CT) bands in a series of [4 + 2] cycloadditions appeared to support this argument since, in addition, a relationship between the wavelength of the CT absorption and the rate of reaction was observed.[4] The light-induced electron transfer by means of picosecond laser excitation of CT bands was recently studied. The results, however, provided no confirmation for the involvement of radical ion pairs as intermediates in the [4 + 2] cycloaddition.[5]

In order to induce an electron transfer between diene and dienophile in a normal Diels-Alder reaction, model compounds with a high-lying HOMO in the diene and a low-lying LUMO in the dienophile must be chosen. For this reason, the dienes **1** and **2** were synthesized.[6] **1** is

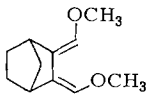
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[**] This work was supported by the Ministerium für Wissenschaft und Forschung des Landes Nordrhein-Westfalen.

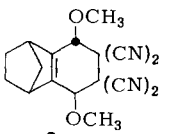
formed by the reaction of *trans*-2,3-norbornanedicarbaldehyde with tetrakis(dimethylamino)titanium[7] in 61% yield as a liquid mixture of isomers with a ratio of *trans/cis* : *trans/trans* = 3.3 : 1; **2** is formed exclusively in the *trans/cis* form in a yield of 88% via elimination of methanol twice from the bisdimethylacetal of *trans*-2,3-norbornanedicarbaldehyde in the presence of phosphoric acid and pyridine.



1

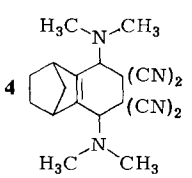


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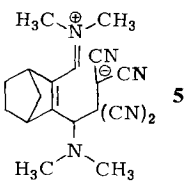


3

The reaction of **2** with tetracyanoethylene (TCNE) leads at room temperature in the absence of solvent to **3** (80%, colorless crystals, m.p. = 158—161 °C).[6] However, when the isomeric mixture of **1** is treated in tetrahydrofuran (THF) at room temperature with TCNE in ca. 1 M concentrations in a ratio of 1 : 1, a deep colored solution immediately forms, from which a finely crystalline, colorless precipitate begins to deposit after 5 min. After completion of the precipitation by addition of cyclohexane, a 1 : 1 adduct (correct elemental analysis) is obtained in quantitative yield; it melts with decomposition at 72 °C, turns brown in air as it slowly decomposes, and is light sensitive.



4

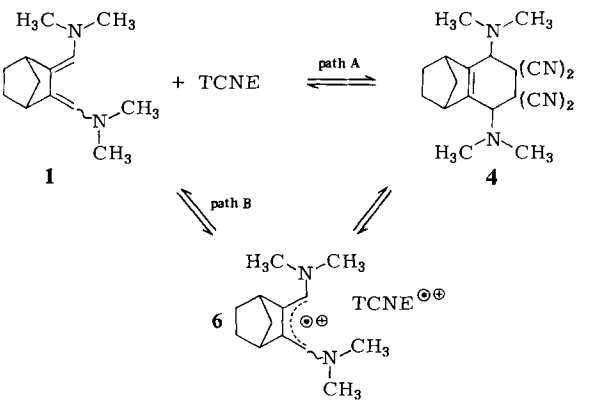


5

The IR spectrum of the adduct in Nujol exhibits a very weak band ($\nu_{C\equiv N}$ vibration) at 2236 cm^{-1},[8] which is characteristic for cycloadducts of **1** and cyanoolefins (Table 1) and therefore supports the structure **4** for the solid. The possible alternative structure, zwitterion **5**, should exhibit $\nu_{C\equiv N}$ bands at 2110—2120 and 2170—2180 cm^{-1}.[9,10] In a KBr pellet (prepared under nitrogen), the adduct shows a completely different IR spectrum: a broad, intense $\nu_{C\equiv N}$ absorption is observed at 2199 ± 5 cm^{-1} (two unresolved bands), which is typical for $\nu_{C\equiv N}$ vibrations of the TCNE radical anion;[11] this result is interpreted as indicating dissociation of **4** to the radical ion pair **6** in KBr (Scheme 1). The ESR spectrum of the crystalline compound contains a poorly resolved multiplet at $g = 2.00281 \pm 0.00001$, the main line of which (corresponding to the *g*-value of $TCNE^{\odot\ominus}$[11]) can be saturated, leaving a broad multiplet. By comparison with a standard (diphenylpicrylhydrazyl, DPPH), the amount of the radical ion pair **6** in the solid cycloadduct was shown to be ca. 0.001%. Dissolved in THF, **4** exhibits the intense ESR spectrum of $TCNE^{\odot\ominus}$ and, at higher gain, a highly resolved multiline spectrum, which is assigned to the radical cation of **1**; this spectrum, in contrast to that of $TCNE^{\odot\ominus}$, disappears after a relatively short time (1—2 h). This spectrum is also observed when **1** is oxidized with $AgBF_4$ in CH_2Cl_2.[12] The concentration of the radical ion pair in THF is ca. 0.001%, as it is in the solid. When a sample of the solid adduct is heated under argon to 60—70 °C in an ESR spectrometer, an increase in the intensity of the ESR signal (factor of 100) is observed: i.e., thermal dissociation to radical ions occurs. When the adduct is dissolved in polar acetonitrile, the amount of $TCNE^{\odot\ominus}$ increases by a factor of 2000. The increased dissociation is, however, also accompanied by a faster reaction to give non-radical secondary products.

Dilute solutions of **4** or of the reaction partner **1** and TCNE are not stable. An accurate UV/VIS investigation is extremely difficult since fresh solutions change their color several times within a short period of time. However, $TCNE^{\odot\ominus}$ bands could be identified unambiguously.[11]

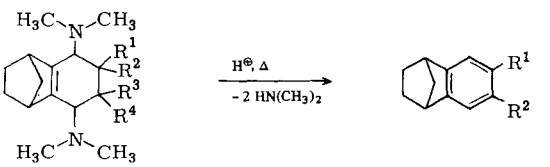
Owing to the half-wave redox potentials of the diene[13] and of the dienophile TCNE (Table 1), a quantitative electron transfer is expected upon mixing of the partners. ESR spectra, taken immediately after mixing, support this expectation. The adduct **4** crystallizes out of a concentrated solution of **1** and TCNE; **4** reacts further irreversibly in solution via the radical ions to give subsequent products.



1 **4** **6**

Scheme 1.

These observations are accounted for by Scheme 1. Although the direct formation of **4** from **1** and TCNE (path A) cannot be excluded, the results appear to better support the path via the radical ion pair (path B).



12a, R^1=CO_2CH_3, R^2=R^3=R^4=H
12b, R^1=CN, R^2=R^3=R^4=H
12c, R^1=R^3=CO_2CH_3, R^2=R^4=H
12d, R^1=R^3=CN, R^2=R^4=H
12e, R^1=R^2=CO_2CH_3, R^3=CN, R^4=H

13a, R^1=CO_2CH_3, R^2=H
13b, R^1=CN, R^2=H
13c, R^1=R^2=CO_2CH_3
13d, R^1=R^2=CN

Table 1. Reaction of 2,3-bis(*N,N*-dimethylaminomethylene)norbornane **1** with the dienophiles **7**—**11** to give the cycloadducts **12a**—**12e**.

Dienophile	Yield [%]	$E_{1/2}$ vs. SCE [V] [a]	ν (C≡N) [cm^{-1}] [b]
H_2C=CH–CO_2CH_3 **7**	92	< −2.2	—
H_2C=CH–C≡N **8**	80	< −2.2	2230
trans-H_3CO_2C–CH=CH–CO_2CH_3 **9**	93	−1.45	—
trans-NC–CH=CH–CN **10**	82	−1.29	2240
NC–CH=C(CO_2CH_3)$_2$ **11**	100 (crude)	−0.93	2235
$(NC)_2C$=$C(CN)_2$	100	+0.23	2236

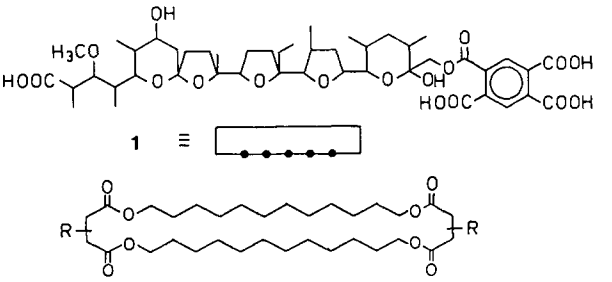
[a] In acetonitrile/0.1 M tetraethylammonium perchlorate. [b] ν(C≡N) of the cycloadducts.

In THF at room temperature, **1** reacts with less reactive dienophiles such as **7**—**11** (Table 1) to give the cycloadducts **12**[6] in high yield; intermediate radical ions are not detected. The adducts **12a**—**12d** split off two equivalents of dimethylamine at 140—160 °C under acid catalysis with formation of the compounds **13a**—**13d** (yield 50—70%).

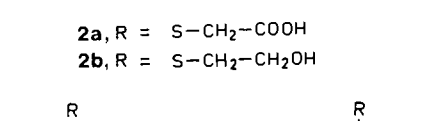
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CAS Registry numbers:
trans,cis-**1**, 95765-38-1; *trans,trans*-**1**, 95765-39-2; *trans,cis*-**2**, 95765-40-5; **3**, 95765-42-7; **4**, 95765-43-8; **6**, 95765-45-0; **7**, 96-33-3; **8**, 107-13-1; **9**, 624-49-7; **10**, 764-42-1; **11**, 62693-70-3; **12a**, 95765-46-1; **12b**, 95765-47-2; **12c**, 95765-48-3; **12d**, 95765-49-4; **12e**, 95765-50-7; **13a**, 82960-22-3; **13b**, 16513-55-6; **13c**, 33694-65-4; **13d**, 52477-73-3; TCNE, 670-54-2; $Ti(NMe_2)_4$, 3275-24-9; *trans*-2,3-norbornanedicarboxaldehyde, 36390-64-4; *trans*-2,3-bis(dimethoxymethyl)norbornane, 95765-41-6.

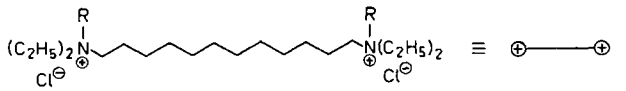
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[8] The IR spectra were recorded on Perkin Elmer 397 and 580 instruments. Calibration bands: CO_2 and polystyrene.
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[11] O. W. Webster, W. Mahler, R. E. Benson, *J. Am. Chem. Soc. 84* (1962) 3678.
[12] An interpretation of this spectrum (g-value $\approx 2.00310 \pm 0.00005$) is difficult since several 1000 hyperfine lines are expected for the radical cation; total width ca. 7—8 mT.
[13] $E_{1/2} = -0.35$ V vs. SCE in acetonitrile/0.1 M tetraethylammonium perchlorate.



1 ≡



2a, R = S—CH_2—COOH
2b, R = S—CH_2—CH_2OH



3a, R = C_2H_5
3b, R = H

Sealing and Opening Porous Monolayer Vesicle Membranes

By *Jürgen-Hinrich Fuhrhop,* Ulrich Liman,* and *Hans Hermann David*

We have recently reported on the pore-forming monensin pyromellitate **1**, which makes a monolayer vesicle membrane of **2a** permeable to lithium ions; as little as ten molecules of **1** suffice for generation of a lithium pore in a vesicle of about 10^5 molecules of **2a**.[1] Herein, we report on the further development of the porous vesicle to give a sealed vessel of molecular dimensions (diameter ca. 1000 Å, wall thickness ca. 25 Å), which can be opened by acidification. Analogous systems are so far known only for protein-containing cell membranes[2] and polymeric vesicular and capsular membranes with intercalates of monomeric disulfides[3] or with grafted polyelectrolytes.[4]

A prerequisite for sealing the negatively charged pores made from **1** with the positively charged bolaamphiphiles[5] **3a** and **3b** was the use of an *uncharged* membrane composed of **2b**. Salt-filled vesicles of the diol **2b** with pores of **1** were prepared by ultrasonication of 1.0 mmol **2b** and 10^{-2} mmol (≙ 1.0 mol-%) **1** in 10 mL of a 0.03 M LiCl solution. After gel-filtration over Sephacryl with 0.03 M NaCl solution the vesicle solutions did not contain any more lithium ions (Table 1). The porous vesicles of **2b** with 1.0 mol-% **1** are stable for long periods,[6] while vesicle solutions without **1** rapidly become turbid. $Li^{\oplus}$-permeable membranes of **2b** are formed only at relatively high concentrations (≥ 1.0 mol-%) on pore formers **1**; in the case of the membrane of negatively charged **2a**, concentrations of **1** a hundred times smaller suffice for generation of pores. We attribute both these findings to the de-aggregating action of the negative charges of **1** which only comes into effect in an uncharged but not in a negatively charged membrane.

Table 1. $Li^{\oplus}$ concentration of [a] gel filtered vesicles [b] with pore former **1**.

[1] [mol-%]	[$Li^{\oplus}$] [ppb] Vesicle of **2a**	[$Li^{\oplus}$] [ppb] Vesicle of **2b**
0	29	28
0.001	28	—
0.01	0	—
0.1	0	25
1.0	0	0
100	0	0

[a] Determined by atomic emission spectroscopy [1]. [b] 1 mL of the vesicle dispersion (1.0×10^{-3} mol in 3×10^{-2} M LiCl) was passed through a Sephacryl-S 1000 column (1 × 20 cm, 0.03 M NaCl). The 4—6 mL fraction contained the vesicle.

When 10^{-1} mmol (≙ 10 mol-%) of the bolaamphiphiles **3a** or **3b** were added during the sonication, the $Li^{\oplus}$ ions enclosed in the vesicle were not removed by gel filtration at pH 7 or 12.5. The pore was "sealed". However, when the vesicle sealed with **3b** was filtered at pH 3 over a Sephacryl gel, no more $Li^{\oplus}$ was detectable. When the solution was acidified for only a few seconds (pH 3), neutralized, and then chromatographed, the $Li^{\oplus}$ was likewise completely diffused out of the vesicle. Analogous experiments with bis(tetraalkylammonium) "stoppers" **3a** did not lead in any instance to a liberation of $Li^{\oplus}$ ions from the vesicle cavity (Table 2). **3a** is thus a "stopper" that cannot be removed again.

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Table 2. $Li^{\oplus}$ concentration [a] of gel filtered [b] vesicles of different composition [c].

pH	[$Li^{\oplus}$] [ppb] 1.0 mol-% **1**	[$Li^{\oplus}$] [ppb] 10 mol-% **3b**	[Li] [ppb] 10 mol-% **3b** 1.0 mol-% **1**	[$Li^{\oplus}$] [ppb] 10 mol-% **3a** 1.0 mol-% **1**
3	0 [d, f]	44 [d]	0 [d]	26 [d]
7	0 [f]	30	26	24
12.5	0 [e, f]	—	20 [e]	22 [e]

[a] Determined by atomic emission spectroscopy [1]. [b] 1 mL of vesicle dispersion (1.0×10^{-3} mol in 3×10^{-2} M LiCl) was passed through a Sephacryl-S 1000 column (1 × 20 cm, 0.03 M NaCl). The 4—6 mL fraction contained the vesicle. [c] The components were sonicated together and the vesicle dispersion immediately transferred to the Sephacryl column. [d] 0.058 M NaCl and 0.002 M HCl instead of 0.03 M NaCl. [e] 0.03 M NaOH instead of NaCl. [f] Fluorescent pyranine could be enclosed in the porous vesicle.

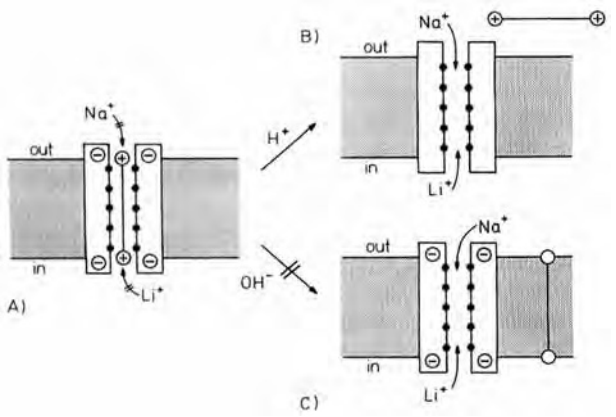


Fig. 1. A) The bolaamphiphiles **3a** and **3b** seal the negative pores of **1**. B) On acidification at pH 3 the carboxylate groups in **1** are neutralized, and the water-soluble stopper **3b** leaves the pore. C) On neutralization of the ammonium head-groups of **3b**, (reversible) diffusion of the amine from the pore into the hydrophobic membrane was expected; this does not occur.

We conclude from the above observations that the cases A and B of the model in Figure 1 can be realized with the diamine **3b**; opening of the sealed pore does not function in alkali (model C). To our knowledge the pore of **1** and the "stoppers" **3a** ("irreversible") and **3b** (partially "reversible") represent the first system in which a controllable formation and destruction of domains of foreign molecules closes or opens a lipid membrane for flow of ions.

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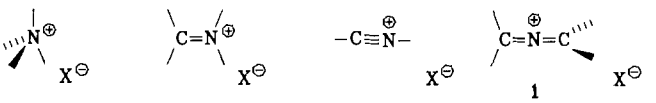
CAS Registry numbers:
1, 91003-04-2; **2a**, 95742-08-8; **2b**, 95742-07-7; **3a**, 95742-09-9; **3b**, 95742-10-2; Li, 7439-93-2; Na, 7440-23-5; hydrogen ion, 12408-02-5.

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[6] The slightly clouded vesicle solution of **2b** (10^{-3} M) became clear on sonication in the presence of **1** (10^{-5} M). The solution remained unchanged after three days. After a few weeks the vesicle precipitated, but could be quantitatively redissolved by ultrasonication.

A New, Facile Route to 2-Azaallenium Salts—Bis(2-adamantylidene)ammonium Hexachloroantimonate**

By *Ernst-Ulrich Würthwein,* Rainer Kupfer, Peter H. M. Budzelaar, Cornelia Strobel,* and *Horst P. Beck*

2-Azaallenium salts **1**, like ammonium, alkylideneammonium, and nitrilium salts, constitute a class of compounds with (formally) positively charged "octet" nitrogen atoms.



Ammonium salts	Alkylidene-ammonium salts	Nitrilium salts	2-Azaallenium salts
			1

The salts **1**, which are now accessible by several synthetic methods,[1,2] have been proposed as intermediates in S_N1 reactions.[3] Their gas-phase chemistry has been studied theoretically[4] and experimentally[5] and the structure of a derivative has been determined by X-ray analysis.[6]

We report here a simple, one-step synthesis of the salts **1**, starting from non-enolizable aldehydes and ketones.

Jochims et al.[2,6] use substituted chloromethyl isocyanates **2**, accessible from imines and phosgene,[7] as starting materials in their synthesis. The compounds **2** react with carbonyl compounds and Lewis acids to give 2-azaallenium salts **1**, analogously to the procedure reported by *Staudinger* et al.[8] for aryl isocyanates.

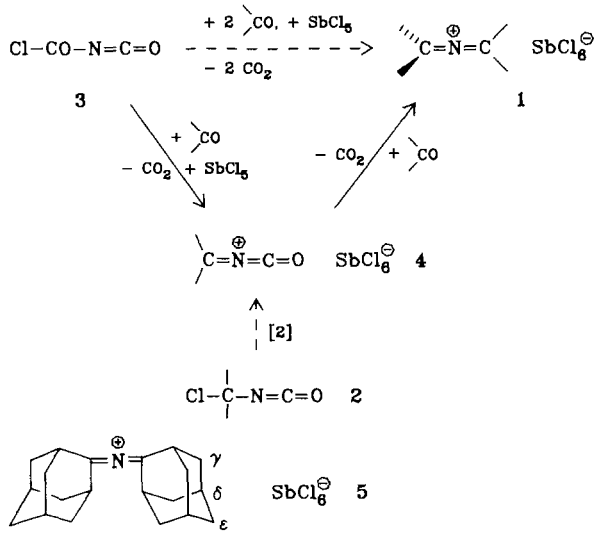
In our method we use this isocyanate reaction *twice* by reacting the commercially available chlorocarbonyl isocyanate **3** with two mole equivalents of the carbonyl compound in the presence of antimony pentachloride as Lewis acid. We thus obtain the salts **1** without the synthesis of imines, which are often very sensitive, and without use of phosgene. Chlorocarbonyl isocyanate **3** functions here as a reagent for the "$=\overset{\oplus}{N}=$" synthon, since only the nitrogen atom of **3** is present in the product **1**. Our ^{13}C-NMR experiments suggest that **3** is complexed and activated by $SbCl_5$, but not dissociated to the $O{=}C{=}\overset{\oplus}{N}{=}C{=}O$ ion, which has not yet been observed (see also [9]). As in the experiments of *Jochims* et al.,[2,6] 1-Oxa-3-azabutatrienium salts **4** are likely intermediates in this reaction.

In the absence of Lewis acids, **3** reacts with carbonyl compounds to give α-chloroalkyl isocyanatocarbonates.[10]

The aromatic carbonyl compounds benzaldehyde and benzophenone react smoothly to give the corresponding salts **1** in 59 and 75% yield, respectively (see also [11]). The reaction with pivaldehyde or di-*tert*-butyl ketone does not yield the expected salts **1**, possibly because of the chlorinating properties of antimony pentachloride. Adamanta-

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none, however, leads to the hitherto unknown bis(2-adamantylidene)ammonium hexachloroantimonate **5** in 28% yield;[11] the cation of **5**, the first alicyclic 2-azaallenium salt, is isoelectronic with bis(adamantylidene)methane, first synthesized by *Wynberg* et al.[12]

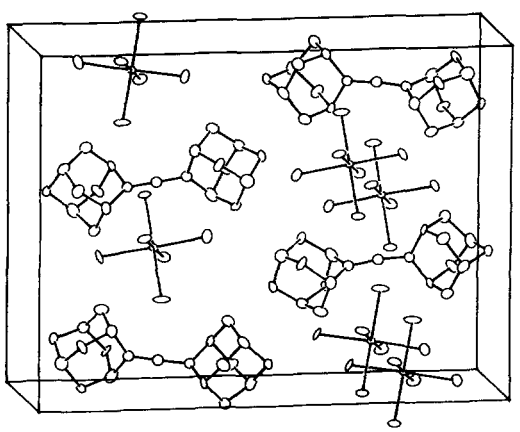


Fig. 1. ORTEP diagram of a unit cell of bis(2-adamantylidene)ammonium hexachloroantimonate **5**. View on (001). Vibration ellipsoids with 10% probability. The crystals are disordered, mainly with respect to rotations around the C=N=C axis of the cation.

The crystal structure of **5** was determined by X-ray analysis.[13] As with other highly symmetric molecules, the crystals of **5** are significantly disordered ($R = 0.092$)[14] (see Fig. 1). The theoretically predicted structural flexibility of this class of compounds[4] is indicated by the large temperature factors of the C=N=C bridging atoms (in Fig. 1 isotropic). The measured C=N bond lengths (130, 135±9 pm) and the C–N–C bond angle (167±10°) are too crude for a detailed conformational analysis, but the orthogonality of the skeleton of **5** is easily recognized in Figure 1. Surprisingly, the crystal packing strongly resembles the CaC_2 structure; a slight tilting of the dumb-bell shaped cations of **5** in the *c*-direction causes the observed hyperstructure (*c* is doubled in comparison to the CaC_2 structure). In other words, the structure of **5** may be regarded as being built up from layers of the cations of **5** parallel to 012 with the $SbCl_6$ anions in a separate layer above the gaps of the cation layer. A low-temperature X-ray structure determination of **5** is in preparation.

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CAS Registry numbers:
1 (R = Ph, R′ = H), 76058-07-6; **1** (R = R′ = Ph), 20055-29-2; **1** (R = Bu-*t*, R′ = H), 95407-73-1; **1** (R = R′ = Bu-*t*), 95407-75-3; **3**, 27738-96-1; **5**, 95407-77-5; $SbCl_5$, 7647-18-9; benzophenone, 119-61-9; pivalaldehyde, 630-19-3; di-*tert*-butyl ketone, 815-24-7; adamantanone, 700-58-3; benzaldehyde, 100-52-7.

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[11] A solution of **3** (1.06 g, 10.0 mmol) in anhydrous chloroform (10 mL) was added dropwise at −50 to −60 °C to a solution of $SbCl_5$ (3.0 g, 10.0 mmol) in $CHCl_3$ (20 mL) with stirring under dry N_2. After addition of a solution of adamantanone (3.5 g, 2.3 mmol) in $CHCl_3$ (20 mL), the reaction mixture was allowed to warm to room temperature and then refluxed for 12 h. The precipitate was filtered off, dissolved in hot nitromethane (or acetonitrile) with addition of little charcoal, and filtered hot (with sea sand). Small colorless plates were obtained on cooling, washed with 2 × 10 mL of dichloromethane and 2 × 10 mL of diethyl ether, and dried in vacuo; yield 1.7 g **5** (28%); IR ($CHBr_3$): $\nu = 1935\ cm^{-1}$ (cumulene).
[12] J. Strating, A. H. Alberts, H. Wynberg, *Chem. Commun. 1970*, 818.
[13] Orthorhombic crystals; m.p. = 269 °C; space group $Pna2_1$, $Z = 4$, $a = 15.788$, $b = 20.282$, $c = 7.938$ Å; intensity measurements at RT (AgK_α, graphite monochromator) on a Philips four-circle diffractometer PW 1100; structure determination using SHELX 76. 25 132 reflections, 2534 symmetry independent; $R = 0.0922$ (anisotropic, γ-, δ-, ε-adamantane carbon atoms fixed, C=N=C isotropic). Further details of the crystal structure investigation are available on request from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen (FRG), on quoting the depository number CSD 51 068, the names of the authors, and the journal citation.
[14] O. Ermer, *Angew. Chem.* 95 (1983) 251; *Angew. Chem. Int. Ed. Engl.* 22 (1983) 251.

Stable Triaziridines**

By *Gerd Kaupp*,* *Oswald Dengler*, *Klaus Burger*,* and *Silvia Rottegger*

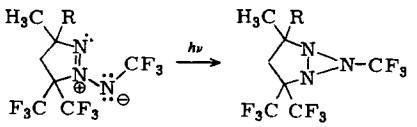
Many years of intense efforts to synthesize nitrogen homocycles afforded, apart from aromatic pentazoles,[1] only recently triaziridines, which, however, proved to be unstable at room temperature.[2] Triaziridines have also been postulated as intermediates in the photoisomerization of azimines.[3]

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We report now[4] the synthesis of triaziridines that are stable to at least 80°C by irradiation of suitably substituted azimines. In this process, both the steric stabilizing effect of *tert*-alkyl groups[5] and, in particular, the electronic stabilizing effect of perfluoroalkyl groups[6] are exploited.

The educts **1**[3] are readily available from trifluoromethyl-substituted azomethine imines[7] and trifluoronitrosomethane via dipole metathesis.[8] When the azimines **1** are irradiated with light of wavelength $\lambda = 253.7$ nm at room temperature, the triaziridines **2** are formed in very good yields; they can be purified by fractional distillation.[9]

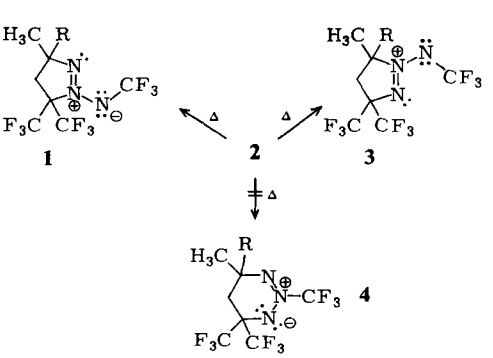


1 **2**

a, R = CH_3; **b**, R = $C(CH_3)=CH_2$; **c**, R = C_6H_5

The structure assignment of **2** is based on the spectroscopic data. The characteristic IR absorption of the azimine function in the region 1495–1500 cm^{-1}[3] and the UV absorptions of **1** at $\lambda_{max} = 257$ nm are gone. The NMR spectra of **2a** (only one isomer) show the magnetic nonequivalence of the methyl groups and of the trifluoromethyl groups bonded to the five-membered ring [^1H NMR (200 MHz; $CDCl_3$): $\delta = 1.48$ (s, br.; CH_3), 1.52 (s; CH_3); ^{13}C NMR (50.24 MHz; $CDCl_3$): $\delta = 26.2$ (q, $J_{CF} = 3.3$ Hz; CH_3), 26.8 (s, CH_3); ^{19}F NMR (56.43 MHz; $CDCl_3$, trifluoroacetic acid as external standard): $\delta = 8.0$ (q, $J = 10.5$ Hz; CCF_3); 10.5 (q, $J = 10.5$ Hz; CCF_3); 5.7 (s; NCF_3)]. Since the five-membered ring is still intact (CH_2: $\delta = 2.22$; AB degenerated to a singlet), this result can only be accounted for by a ring closure of the azimine group. An NN double inversion[10] cannot be observed in the range of stability of **2**. Accordingly, for **2b** and **2c** (R ≠ CH_3), diastereomeric mixtures (two isomers each) are obtained;[9] these can be separated by capillary gas chromatography and identified by mass spectrometry.

Since triaziridines,[2,3] like other three-membered heterocycles, are valence tautomers of open-chain 1,3-dipoles,[11] the thermolysis of **2** above 100°C also confirms the structure. It results in the cleavage of either one of the nearly equivalent peripheral N–N bonds to give **1** and **3**,[9] as expected, in a ratio of ca. 1:1 (**3a**–**c** also give **2** upon photolysis, as shown by UV analysis); a ring enlargement to give the six-membered-ring azimine **4** could not be detected by ^{19}F-NMR spectroscopy. At 113.2°C in *n*-dodecane, the rate constants for formation of the azimine (UV-kinetics) from **2a**–**c** are $k_1 = 3.34 \times 10^{-4}$, 2.55×10^{-4}, and 2.42×10^{-4} s^{-1}, respectively. The Arrhenius parameters for the formation of **1a** + **3a** from **2a** were determined to be $E^a = 125$ kJ/mol and $\log A = 13$. In contrast, the tricyclic triaziridine ($E^a = 100$ kJ/mol) described in [2] already decomposes at room temperature.



1 **2** **3** **4**

The stability of the triaziridines **2** makes possible extensive physical investigations on this theoretically interesting ring system (see also [11]).

Experimental Procedure

1 [3] (1.0 g) is irradiated in anhydrous *n*-pentane (50 mL) for 2 h at room temperature under argon with a low-pressure mercury lamp (Hanau TNN 15). After evaporation of the solvent in vacuum and reflux (ca. 1 h; bath at 60°C), **2** is distilled (air bath heated with a heat gun) at 0.1 to 0.001 torr, condensed onto a cold finger at −30°C, and collected in a condenser cooled with liquid nitrogen; it is thus separated from a small amount of residue (45; 60; 55 mg). Analytically and spectroscopically pure **2a** (80%), **2b** (79%), and **2c** (85%) (not optimized) are obtained [9].

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1a, 85122-33-4; **1b**, 85122-34-5; **1c**, 85122-35-6; **2a**, 95388-86-6; **2b**, 95388-87-7; **2c**, 95388-88-8.

[1] I. Ugi in A. R. Katritzky, C. W. Rees: *Comprehensive Heterocyclic Chemistry, Vol. 5*, Pergamon Press, Oxford 1984, p. 839.
[2] L. Hoesch, C. Leuenberger, H. Hilpert, A. S. Dreiding, *Helv. Chim. Acta 65* (1982) 2682.
[3] K. Burger, O. Dengler, A. Gieren, V. Lamm, *Chem.-Ztg. 106* (1982) 408; O. Dengler, Dissertation, Technische Universität München 1983.
[4] S. Rottegger, presented at the 1. Deutschen Fluortag, Königstein, October 1984.
[5] W. Adam, O. L. Chapman, O. Rodriguez, R. Rucktäschel, P. W. Wojtkowsky, *J. Am. Chem. Soc. 94* (1972) 1365.
[6] D. M. Lemal, L. H. Dunlap, Jr., *J. Am. Chem. Soc. 94* (1972) 6562.
[7] K. Burger, W. Thenn, R. Rauh, H. Schickaneder, A. Gieren, *Chem. Ber. 108* (1975) 1460.
[8] K. Burger, H. Schickaneder, C. Zettl, *Angew. Chem. 89* (1977) 60; *Angew. Chem. Int. Ed. Engl. 16* (1977) 54.
[9] Correct elemental analyses were obtained for all compounds.
[10] M. Kaftory, *J. Am. Chem. Soc. 105* (1983) 3832.
[11] Three-membered rings that contain at least one heteroatom with a lone electron pair can in principal open photochemically and thermally to give 1,3-dipoles. With triaziridine **2a**, we achieved the first photochemical ring opening to the 1,3-dipoles **1a** and **3a** by gas-phase photolysis ($\lambda = 184.9$ nm).

Reductive Alkylation of Bituminous Coal: Coal-Propanesulfonic Acids Having Remarkable Solubilities

By *Matthias W. Haenel*,* *Udo-Burckhard Richter*, and *Heribert Hiller*

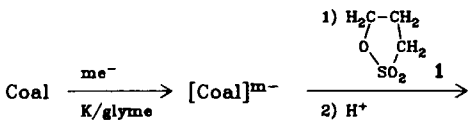
Dedicated to Professor Günther Wilke on the occasion of his 60th birthday

To study the chemistry of bituminous coal, soluble derivatives are needed which largely retain the original coal structure. In certain cases, remarkable solubilities in pyridine are found for coal derivatives that have been obtained by reducing bituminous coal with the "blue solutions" formed by potassium in oligomeric polyethylene glycol dimethyl ethers and quenching the "coal anions" so generated with dimethyl sulfate or alkyl halides.[1] New products

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having interesting solubilities were expected by the use of the γ-sultone of 3-hydroxypropanesulfonic acid **1** in the reductive alkylation of bituminous coal, since nucleophiles, including organometallic carbanion species, open the sultone ring, forming 3-substituted propanesulfonic acids.[2]

Accordingly, the reductive alkylation of a medium volatile bituminous coal from the Ruhr coalfield (Table 1) by treatment of the finely ground coal with potassium in a mixture (6:1) of dimethoxyethane and "octaglyme"[1] at −25°C and subsequent addition of **1** yielded coal-propanesulfonic acids **2**.



Coal−$(CH_2-CH_2-CH_2-SO_3R)_n$ **2**, R = H;
3, R = CH_3 ; **4**, R = NR_4^+

Elemental analyses and acidimetric determinations of the acid groups (Table 1) indicate that the average composition changes—neglecting the heteroatoms—from $C_{100}H_{63}$ in the starting coal to $C_{100}H_{76}(CH_2-CH_2-CH_2-SO_3H)_5$ in **2**. Hence, in addition to the alkylation with **1**, the coal was hydrogenated, having taken up ca. 13 hydrogen atoms per 100 carbon atoms via Birch-Hückel reduction of polycyclic arenes and/or reductive cleavages of ether bonds and benzylic C−C bonds.[3] ^{13}C-NMR spectra indicate that mainly the aliphatic (benzylic) C atoms of the "coal-anions" were alkylated in the analogous reductive methylation with [^{13}C]methyl iodide.[1b] Therefore, the majority of the propanesulfonic acid groups in **2** should be bonded in the same manner to C atoms of the coal skeleton.

2 and the sodium salts of **2** are up to 89% soluble in water; therefore, taking into consideration the mineral matter (4.1% ash, Table 1), only ca. 7% of the coal remains undissolved. This surprising water solubility apparently has to be attributed to the solvation of dissociated ions since the acids **2** are precipitated by concentrated hydrochloric acid and their methyl esters **3** (Table 1, prepared from **2** and trimethyl orthoformate[4]) are water-insoluble. Quaternary organic ammonium salts such as Hyamine 10-X[5] precipitate **4** (Table 1) from the black aqueous solutions of the sodium salts of **2** so completely that the supernatant solution above the black precipitate becomes water-clear. The ammonium salts **4** are soluble in polar organic solvents such as pyridine, methanol, and ethanol, indicating that undissociated ion pairs are probably present.[6] The salts of **2**, which, depending on the cation, can dissolve in water as well as in organic solvents, are therefore attractive coal-derivatives for further chemical and spectroscopic studies.

Table 1. Composition (expressed as normalized atomic ratios) and solubilities of the starting coal and of the coal derivatives **2**, **3**, and **4** [Westerholt mine, seam "Robert", 23.6% volatile matter, 4.1% ash, 0.7% water, 89.4% C, 4.7% H, 1.8% N, 3.8% O, 1.9% S]. **a**, **b**: representative examples.

	C	H	N	O [a]	S	H^+/100C [b, c]	n/100C [c]	Solubility [e]
Starting coal	100	63	1.7	3.2	0.8	—	—	12% (p)
2a	100	102.5	0.8	23.3	5.4	5.3	≈5	89% (w)
2b	100	98.1	1.3	19.5	5.0	5.6	≈5	
3a	100	110.0	0.4	21.5	5.2		≈5	< 5% (p)
4a [d]	100	130.5	2.8	13.0	2.4		≈5	>90% (pme)
4b	100	128.8	2.6	13.3	2.3		≈5	

[a] Determined directly. [b] Determined acidimetrically. [c] Relative to 100C of the starting coal. [d] R_4N^+ = cation of Hyamine 10-X. [e] In pyridine (p), water (w), methanol (m), ethanol (e).

The solubility of the ammonium salts **4** in pyridine was utilized to obtain information on the molecular weights by carrying out preparative gel permeation chromatography (column: diameter 5.3, length 125 cm; volume 2750 cm^3, Sephadex LH 60, pyridine, 60°C) and subsequently determining the molecular weights of the individual GPC fractions by means of vapor-phase osmometry (pyridine, 60°C).[7] The satisfactory linear correlation found between the measured molar masses M_{ni} and the elution volumes EV_i (Fig. 1) demonstrates that the separation was mainly due to size exclusion chromatography and that interfering polar adsorption was essentially avoided.[7] From the molecular weight distribution between 800 and 15000 g mol^{-1}, which was plotted versus the weight percents m_i (Fig. 2), a calculated number average molecular weight of $\overline{M}_n$ = 2670 g mol^{-1} is obtained. Within the limits of experimental error, this corresponds to the value $\overline{M}_n$ = 3005 g mol^{-1} determined directly for the total product **4**.

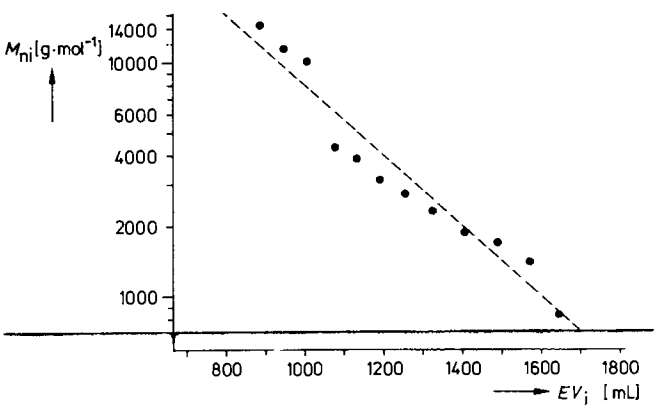


Fig. 1. Measured molecular weights M_{ni} of the GPC fractions of **4** versus the elution volumes EV_i (Sephadex LH 60, pyridine, 60°C).

If the mass fractions of the propanesulfonic acid groups and the quaternary ammonium cations in **4** are taken into consideration, molecular weights between 400 and 7000 g mol^{-1} are obtained for the bituminous coal investigated here.[8] However, it is not possible to deduce from these values the molecular sizes in the original coal since the de-

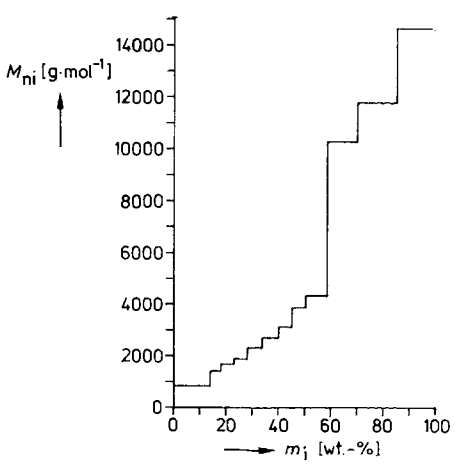


Fig. 2. Molecular weight distribution of **4** (M_{ni} versus weight percents m_i).

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gradation that occurs through cleavage of ether and C–C bonds[3] in the potassium reduction cannot be quantified. We are therefore attempting to attach alkanesulfonic acid groups to the coal skeleton via non-reductive reactions.

Experimental procedure

Finely ground coal (10 g, average particle diameter 60 μm) was stirred at −25 °C for 24 h in a "blue solution", which had been prepared by adding potassium (10 g, 256 mmol) in small pieces to 300 mL of dimethoxyethane and 50 mL of polyethylene glycol dimethyl ether ("octaglyme").[1] After unreacted potassium (ca. 3.4 g) had been removed **1** (31.2 g, 256 mmol), dissolved in 20 mL of dimethoxyethane, was added within 10 min and the mixture was then stirred for 24 h at −25 °C. After the solvent had been distilled off, the residue was extracted with ether in a Soxhlet apparatus for 3 d and dried. All water-soluble reagents were removed by suspending the material in 200 mL of hydrochloric acid (50% v/v) and centrifuging in order to isolate the product; this process was carried out six times. The residue, after washing once more on a glass filter with acetone and drying (3 d at 10^{-3} torr and 25 °C), yielded 13.1 g dark **2**.[9]

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[1] a) K. Niemann, U.-B. Richter, *Fuel 61* (1981) 423; K. Niemann, U.-B. Richter, M. W. Haenel, *Erdöl Kohle Erdgas Petrochem. 34* (1981) 307; b) M. W. Haenel, R. Mynott, K. Niemann, U.-B. Richter, L. Schanne, *Angew. Chem. 92* (1980) 653; *Angew. Chem. Int. Ed. Engl. 19* (1980) 636; and references cited therein.

[2] J. H. Helberger, R. W. Heyden, H. Winter, *Justus Liebigs Ann. Chem. 586* (1954) 147; W. E. Truce, F. D. Hoerger, *J. Am. Chem. Soc. 77* (1955) 2496; R. F. Fischer, *Ind. Eng. Chem. 56* (1964) 41.

[3] L. Schanne, M. W. Haenel, *Tetrahedron Lett. 1979*, 4245; E. Grovenstein, Jr., A. M. Bhatti, D. E. Quest, D. Sengupta, D. van Derveer, *J. Am. Chem. Soc. 105* (1983) 6290; and references cited therein.

[4] In analogy to H. Cohen and J. D. Mier, *Chem. Ind. (London) 1965*, 349.

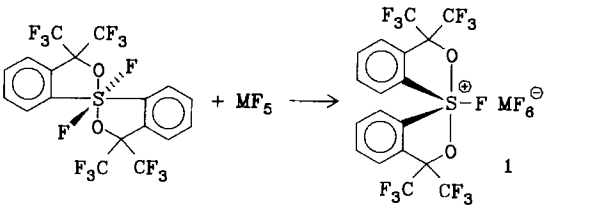
[5] Hyamine 10-X ((diisobutylcresoxyethoxyethyl)dimethylbenzylammonium chloride monohydrate, Röhm & Haas) precipitates lignin sulfonates from aqueous solutions as quarternary ammonium salts which are soluble in methanol: G. R. Quimby and O. Goldschmid, *Tappi 49* (1966) 562: *Chem. Abstr. 66* (1967) 47475m.

[6] The molar mass determined by vapor-phase osmometry corresponds to the undissociated ion pair for the ammonium salt formed between Hyamine 10-X and *p*-toluenesulfonic acid in pyridine.

[7] L. Schanne, M. W. Haenel, *Fuel 60* (1981) 556.

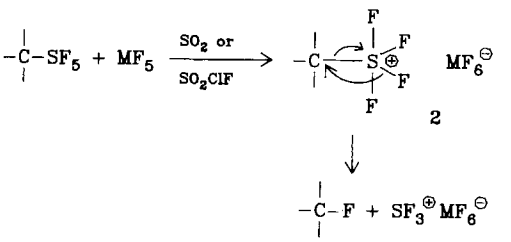
[8] Some similar but also some much higher molecular weights are suggested for soluble coal products. Cf. H. P. Hombach, W. Hodek, G. Kölling, *Erdöl Kohle Erdgas Petrochem. 32* (1979) 134; K. Ouchi, Y. Hirano, M. Makabe, H. Itoh, *Fuel 59* (1980) 751; R. M. Davidson in M. L. Gorbaty, J. W. Larsen, I. Wender: *Coal Science, Vol. 1*, Academic Press, New York 1982, p. 84; C. J. Collins, R. Triolo, M. H. Lietzke, *Fuel 63* (1984) 1202; and references cited therein.

[9] We thank the Raschig GmbH, Ludwigshafen (FRG), for a donation of 1,3-propanesultone.



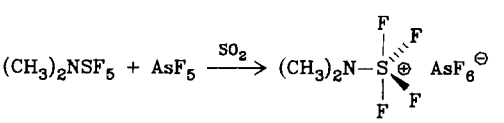
1a, M = P; **1b**, M = As

The *S*-alkyl salts **2**[3,4] could only be detected in solution at low temperatures (−100 to −40 °C) by NMR spectroscopy. At higher temperatures, they rapidly decompose.

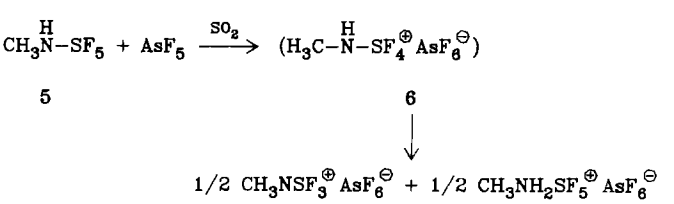


For the amino derivatives **4**, which are analogous to **2**, the corresponding decomposition is not possible; moreover, dialkylamino groups should stabilize the cationic center. Thus, **3**[7] reacts with AsF_5 in liquid SO_2 at room temperature to give quantitatively the exceptionally stable salt **4**.[8] The salt **6**, which is expected from **5**[9] and contains a monoalkylamino group, is not stable and decomposes into **7**[10] and **8**.[11] In the amino sulfurpentafluorides **5** and **3**, the nitrogen is still basic,[12] as shown by the formation of **8** and **9**,[13] respectively.

The adduct $F_5S(CH_3)_2NAsF_5$ may be considered as a structural alternative to the salt **4**. The ^{19}F-NMR spectrum (Fig. 1) provided the unequivocal proof for the formation of **4**; at low temperatures, it shows the expected 14 lines of the A_2B_2 splitting pattern. The septet of each resonance is



3 **4**



5 **6** **7** **8**



9

$(CH_3)_2NSF_4^{\oplus}AsF_6^{\ominus}$—Synthesis and Stability of a Simple Pentacoordinated Sulfur(VI) Cation**

By *Thomas Meier* and *Rüdiger Mews**

Whereas pentacoordinated phosphoranes are well studied,[1,2] little information is available on the isoelectronic pentacoordinated sulfur(VI) cations,[3–6] which have also been called "persulfuranonium"[3,4] or "persulfonium"[5,6] ions. Up to now, only the salts **1a**, **b**, containing such an ion, have been described.[5,6] The chelating ligand is thought to be decisive for their stability.[4]

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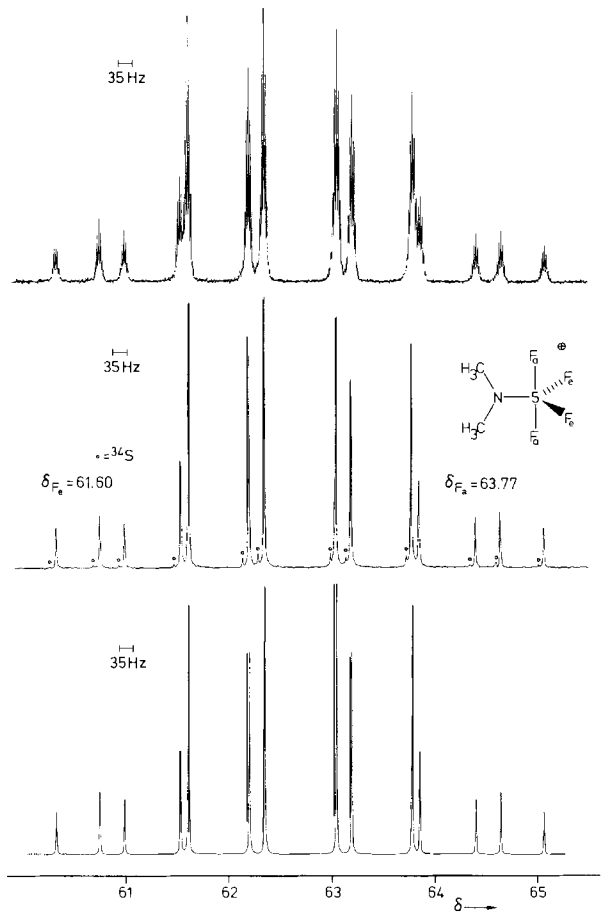


Fig. 1. Top: ^{19}F-NMR spectrum of the cation in **4** (Bruker AM 250, -55°C, 30 percent in SO_2); middle: same as above but proton-decoupled; bottom: calculated spectrum.

caused by interaction with the six protons of the dimethylamino group. The NMR data (Table 1) show that the cation in **4** exhibits trigonal bipyramidal coordination at the central sulfur. The dimethylamino group should occupy one of the equatorial positions[16] as in the isoelectronic phosphorane $(CH_3)_2NPF_4$.[1, 2, 14, 15]

Table 1. ^{19}F- and ^{1}H-NMR data for $(CH_3)_2NSF_4^{\oplus}$ (-55°C, 30 percent in $SO_2/CDCl_3/CFCl_3$; $\delta(^1H)$ relative to TMS) and $(CH_3)_2NPF_4$ (-90°C, toluene, $CFCl_3$ (^{19}F): room temperature, pure substance, TMS (^{1}H)) [14].

	$\delta(F_a)$	$\delta(F_e)$	$^2J(F_aF_e)$ [Hz]	$\delta(CH_3)$	$^4J(HF)$ [Hz]
$(CH_3)_2NSF_4^{\oplus}$	63.77	61.60	220.6	3.76	4.0
$(CH_3)_2NPF_4$	-59.0	-75.9	72	2.85	2.05

In contrast to **4**, only one signal is found in **2** for the different fluorine atoms of the cation.[3, 4] For the isoelectronic alkyltetrafluorophosphoranes RPF_4, the intramolecular motion can only be slowed down enough to observe the separate signals for F_a and F_e in the ^{19}F-NMR spectrum when R is the extremely bulky 2,4,6-(tBu)$_3$C$_6$H$_2$ group.[17] The NMR data presented in Table 1 show that the spectra of the isoelectronic species $(CH_3)_2NSF_4^{\oplus}$ and $(CH_3)_2NPF_4$ show a similar trend with regard to both the relative chemical shifts and the coupling constants. The assignment of the high-field signals to F_e in **4** was made in analogy to the phosphorane system.[18, 19] In contrast to $(CH_3)_2NPF_4$, no clean septet for the fluorine signal of **4** is found even at room temperature. The activation barrier for the pseudorotation in the cation is appreciably higher (≈ 55 kJ/mol at an estimated coalescence temperature of 35°C) than in the isoelectronic neutral compound (36.8 kJ/mol at -85°C).[15] The low-temperature spectra (-40°C) of **4** show no evidence of hindered rotation around the S–N bond. The splitting pattern of the ^{13}C-NMR signal (62.89 MHz, TMS: $\delta = 50.6$, $^3J(CF_a) \approx 7$ Hz, $^3J(CF_e) \approx -1.7$ Hz)[20] can be interpreted as the A part of an AX_2Y_2 spin system; the spectral type $AXX'Y_2$ would be expected for hindered rotation.

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CAS Registry numbers:
3, 56641-35-1; **4** (M = As), 95313-50-1; **5**, 95313-51-2; **6**, 95313-53-4; **7**, 66901-77-7; **8**, 95313-55-6; **9**, 95313-57-8; AsF_5, 7784-36-3; $(CH_3)_2NPF_4$, 51922-00-0.

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[11] **8**: colorless solid, decomp. 66°C. NMR data: ^{19}F NMR: (235.35 MHz, $SO_2/CFCl_3$, -70°C). $\delta = 65.74$ (^2J(FF) 155.3 Hz, SF_4), 54.35 (SF); ^{1}H NMR: (250.13 MHz, SO_2) $\delta = 3.45$ (quint. ^4J(HF) 1.2 Hz, CH_3), 8.82 (s, NH_2).
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[13] NMR Data for **9**: ^{19}F NMR: $\delta = 57.49$ (^2J(FF) 152.2 Hz, SF_4), 55.88 (SF); ^{1}H NMR (-40°C): $\delta = 3.48$ (quint. ^4J(HF) 2.1 Hz, CH_3), 8.91 (s, NH).
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[16] In the pentacoordinated dimethylaminoperfluoro derivatives $(CH_3)_2NPF_4$, studied by electron diffraction (L. V. Vilkov, V. C. Mastrjakov, H. J. Sagova: *Bestimmung des geometrischen Baus freier Moleküle*, Ausgabe Chemie, Leningrad 1978, p. 178/79 (russ.)) and $(CH_3)_2NSF_3$ (H. Oberhammer, R. Mews, H. Henle, unpublished), the planar $(CH_3)_2N$ group is almost perpendicular to the equitorial plane.
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[20] We thank *W. Zolke* for the recording and simulation of the NMR spectra.

Coupling of 3-Diazo-3*H*-pyrazoles with 2-Alkoxy-1,6-methano[10]annulenes and Oxidative Cyclization to Pyrazolotriazines**

By *Richard Neidlein,* Uwe Jäschke, Alfred Gieren,* Gabriela Weber,* and *Thomas Hübner*

Dedicated to Professor Günther Wilke on the occasion of his 60th birthday

Coupling reactions of aryldiazonium salts with 2-alkoxy-1,6-methano[10]annulenes[1] usually lead via cleavage of ether to formation of "quinonehydrazones", i.e. 5-(arylhydrazono)-1,6-methano-1(10),3,6,8-cyclodecatetraen-2-ones.[2] Coupling of the 3-diazo-3*H*-pyrazoles **1a**, **b** and of the 3-diazo-3*H*-indazole **1c**[3] with 2-alkoxy-1,6-methano[10]annulenes **2a**–**c**[4,5] enables the synthesis of the pure azo dyes **3** in good yields under mild, neutral[6] conditions (Table 1).

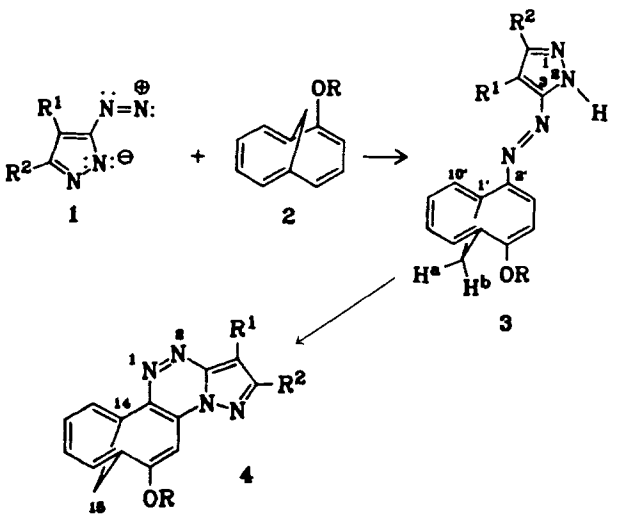


Table 1. Azo dyes **3** and pyrazolotriazines **4** that have been synthesized.

1	R^1	R^2	2	R	3,4	3		4	
						M.p. [°C]	Yield [%]	M.p. [°C]	Yield [%]
a	Ph	Me	**a**	Me	**aa**	219	92	190	70
a	Ph	Me	**b**	Et	**ab**	199	70	159	55
a	Ph	Me	**c**	*i*Pr	**ac**	92	75	171	60
b	Me	Ph	**a**	Me	**ba**	93	90	186	55
b	Me	Ph	**b**	Et	**bb**	160	65	156	75
b	Me	Ph	**c**	*i*Pr	**bc**	186	70	162	65
c	$-(CH{=}CH)_2-$		**a**	Me	**ca**	176	85	137	70
c	$-(CH{=}CH)_2-$		**b**	Et	**cb**	103	65	155	55
c	$-(CH{=}CH)_2-$		**c**	*i*Pr	**cc**	96	80	161	80

Cyclization of the *E*-configurated azo dyes **3** to triazine derivatives **4** (Table 1) was accomplished by irradiation of **3** in dioxane with a high-pressure Hg immersion lamp in the presence of 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ). This oxidative ring-closure of **3** is, as expected, only possible in the case of the *Z*-isomer.[7]

4ab was characterized by X-ray structure analysis[8] (Fig. 1). In the perimeter of the 1,6-methano[10]annulene, only slight differences in the bond lengths occur in the unsubstituted seven-membered ring, whereas a stronger alternation between formal single and double bonds is recognizable in the substituted seven-membered ring. Both seven-membered rings are boat-shaped. The annelated pyrazolo[5,1-*c*][1,2,4]triazine system is almost planar; the largest deviation from the best plane is 0.05 Å. The bond lengths in this bicyclic 10π-electron system are, as expected, between those of single and double bonds.

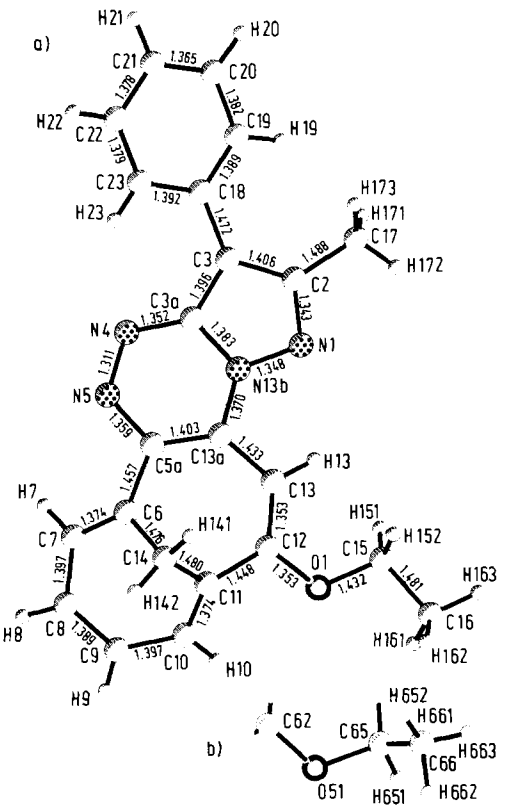


Fig. 1. a) Structure of **4ab** in the crystal, with bond lengths averaged over both molecules of the asymmetric unit. The standard deviations of the bond lengths without averaging are $0.001 \leq \sigma \leq 0.003$ Å. b) Deviating conformation at the O–C bond of the ethoxy moiety.

The crystal lattice contains two symmetry-independent molecules which differ from each other only in certain parts. Significantly different torsion angles occur with the ethoxy substituent: In one of the molecules the methyl group and the annulene ring are almost antiperiplanar (Fig. 1a, torsion angle C12–O1–C15–C16: 167.6°), in the other synclinal (Fig. 1b, C62–O51–C65–C66: 84.0°). In addition, the C6–C14–C11 angle differs by 3.4(1)°. The smaller angle is accompanied by a decrease in the distance between the bridge atoms C6, C11 from 2.21 to 2.14 Å and a decrease in the, albeit already small, difference in the bond lengths in the unsubstituted triene fragment ($\Delta(\max) = 0.02$ compared to 0.04 Å).

Experimental:

3: A solution of **2** (5 mmol) in CH_2Cl_2 (10 mL) was added dropwise to a stirred solution of **1** (5 mmol) in CH_2Cl_2 (250 mL) at 20°C. The solution immediately turned red in color. After two hours' stirring, the solvent was removed by distillation and the remaining black-red oil was purified by column chromatography (silica gel, 30 cm, ∅ 3 cm, eluent CH_2Cl_2/ether = 4/1). Recrystallization from ether/petroleum ether (1/10) furnished red or orange-red crystals.—**3ab**, ^{13}C-NMR (62.89 MHz, $CDCl_3$, δ values): C_6H_5: 132.4 (s), 126.8–130.1 (5d); CH_3: 13.3 (q); C_2H_5: 14.8 (q), 66.3 (t); 162.3 (s, C-5'), 151.3 (s, C-3), 146.9 (s, C-5), 148.8 (s, C-2'), 134.4 (d, C-3'), 125.8–131.5 (4d,

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C-7′ to C-10′), 119.1 (s, C-4), 110.6 (s, C-6′), 110.4 (s, C-1′), 105.0 (d, C-4′), 32.6 (t, C-11′). – ^{1}H-NMR (250 MHz, $CDCl_3$, δ values): C_6H_5: 7.2–7.6 (m, 7H, including 5H of C_6H_5); CH_3: 2.5 (s, 3H); C_2H_5: 3.9 (m, 1H), 4.3 (m, 1H), 1.4 (t, 3H); –0.56 (d, J = 10.3 Hz, 1H, H-11′a), 0.77 (d, J = 10.3 Hz, 1H, H-11′b), 6.3 (d, J = 10.2 Hz, 1H, H-3′), 7.6–7.7 (m, 3H, contains NH); 8.0 (d, J = 7.7 Hz, 1H, H-7′).

4: 1.5 mmol DDQ and 1 mmol **3** were dissolved in 200 mL dioxane. The solution was vigorously stirred at 20°C and irradiated with a high-pressure TQ150 Hg-immersion lamp (Heraeus, Hanau) for 40 min. After twofold adsorptive column filtration (silica gel, 10 cm, Ø 10 cm, eluent: CH_2Cl_2) and removal of solvent by distillation, **4** could be recrystallized from ether. – **4ab**, ^{13}C-NMR (62.89 MHz, $CDCl_3$, δ values): C_6H_5: 131.6 (s), 126.8–129.2 (5d); CH_3: 14.5 (q); C_2H_5: 14.4 (q), 66.6 (t); 167.4 (s, C-8), 151.0 (s, C-2a), 145.7 (s, C-4), 137.4 (s, C-14a), 128.7 (s, C-6a), 124.9–130.3 (4d, C-10 to C-13), 111.4 (s, C-3), 106.0 (s, C-9), 102.0 (s, C-14), 88.9 (d, C-7), 31.2 (t, C-15). – ^{1}H-NMR (250 MHz, $CDCl_3$, δ values): C_6H_5: 7.4–7.6 (m, 5H); CH_3: 2.8 (s, 3H); C_2H_5: 4.1 (m, 1H), 4.5 (m, 1H), 1.5 (t, 3H); 0.04 (d, J = 9.9 Hz, 1H, H-15), 1.41 (d, J = 9.9 Hz, 1H, H-15), 7.3 (s, 1H, H-7), 7.9–8.0 (m, 4H, H-10 to H-13).

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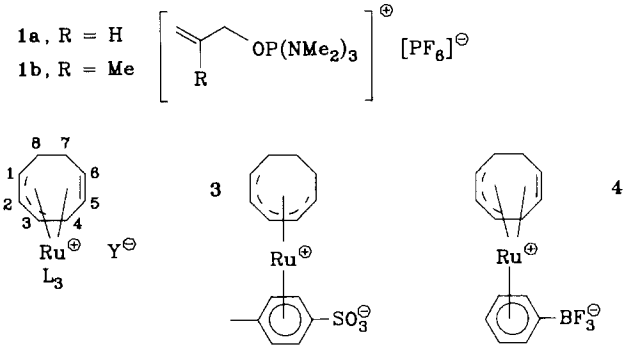
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[4] H. Klenk, W. O. Storer, F. Effenberger, *Chem. Ber. 109* (1976) 777; cf. regiospecific bromination.
[5] **2b** and **2c** were prepared analogously to **2a**, as described in [4]. Similar yields were obtained.
[6] From **1** and **2**, the quinonehydrazones are also formed analogously to **3** at pH 5.
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[8] **4ab**: Triclinic $P\bar{1}$, a = 9.760(1), b = 13.590(2), c = 14.357(3) Å, α = 84.95(1), β = 88.47(1), γ = 76.10(1)°, V = 1841.3 Å^3, Z = 4, $\rho_{calc.}$ = 1.329 g cm^{-3}; CAD4, $Mo_{K\alpha}$, graphite monochromator, 5199 independent, observed reflections ($I > 2\sigma(I)$), $0° < \theta \leq 25°$. Direct methods, R = 0.038; C,N,O atoms with anisotropic, H atoms with isotropic temperature parameters. Further details of the crystal structure investigation are available on request from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2, on quoting the depository number CSD 51233, the names of the authors, and the full citation of the journal.

Cationic Allylruthenium Complexes via Interchange of Allyl Moieties**

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Dedicated to Professor Günther Wilke on the occasion of his 60th birthday

Cationic allylnickel, allylpalladium, and allylplatinum complexes are reported to be active catalysts for the oligomerization,[1] telomerization,[2] and isomerization[3] of unsaturated substrates. Moreover, cationic allylmetal species have been suggested as intermediates in these processes.[3,4] In order to examine the scope and limitations of the use of such complexes, we extended to ruthenium the general synthetic procedure described for nickel and palladium consisting of the oxidative addition of allyloxyphosphonium salts **1** to zerovalent metal centers.[5] We now report a new type of reaction leading to η^3-allyl interchange on a metal center and preliminary results on the chemistry of and catalysis with cationic allylruthenium complexes.



2a, L_3 = 1,3,5-C_8H_{10}, Y = PF_6
2b, L_3 = C_6H_6, Y = PF_6
2c, L = CO, Y = BF_4
2d, L = CO, Y = PF_6
2e, L = $P(OMe)_3$, Y = PF_6

The reaction of **1a** and **1b** with [Ru(η^4-C_8H_{12})(η^6-C_8H_{10})] surprisingly leads to the quantitative evolution of propene and 2-methylpropene, respectively. The cationic complex **2a** is obtained in 78% yield.[6] Similarly, **2b** is obtained in 88% yield starting from [Ru(η^4-C_8H_{12})(η^6-C_6H_6)]. Structures **2a** and **2b** were assigned on the basis of ^{1}H- and ^{13}C-NMR spectra (Table 1).

Table 1. NMR data for the complexes **2a**, **2b**, and **2e**.

2a: ^{1}H-NMR (250 MHz, $(CD_3)_2CO$): δ = 0.22 (m, 1H), 1.80 (m, 1H), 2.15 (m, 1H), 2.50 (m, 4H), 2.80 (m, 1H), 3.25 (m, 1H), 3.47 (m, 1H), 5.02 (m, 1H), 5.95 (m, 1H), 6.21 (m, 2H), 6.41 (m, 2H), 6.45 (m, 2H); ^{13}C-NMR (62.9 MHz, $(CD_3)_2CO$): δ = 19.4 (C4), 27.0 ($-CH_2-$), 27.5 ($-CH_2-$), 34.9 (C8), 36.4 (C7), 40.2 (C3), 44.4 (C5), 79.0 (C1), 87.7 (C6), 94.4 (C2), 95.0 (–CH–), 96.0 (–CH–), 97.0 (–CH–), 99.3 (–CH–), 100.6 (–CH–).

2b: ^{1}H-NMR (250 MHz, $(CD_3)_2CO$): δ = 1.75 (m, 1H), 2.12 (m, 1H), 2.48–2.60 (m, 2H), 2.81 (m, 1H), 3.17 (m, 1H), 3.57 (m, 1H), 4.22 (t, J(HH) = 7.3 Hz, 1H), 4.51 (m, 1H), 5.12 (dd, J(HH) = 6.9, 7.9 Hz, 1H), 5.61 (m, 1H), 6.47 (s, 6H); ^{13}C-NMR (62.9 MHz, $(CD_3)_2CO$): δ = 19.2 (C4), 27.9 (C8), 29 (C3 [7]), 33.4 (C5), 35.9 (C7), 72.7 (C1), 79.8 (C6), 84.6 (C2), 92.3 (C-benzene).

2e: ^{1}H-NMR (250 MHz, $(CD_3)_2CO$): δ = 1.10 (t, J(HH) = 7 Hz, 1H), 1.82 (br. m, 1H), 2.80 (br. m, 2H), 3.00 (br. m, 1H), 3.90 (br. m, 9H), 4.40 (br. m, 9H), 4.55 (br. m, 1H), 4.80 (br. m, 1H), 5.00 (br. m, 1H), 5.45 (br. m, 1H), 5.80 (br. m, 1H), 7.45 (m, 1H).

According to the ^{13}C-NMR spectra, **2a** and **2b** are not symmetric; five $^{13}CH_2$-, and eleven ^{13}CH-signals are present in the spectrum of **2a**, and three $^{13}CH_2$- and six ^{13}CH-signals in that of **2b**.[7] In fact, the ^{13}C-NMR spectrum of **2b** is very different from that of **3**, which has been recently obtained by *Bailey* et al. from the reaction of $[Ru(H_2O)_6][p\text{-}MeC_6H_4SO_3]_2$ with 1,3-cyclooctadiene.[8] On the other hand, it is very similar to that reported by *Singleton* et al. for the η^5-C_8H_{11} complex **4**, which has been characterized by a single-crystal X-ray diffraction study.[9] Moreover, the data agree well with those reported for the corresponding tricarbonyl complex **2c**.[10] No evidence for an equilibrium of the type $[(\eta^3\text{-allyl})Ru]^{\oplus} \rightleftarrows [(\eta^4\text{-diene})RuH]^{\oplus}$, which has been recently demonstrated,[11] is detected in the ^{1}H-NMR spectra of **2a** and **2b**. **2a** reacts with CO and $P(OMe)_3$ to

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[**] Cationic allylmetal complexes, Part 11. This work was supported by the CNRS. – Part 10: [1f].

give **2c** and **2d**, respectively. The "masked hydride" character of **2a** and **2b** is evidenced by the formation of

$[RuH(dppe)_2(CH_3CN)]^{\oplus}[PF_6]^{\ominus}$ **5**

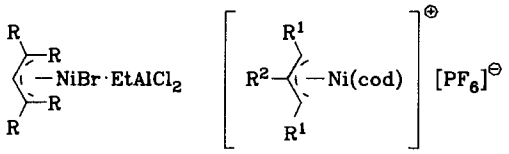
upon treatment of **2a** and **2b** with two equivalents of bis(diphenylphosphino)ethane (dppe) in acetonitrile.[12] In these reactions, two equivalents of 1,3,5-cyclooctatriene (1,3,5-cot) are evolved from **2a** and one equivalent of both 1,3,5-cot and benzene from **2b** according to gas chromatographic analysis.

Complex **2a** is a catalyst precursor for the dimerization of ethylene (turn-over number (TON) = 160; 1-butene : *cis*-2-butene : *trans*-2-butene = 18 : 30 : 51), the ring-opening polymerization of norbornene to a mixture of *cis*- and *trans*-polynorbornenes (TON = 480 in refluxing ethanol; TON = 350 in dichloromethane at room temperature), and the polymerization of butadiene to mainly *trans*-1,4-polybutadiene (TON = 150). **2a** is also a catalyst precursor for the isomerization and hydrogenation of alkenes. The isomerization only occurs under hydrogen and is *faster* than hydrogenation: from 1-hexene 1% hexane and 10% 2-hexenes are produced (TON = 40) after 3 h under 1 bar H_2, and 29.5% hexane and 70.5% 2-hexenes are obtained (TON = 870) after 20 h under 20 bar H_2. Noteworthy is the fact that mixtures of **2a** and dppe or **2a** and **5** are practically inactive for isomerization and hydrogenation.

The mechanism of formation of **2a** and **2b** deserves some comments. Although both compounds are also obtained by hydride abstraction of one allylic proton of 1,5-cyclooctadiene with $[Ph_3C]^{\oplus}[PF_6]^{\ominus}$, the reactivity pattern observed for the reaction of **1** with Ni^0 and Pd^0 species[5] led us to suggest another mechanism: the oxidative addition of **1** to an initially formed 16-electron species is followed by the activation of one allylic hydrogen of the coordinated 1,5-cyclooctadiene by the *electrophilic* ruthenium center, leading to a hydridoruthenium(IV) cation.[12] Reductive elimination of the hydrido and allyl ligands[13, 14] results in the evolution of propene or 2-methylpropene and the formation of **2a** or **2b**. Therefore, these complexes formally result from an interchange of allyl ligands [Reaction (a)].

$$[M(\eta^3\text{-allyl})^1(\eta^2\text{-alkene})^2]^{\oplus} \rightleftharpoons [M(\eta^2\text{-alkene})^1(\eta^3\text{-allyl})^2]^{\ominus} \qquad (a)$$

This reaction has little precedent in the case of ruthenium.[15] However, this behavior could be typical for cationic allylmetal complexes; e.g., the transformation of **6** and **7** reported by *Bogdanovic*[1b] and *Pardy* and *Tkatchenko*,[1c] respectively, could be interpreted in a similar way.



6a, R = Ph **7a**, R^1 = H, R^2 = Me

6b, R = H **7b**, R^1 = R^2 = Me

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1a, 54739-05-8; **1b**, 63936-88-9; **2a**, 95740-28-6; **2b**, 95740-30-0; **2d**, 95740-32-2; **2e**, 95740-34-4; **5**, 95740-36-6; $[Ru(\eta^4\text{-}C_8H_{12})(\eta^6\text{-}C_8H_{10})]$, 42516-72-3; $[Ru(\eta^4\text{-}C_8H_{12})(\eta^6\text{-}C_6H_6)]$, 54913-13-2; 1-butene, 106-98-9; *cis*-2-butene, 590-18-1; *trans*-2-butene, 624-64-6; polynorbornene, 25038-76-0; *trans*-1,4-polybutadiene, 9003-17-2; hexane, 110-54-3; 2-hexene, 592-43-8; ethylene, 74-85-1; norbornene, 498-66-8; butadiene, 106-99-0; 1-hexene, 592-41-6.

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[6] Satisfactory analyses were obtained for all the complexes reported.

[7] The ^{13}C-NMR signal at $\delta = 29$ overlaps with those of the solvent acetone.

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Strongly Preferential Alkylation and Carbonyl Olefination of α- and β-Hydroxycarbonyl Compounds by Organo-Transition Metal Reagents in Competition Experiments with the Corresponding Deoxy Compounds**

By *Thomas Kauffmann,* Thomas Möller, Heidi Rennefeld, Siegfried Welke,* and *Raphael Wieschollek*

The functional groups of organic compounds usually have lone electron pairs or π-electron pairs and thus are almost always potential ligands for metals with empty d-orbitals. Therefore, it is not surprising that alkyl transition-metal complexes, which have proved to be very selective towards single electrophilic functional groups,[2] can also react in a highly selective fashion with arrangements of functional groups ("multigroup selectivity").

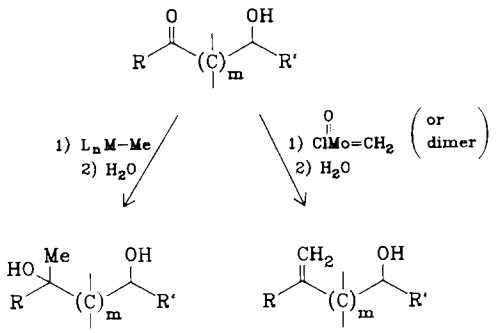
The high diastereoselectivity in the alkylation of alkoxy- and some hydroxycarbonyl compounds with alkyltitanium and alkylzirconium compounds indicates chelate control;[1,3,4] i.e., the reagents are bound to the oxygen of the alkoxy or hydroxy group during the alkylation process. We presumed, therefore, that ketones and aldehydes that contain an oxygen-donor group in the vicinity of the carbonyl group would be attacked more quickly by alkyl transition-metal compounds than those lacking such a donor group.

Since the metal-carbon bond in alkylchromium and alkyltitanium compounds is surprisingly resistant towards hydroxy groups,[1] we examined by means of competition experiments whether α- and β-hydroxycarbonyl ketones are easily alkylated by such reagents. Corresponding experiments were carried out with the carbonyl olefination

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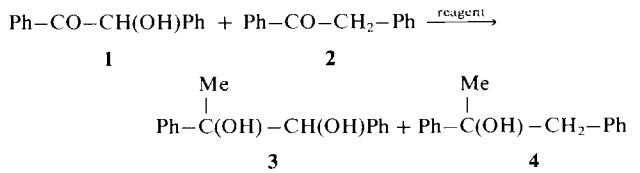
[**] Transition-metal-activated organic compounds, Part 18. This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie. – Part 17: [1].

reagent $ClMo(O)=CH_2$, which is especially resistant towards hydroxy groups.[5] We found, as expected, chemoselective methylation and carbonylolefination according to Scheme 1 (the reaction is usually carried out at $-60°C$ and the reaction mixture is warmed over the course of ca. 12 h to room temperature).



Scheme 1. m = 0, 1.

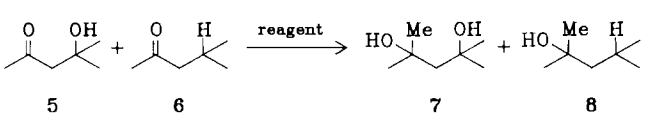
The fixation of the metal atom to the hydroxy group supposedly plays an essential role in these reactions. However, the activating effect, the $-I$ effect, of the hydroxy group of **1** and the deactivation of **2** via enolate formation have to also be taken into consideration.



Scheme 2. For yields see Table 1 [6].

Table 1. Competition experiments according to Scheme 2.

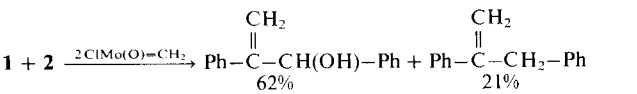
Reagent	Mole ratio substrate : reagent	Yield [%] 3	4	Recovery [%] 1	2
Cl_2Cr–Me	1 : 1 : 1	40	0	52	96
Cl_2Cr–Me	1 : 1 : 2	52	0	36	99
$(iPrO)_3Ti$–Me	1 : 1 : 2	56	0	—	89
IMg–Me	1 : 1 : 1	15	20	67	75
IMg–Me	1 : 1 : 2	38	29	58	61
Li–Me	1 : 1 : 2	23	41		



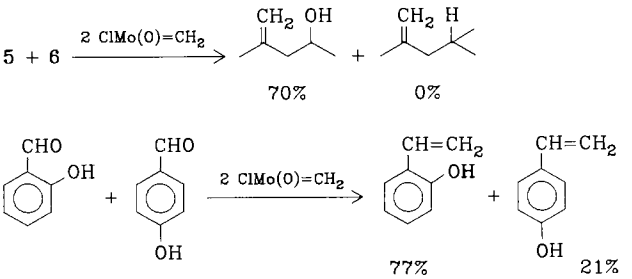
Scheme 3. For yields see Table 2 [6].

Table 2. Competition experiments according to Scheme 3.

Reagent	Mole ratio substrate : reagent	Yield [%] 7	8	Recovery [%] 5	6
Cl_2Cr–Me	1 : 1 : 1	31	1	41	84
Cl_2Cr–Me	1 : 1 : 2	50	1	29	80
$(iPrO)_3Ti$–Me	1 : 1 : 2	42	1	—	80
IMg–Me	1 : 1 : 1	13	22	65	70

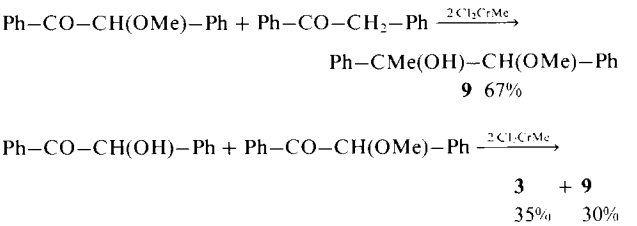


Scheme 4 [6].



Scheme 5 [6].

That methoxy groups also facilitate the attack on a neighboring carbonyl group is shown by a result of *Reetz*[7] as well as the first experiment depicted in Scheme 6, in which **4** is not formed at all. The second experiment depicted in Scheme 6 shows that the chromium reagent only weakly prefers the hydroxy over the corresponding methoxy compound.



Scheme 6 [6].

Since the *erythro* isomer of **3** is formed practically exclusively in the separate reaction of benzoin **1** with two equivalents of $(iPrO)_3Ti$–Me,[4] the diol **3** obtained in our competition experiments with $(iPrO)_3Ti$–Me and Cl_2Cr–Me is most probably also the *erythro* isomer. This has not yet been possible to show since no NMR data is given in the literature for *erythro*-**3**. Whether **9** also is present as only one diastereomer, as may be assumed, is also not yet certain.

The chemoselective reactions according to Scheme 1 (*nucleophilically* active ligands) are a direct analogy of the chemoselective oxidations of allyl- and homoallyl alcohols by *Sharpless* et al.[8] (*electrophilically* active ligand in the form of a peroxide group). Thus a general reaction principale is illustrated here.

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[1] T. Kauffmann, R. Abeln, D. Wingbermühle, *Angew. Chem.* 96 (1984) 724; *Angew. Chem. Int. Ed. Engl.* 23 (1984) 729.
[2] The best known is the marked aldehyde selectivity in competition experiments with aldehyde/ketone pairs: Ti, Zr, Mn: review by D. Seebach, B. Weidmann, L. Widler, and by J. F. Normant in R. Scheffold: *Modern Synthetic Methods 1983*, Salle, Frankfurt 1983; Nb, Ta: T. Kauffmann, E. Antfang, B. Ennen, N. Klas, *Tetrahedron Lett.* 23 (1982) 2301; Cr: [1], and references therein.
[3] M. T. Reetz, *Angew. Chem.* 96 (1984) 542; *Angew. Chem. Int. Ed. Engl.* 23 (1984) 556; M. T. Reetz, A. Jung, *J. Am. Chem. Soc.* 105 (1983) 4833.
[4] M. T. Reetz, *Top. Curr. Chem.* 106 (1982) 1, and particularly reference [83] therein.

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[5] T. Kauffmann, P. Fiegenbaum, R. Wieschollek, *Angew. Chem. 96* (1984) 500; *Angew. Chem. Int. Ed. Engl. 23* (1984) 531.
[6] Procedures: Schemes 2 and 3: 10 mmol of each of the two carbonyl compounds in 20 mL tetrahydrofuran (THF); Scheme 4: 2.5 mmol of each of the two carbonyl compounds in 17 mL THF; Schemes 5 and 6: 2.3 mmol of each of the two carbonyl compounds in 50 mL THF.
[7] According to *Reetz* [4], the methoxy compound is strongly preferentially methylated in the reaction of $(i\mathrm{PrO})_3\mathrm{Ti-Me}$ with *o*-methoxybenzaldehyde and benzaldehyde in competition experiments (mole ratio of methylated products, 87 : 13; no yield given).
[8] K. B. Sharpless, T. Verhoeven, *Aldrichimica Acta 12* (1979) 63.

Isolation of the (*E*)-Enols of β-Ketocarboxylic Acid Derivatives**

By *Herbert Meier,* Wolfgang Lauer,* and *Friedrich Ulrich Scholter*

Dedicated to Professor Dietrich Schulte-Frohlinde on the occasion of his 60th birthday

β-Ketocarboxylic acid derivatives are of great importance as intermediates in organic synthesis.[1] The Wolff-rearrangement of 2-diazo-1,3-dicarbonyl compounds provides a facile entry;[2] the intermediary acyl ketenes rapidly add water or other nucleophiles.[3] Even in the absence of nucleophiles and cycloaddition partners, acyl ketenes cannot be isolated, since they rapidly dimerize.[4]

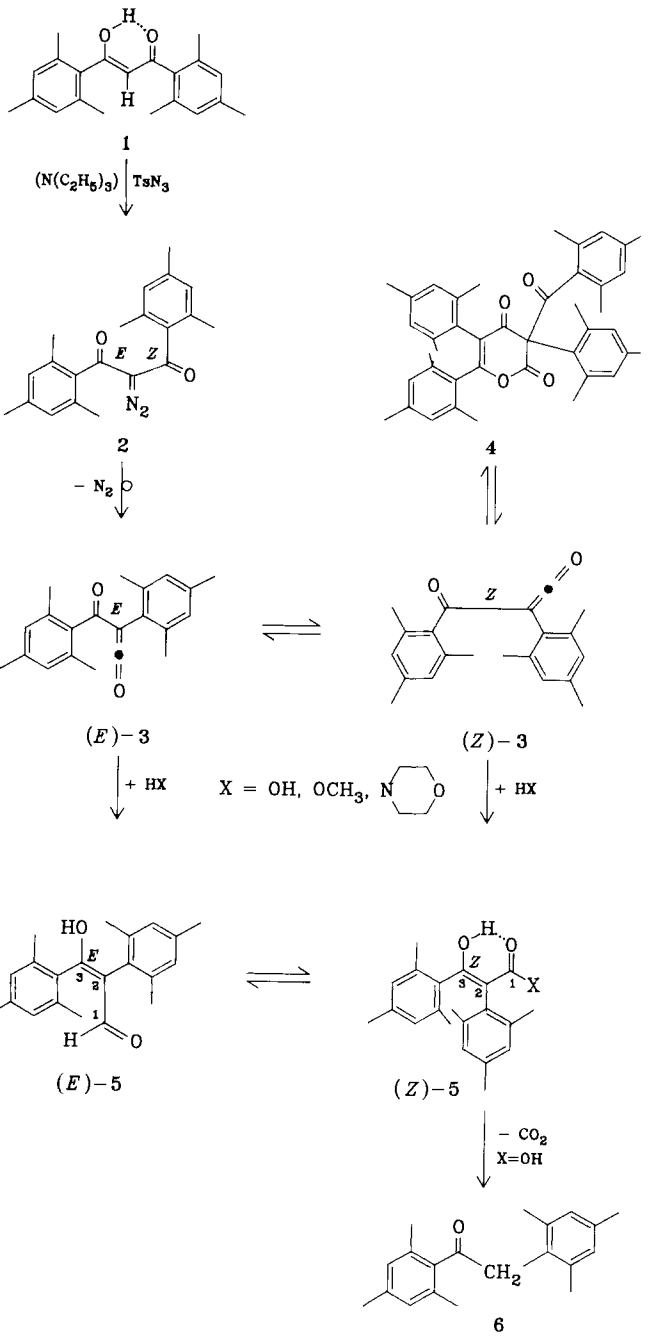
We have now studied the influence of increasing steric hindrance on the reaction behavior of the diazo compounds $R^1CO-CN_2-COR^2$ ($R^1=R^2=C_6H_5$; $R^1=C_6H_5$, $R^2=2,4,6\text{-}(CH_3)_3C_6H_2$; $R^1=R^2=2,4,6\text{-}(CH_3)_3C_6H_2$). The compound **2** containing two mesityl moieties, which is readily accessible from **1** by diazo group-transfer[5] (yield 81—89%, orange-yellow crystals, m.p. 94°C), gave a number of quite surprising results:

1. Photolysis ($\lambda \geq 290$ nm) of the *E,Z*-configurated diazodiketone **2** in anhydrous diethyl ether leads to formation of an acyl ketene **3**, which, as a result of steric hindrance, is partly present in monomeric form (IR spectrum, CCl_4: ketene band at 2090 cm^{-1}). It can be assumed that there is rapid rotation about the central CC single bond, since this bond shows little double-bond character. In contrast to normal ketenes, acyl ketenes such as **3** dimerize (according to their IR and NMR spectra) to six-membered lactones such as **4**.[4]

2. Photolysis in diethyl ether saturated with water leads to the β-ketocarboxylic acid **5** (X = OH), which decarboxylates to **6** only very slowly at room temperature. The half-life of **5** amounts to more than two days (decay with first order kinetics).

3. Photolysis in the presence of methanol affords the methyl ester **5** ($X=OCH_3$), which can be isolated in the *E*- and the *Z*-configuration. On termination of N_2-elimination, a mixture of 52% *Z*-form (m.p. 152°C) and 19% *E*-form (m.p. 125°C) is obtained which can be separated by column chromatography (silica gel/benzene). In an alkaline medium (e.g. triethylamine), on the other hand, the pure *E*-form is obtained.

4. Thermolysis of **2** in morpholine at 50—60°C affords the amide **5** ($X=NC_4H_8O$) in 74% yield. On completion of reaction it is present in the *E*-form (m.p. 142°C) and can be converted into the *Z*-form (m.p. 96°C) either thermally or by acid catalysis.



The existence of (*E*)-enols of β-ketocarboxylic acid derivatives has often been surmised. *Matusch*[6] was able to detect such an enol on examining ethyl acetate NMR spectroscopically. However, the handicap met with is the small amount of *E*-isomer in the mixture with the thermodynamically more favorable (*Z*)-enol (intramolecular six-membered ring hydrogen bridge) and the thermodynamically even more favorable keto-form. By introducing the mesityl moiety, it has now been possible to completely suppress the formation of the keto-form in the case of **5**; concomitantly, the steric hindrance considerably increases the energy content of (*Z*)-**5**. The rate of thermal isomerization is

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so small that it was possible in the cases described here to isolate both stereoisomers in the pure form for the first time. The influence of the alkaline medium manifests itself in the enolate-form[7] being present in the *E*-configuration in the absence of H-bridges. Accordingly, the enol that is liberated therefrom has the *E*-configuration.[8]

The identification of the stereoisomers is possible by means of IR, ^{1}H-, ^{13}C-NMR spectroscopy. The intramolecular H-bridge in the *Z*-form effects a shift in the CO stretching vibration of about 50 cm^{-1} to smaller wave numbers. The reduced electron density of C-1 and C-3 due to the intramolecular hydrogen bridge gives rise to a significant downfield shift of the corresponding ^{13}C-NMR signals (Table 1). δ(C-2), on the other hand, experiences an

Table 1. $\delta(^{13}C)/\delta(^1H)$ of (*E*)-**5** and (*Z*)-**5** ($CDCl_3$, referred to TMS).

5	C-1	C-2	C-3	OCH_3	NCH_2	OCH_2
X = OCH_3, *E*	166.4	108.6	162.5	51.3/3.47	—	—
X = OCH_3, *Z*	174.0	104.0	173.0	52.0/3.76	—	—
X = NC_4H_8O, *E*	168.2	110.8	153.9	—	44.8/3.07	66.3/3.19
X = NC_4H_8O, *Z*	174.2	104.4	172.5	—	45.0/3.24	66.5/3.40
	C_i	C_o	*o*-CH_3	C_m	C_p	*p*-CH_3
X = OCH_3, *E*	128.3	135.5	20.1/2.30	128.3/6.90	138.2	21.0/2.29
	132.6	138.6	20.6/2.36	129.3/6.99	138.4	21.1/2.31
X = OCH_3, *Z*	129.4	135.9	20.4/2.03	128.2/6.71	136.4	20.9/2.18
	131.6	138.1	20.5/2.13	128.3/6.68	138.2	20.9/2.19
X = NC_4H_8O, *E*	131.2	136.3	20.5/2.35	128.5/6.87	137.4	20.9/2.26
	132.9	138.1	21.2/2.36	129.2/6.94	138.2	21.1/2.27
X = NC_4H_8O, *Z*	132.1	135.7	19.9/1.97	128.1/6.63	136.5	20.8/2.15
	132.6	137.6	20.6/2.00	129.0/6.65	137.7	20.9/2.16

upfield shift on going from (*E*)-**5** to (*Z*)-**5**. The assignment of the resonances of C-1 and C-3 was established by heteronuclear double resonance. Also of interest is the observation that chemical equivalence of the corresponding nuclei in the morpholine ring caused by rapid rotation is already achieved at room temperature in the case of the amides **5** (X = NC_4H_8O). That is, in this instance, steric hindrance effects an acceleration of the rotation about the CN-bond in comparison to normal amides, because it reduces the double bond character of the CN bond! This is true, both for the *Z*- as well as the *E*-form.

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CAS Registry numbers:
1, 95694-41-0; **2**, 95694-42-1; **3**, 95694-43-2; **4**, 95694-44-3; (*E*)-**5** (X = OH), 95694-45-4; (*Z*)-**5** (X = OH), 95694-46-5; (*E*)-**5** (X = OCH_3), 95694-47-6; (*Z*)-**5** (X = OCH_3), 95694-48-7; (*E*)-**5** (X = NC_4H_8O), 95694-49-8; (*Z*)-**5** (X = NC_4H_8O), 95694-50-1; **6**, 5796-78-1.

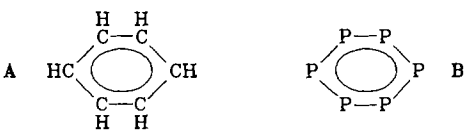
[1] Cf., e.g., H. Henecka: *Chemie der β-Dicarbonylverbindungen*, Springer, Berlin 1950.
[2] H. Meier, K.-P. Zeller, *Angew. Chem. 87* (1975) 52; *Angew. Chem. Int. Ed. Engl. 14* (1975) 32, and references cited therein.
[3] Cf. E. Bothe, H. Meier, D. Schulte-Frohlinde, C. von Sonntag, *Angew. Chem. 88* (1976) 413; *Angew. Chem. Int. Ed. Engl. 15* (1976) 380.
[4] a) C. Wentrup, H.-W. Winter, G. Gross, K.-P. Netsch, G. Kollenz, W. Ott, A. G. Biedermann, *Angew. Chem. 96* (1984) 791; *Angew. Chem. Int. Ed. Engl. 23* (1984) 800; C. Wentrup, K.-P. Netsch, *ibid. 96* (1984) 792 and *23* (1984) 802; b) H. Stetter, M. Schütte, *Chem. Ber. 108* (1975) 3314; H. Stetter, K. Kiehs, *ibid. 98* (1965) 1181; c) G. Jäger, R. J. Singer, *Justus Liebigs Ann. Chem. 1977*, 1799; G. Jäger, J. Wenzelburger, *ibid. 1976*, 1689; G. Jäger, *Chem. Ber. 105* (1972) 137; d) L. Capuano, T. Tammer, *ibid. 114* (1981) 456, and references cited therein.
[5] M. Regitz: *Diazoalkane*, Thieme, Stuttgart 1977, p. 163ff.
[6] R. Matusch, *Angew. Chem. 87* (1975) 283; *Angew. Chem. Int. Ed. Engl. 14* (1975) 260.
[7] Cf. H. H. Vogt, R. Gompper, *Chem. Ber. 114* (1981) 2884.
[8] With phenyl moieties instead of the two mesityl groups, the corresponding β-ketocarboxylic acid derivatives are present almost completely in the keto form, so the problem of *Z*- and *E*-enol form does not arise. For rearrangement of the mesityl-phenyl compound, cf. R. Müller, K.-P. Zeller, H. Meier, *Chem. Ztg. 102* (1978) 107.

Hexaphosphabenzene as Complex Ligand**

By *Otto J. Scherer,* Helmut Sitzmann,* and *Gotthelf Wolmershäuser*

Dedicated to Professor Günther Wilke on the occasion of his 60th birthday

The formal replacement of each CH unit in benzene **A** by an isoelectronic P atom would lead to the phosphaanalogue P_6 **B**.[1] Its synthesis was a fascinating aim. The most promising approach would be expected to be the stabilization of P_6 by complexation.



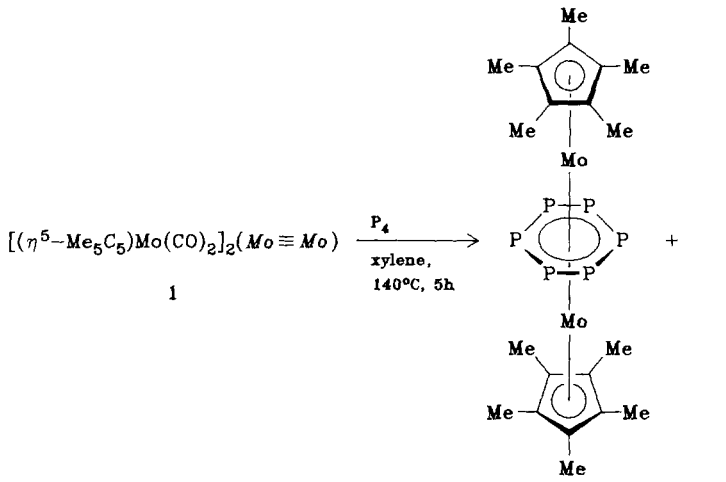
Using this approach we have now, indeed, been able to prepare the triple-decker sandwich complex [{(η^5-Me_5C_5)Mo}$_2$(μ,η^6-P_6)] **2** with hexaphosphabenzene as central bridge-ligand. The reaction proceeded analogously to that of [$CpMo(CO)_2]_2$(*Mo≡Mo*) (Cp = cyclopentadienyl) or [$CpMo(CO)_3]_2$(*Mo–Mo*) with P_4.[2] **2**[3] forms amber-colored, air stable crystals (decomp. >250 °C), which are very sparingly soluble in pentane, moderately soluble in benzene, and readily soluble in dichloromethane. The ^{1}H-NMR spectrum (200 MHz, [D_6]benzene, TMS int.) of **2** shows a septet for the CH_3-groups at $\delta = 0.47$ (standard region of the C_5Me_5 signal $\delta \approx 2$) with $^4J(PH) = 0.45$ Hz, shifted considerably upfield by the anisotropic sphere of the P_6 ring (ring current effect). The $^{31}P\{^1H\}$-NMR spectrum (80.82 MHz, CH_2Cl_2, 85% H_3PO_4 ext.) shows a singlet at $\delta = -315.6$.

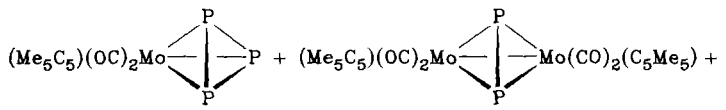
Reaction of **1** with P_4 not only leads to formation of **2**, but also of complexes **3**, **4**, and **5**.[3] As in the case of its Cp-analogue,[2] no restriction to rotation of the P_3-"disk" is observed for **3**, even at ca. −80 °C (otherwise an A_2B spin system would be expected in the $^{31}P\{^1H\}$-NMR spectrum); **3** can also be prepared from **1** and P_4S_3.[4] It follows from the IR band at 1829 cm^{-1} that **4** contains a semibridging CO ligand. An X-ray structure analysis of **5** could not be carried out on the thin, yellowish-brown crystals; their composition was confirmed by elemental analysis and by the mass and NMR spectra.[5] We propose a structure consisting of two P_2Mo_2 tetrahedra with a common Mo–Mo edge and *cis* arrangement of the C_5Me_5- and CO-ligands.

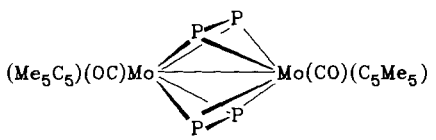
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[+] X-Ray structure analysis.

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$^{31}P\{^1H\}$-NMR spectroscopic monitoring of the reaction showed the presence, not only of **2**–**5** but also of two further products ($\delta = -118$ (s), possibly a *trans*-derivative of **5** or a (μ,η^4-P_4)-complex, and $\delta = -319$ (s), traces), which, however, could not be isolated.

The crystal structure analysis[6] shows that **2** is a centrosymmetric molecule (Fig. 1). Both five-membered rings as well as the P_6 ring are planar and parallel. The average PP distance of 2.170 Å lies in the range to be expected for such a molecule. Thus, P–P bond lengths of 2.004–2.034 Å are found for R–P=P–R,[7] 2.115–2.159 and 2.13–2.20 Å, for complexes with η^3-[2b,8a] and μ,η^3-P_3 ligands[8] and 2.149–2.155 Å for the binary compounds Rb_4P_6[9a] as well as α- and β-K_4P_6.[9b] The MoPMo angle (mean value 62.8°) reveals the interrelationship with P_4 and, in combination with the MoP distance of 2.541 (mean value) gives the Mo–Mo distance 2.647(1) Å which is somewhat shorter than that in [$(CpMo)_2(\mu,\eta^4$-$As_5)$] (Mo–Mo 2.764(2) Å).[10] On the basis of the 18e rule a metal-metal single bond can be discussed for **2**. The angles and bond lengths in the C_5Me_5-ligands show no unusual values.

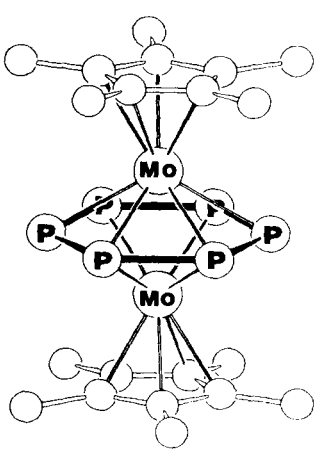


Fig. 1. Structure of **2** in the crystal. Selected bond lengths [Å] and angles [°]: P–P 2.167(3), 2.167(3), 2.175(3), P–Mo 2.541(2), 2.542(2), 2.541(2), mean value Mo–C 2.331, Mo–Mo 2.647(1). The methyl C-atoms lie, on average, 0.1079 Å above the plane of the five-membered ring (distortion about 4°); P–P–P 119.9(1), 120.1(1), 120.0(1), Mo–P–Mo 62.7(1), 62.8(1), 62.8(1).

If one regards the P_6 ring as 6π electron-donor ligand then **2** is a triple-decker sandwich complex with 28 valence electrons (cf. the analogous 26e vanadium complex with benzene as "middle deck"[11] and the 30 and 34e rule[12] for such complexes).

The synthesis of **2** poses the following questions: Can **5** be converted photochemically or thermally into the 26e triple-decker sandwich complex[11] [$\{(\eta^5$-$Me_5C_5)Mo\}_2(\mu,\eta^4$-$P_4)$]? If P_2 can be considered as an acetylene analogue, then a P_6 synthesis is possibly an analogue of the Reppe benzene synthesis ($3\,P_2 \rightarrow P_6$)?[13]

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1, 12132-04-6; **2**, 95675-35-7; **3**, 95675-36-8; **4**, 95675-37-9; **5**, 95675-38-0; $Mo(CO)_6$, 13939-06-5; P_4, 7723-14-0; pentamethylcyclopentadiene, 41539-64-4.

[1] Evidence for the formation of N_6: A. Vogler, R. E. Wright, H. Kunkely, *Angew. Chem. 92* (1980) 745; *Angew. Chem. Int. Ed. Engl. 19* (1980) 717.

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[3] Preparation of **2**–**5**: A stirred solution of $Mo(CO)_6$ (4.0 g, 15.15 mmol) and pentamethylcyclopentadiene (2.7 mL, 15.5 mmol) in xylene (150 mL) was heated under reflux for 24 h. The solution was then treated at room temperature with 2.0 g (16.1 mmol) P_4 and the mixture heated to gentle boiling for 5 h. After removal of solvent by distillation, the residue was extracted three times with 70-mL aliquots of CH_2Cl_2 and the combined extracts evaporated to 30 mL, stirred with 20 mL Florisil, and dried under an oil-pump vacuum until a freely-flowing powder was obtained. The chromatography (column diameter 3 cm, length 35 cm) was started with pentane as eluent. As soon as the eluate showed a yellow coloration, yellow **3** could be eluted from the column with pentane/toluene (2:1). Yield 290 mg (5% referred to $Mo(CO)_6$); $^{31}P\{^1H\}$-NMR: $\delta = -336.5$; IR, *n*-heptane: ν(CO) = 1990 (vs), 1938 (vs) cm^{-1}. Elution with pentane/toluene in the ratio 1:1 gave a red fraction. When this fraction was evaporated down and the residue washed with ca. 5 mL CH_2Cl_2 at room temperature, there remained **2** as a yellow powder, which could be recrystallized from CH_2Cl_2 at −80°C. On evaporation and cooling to 5°C the red solution (mainly $[Me_5C_5Mo(CO)_3]_2$ and **1**) furnished another portion of **2** (total yield 67 mg, 1.4%); $^{13}C\{^1H\}$-NMR (50.28 MHz, CH_2Cl_2): $\delta = 95.6$ (s, C_5Me_5) 11.7 (br, s, CH_3). Elution with pentane/THF (3:1) then afforded a yellowish-red fraction, which, after evaporation to dryness and recrystallization from heptane, furnished thin, yellow-brown needles of **5** (yield 340 mg, 7%). Final elution with pentane/THF (1:1) furnished a cherry-red fraction, from which **4** was isolated (recrystallization from heptane: yield 15 mg, 0.2%; $^{31}P\{^1H\}$-NMR: $\delta = -48.4$ (s); IR ν(CO) = 1980 (s), 1920 (s), 1905 (s), 1829 (s) cm^{-1}). Complications: The fractions containing **3**, **4**, and **5** also contain small amounts of **2**, which are separated as described. Small amounts of **5** are also present in the fractions containing **2** and **4**.

[4] I. Bernal, H. Brunner, W. Meier, H. Pfisterer, J. Wachter, M. L. Ziegler, *Angew. Chem. 96* (1984) 428; *Angew. Chem. Int. Ed. Engl. 23* (1984) 438.

[5] ^1H-NMR (C_6D_6): $\delta = 1.68$ ("quint."); $^{13}C\{^1H\}$-NMR (CH_2Cl_2, 233 K): $\delta = 235.1$ (s, CO), 99.2 (s, C_5Me_5), 12.9 ("quint.", CH_3); $^{31}P\{^1H\}$-NMR: AA'BB'-spin system: $\delta(P_A) = -101.9$, $\delta(P_B) = -131.4$, $^1J(PP) = -499.6$, $^2J(PP) = +15.7$, $+24.1$, $^3J(PP) = +20.5$ Hz. EI-MS (100 eV, 160°C): *m/z* 642 ($M^{\oplus}$, 9%), 586 ($M^{\oplus} - 2CO$, 100%), 293 ($(M^{\oplus} - 2CO)/2$, 15%). IR, ν(CO) = 1988 (vs), 1950 (m).

[6] **2**: $P\bar{1}$, $a = 8.594(2)$, $b = 10.316(2)$, $c = 8.367(1)$ Å, $\alpha = 104.72(2)$, $\beta = 113.51(1)$, $\gamma = 102.01(2)°$, $Z = 1$, $\rho_{calc} = 1.746$ g cm^{-3}. 2625 independent reflections ($Mo_{K\alpha}$, $2\theta \leq 55°$), 2245 observed with $F_0^2 > 2.0\sigma(F_0^2)$, 143 parameters, $R = 0.041$, $R_w = 0.047$. Further details of the crystal structure investigation are available on request from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2, on quoting the depository number CSD 51253, the names of the authors, and full citation of the journal.

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[13] Regarding the problem $P_4+P_2\rightarrow P_6$: E. A. Halevi, H. Bock, B. Roth, *Inorg. Chem. 23* (1984) 4376.

Carbonyliron-Assisted Coupling of Cyclopolyenes with Methyl Acrylate

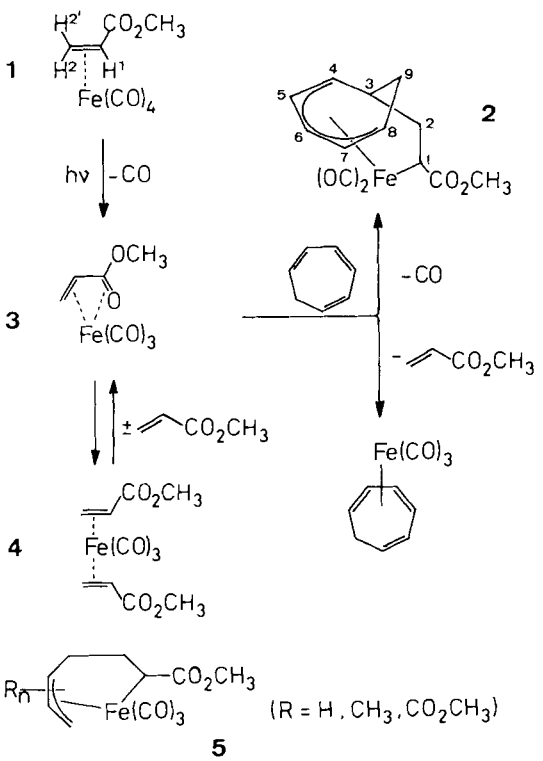
By *Richard Goddard, Friedrich-Wilhelm Grevels,** and *Rosemarie Schrader*

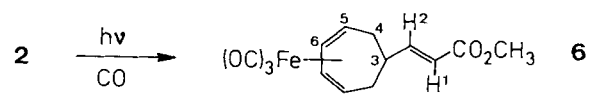
Dedicated to Professor Günther Wilke on the occasion of his 60th birthday

In many cases, substituted cyclohexadienes and cycloheptadienes are obtainable by addition of a nucleophile to $[(\eta^5\text{-cyclohexadienyl})Fe(CO)_3]$ and $[(\eta^5\text{-cycloheptadienyl})Fe(CO)_2L]$ cations, respectively.[1] We present here another way to introduce the $RO_2C-CH_2-CH_2-$ or $RO_2C-CH=CH-$ side chains: the carbonyliron-assisted coupling of acrylic esters with a cyclodiene or cyclotriene followed by a hydrogen shift.

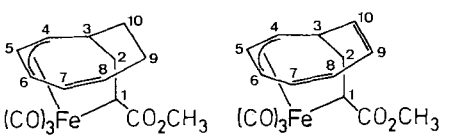
Irradiation of a mixture of the complex **1** and cycloheptatriene affords, in addition to $[(\eta^4\text{-cycloheptatriene})Fe(CO)_3]$ and small amounts of other products, the dicarbonyliron complex **2** (20% yield). In **2**, the adduct of the two organic substrates is σ,η^5-coordinated. The actual photoreaction consists of the dissociation of CO,[2] which is followed by a series of thermal reactions. **2** is also obtained without irradiation starting from the tricarbonyliron complex **4**[3] and introducing cycloheptatriene by thermal ligand exchange (43% yield).[4] These reactions are comparable to the synthesis of compounds of the type **5**.[5,6]

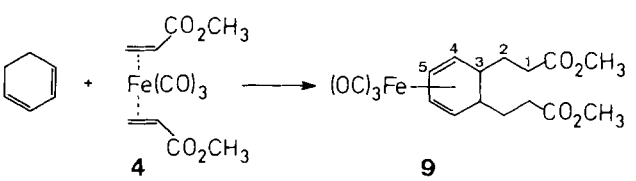
Upon irradiation under CO, **2** is converted into the derivative **6**,[4] which has a double bond in the side chain. In this process, the hydrogen atom is selectively transferred from the 2′-H position to the ring. Analogous experiments with deuterium-labeled **2** (1-H, 2-H = D, or 2′-H = D) show that, in the first case, both D atoms remain in the side chain, whereas, in the second case, D is transferred. Each of the complexes **2** labeled in this way was synthesized from the correspondingly labeled methyl acrylate (1-H, 2-H = D, or 2′-H = D).[7]





Exploratory attempts to couple cyclooctatriene or cyclooctatetraene with methyl acrylate, analogously to the synthesis of **2**, gave the complexes **7** and **8**, respectively, in 10–20% yield.[4]





In the thermal reaction of 1,3-cyclohexadiene with **4**, two acrylic ester moieties are added to the six-membered ring, forming **9**[4] (45% yield). The X-ray structure analysis of **9** (Fig. 1) shows that the $Fe(CO)_3$ group and the two side chains are on the same side of the six-membered ring. Hence it follows that, here too, complexation of the two substrates initially takes place with subsequent formation of a carbonyl(σ,η^3-organo)iron complex, which immediately undergoes rearrangement. In this case, a hydrogen atom is transferred from the ring to the side chain, so that the 1,3-diene unit is retained in the ring and the side chain, detached from the metal, is saturated. When this sequence

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of reactions occurs once again with the second acrylic ester, **9** is formed as the final product.

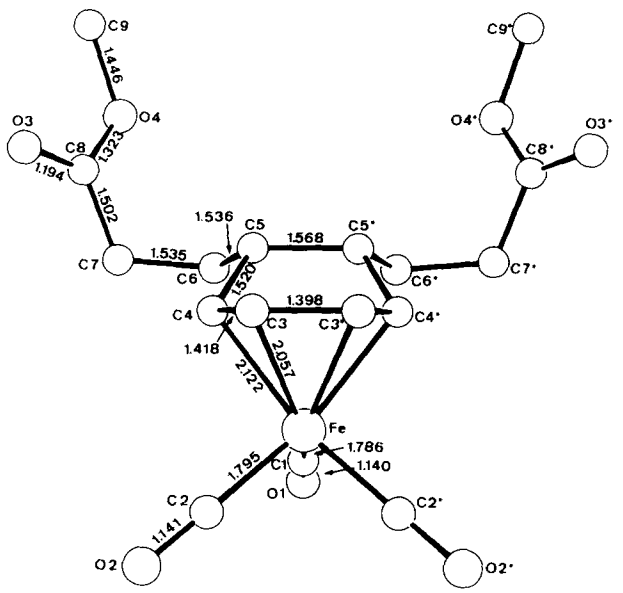
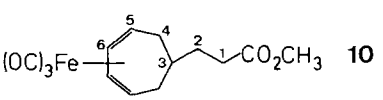


Fig. 1. Molecular structure of **9** in the crystal with selected interatomic distances [Å]. Crystal data: Pnma, $a = 13.898(1)$, $b = 17.465(2)$, $c = 7.237(1)$ Å, $V = 1756.6$ Å^3, $Z = 4$, $\rho_{calcd.} = 1.48$ g cm^{-3}; $\lambda = 0.71069$ Å, $\mu = 8.9$ cm^{-1}, $R = 0.035$, $R_w = 0.035$; 4913 measured reflections [h, k, ±l], of which 1743 were observed ($I > 2.0\sigma(I)$). 158 refined parameters. The molecule has a space-group-determined mirror plane passing through Fe, C1, and O1 and therefore cutting the C3–C3* and C5–C5* bonds. The best plane passing through C4, C3, C3*, and C4* forms an angle of 41.2° with that passing through C4, C5, C5*, and C4*. Further details of the crystal structure investigation may be obtained from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen (FRG), on quoting the depository number CSD 51266, the authors, and the journal citation.

The analogous reaction of 1,3-cycloheptadiene with **4** likewise affords a substituted (η^4-1,3-cyclodiene)Fe(CO)$_3$ complex, **10**,[4] which, however, contains only one acrylic ester moiety (20% yield).



10

We are currently attempting to improve the yields by modification of the reaction procedure; the reaction may eventually be applied to other olefins[8] as well as to substituted cyclopolyenes.

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[2] **3** has been identified as a photoproduct of **1** in low-temperature matrices. In solution, it is present in equilibrium with **4** [3].

[3] F.-W. Grevels, D. Schulz, E. Koerner von Gustorf, *Angew. Chem. 86* (1974) 558; *Angew. Chem. Int. Ed. Engl. 13* (1974) 534.

[4] **2**: Procedure: A solution of 3.7 g (40 mmol) cycloheptatriene in 120 mL diethyl ether is added to 2.5 g (8 mmol) **4** at −30°C and the reaction mixture is warmed with stirring to room temperature. After 3 h, the solution is evaporated in vacuum and the residue chromatographed on silica gel. The side products are eluted with pentane, followed by **2** with diethyl ether (1.0 g, 43%); yellowish orange crystals, m.p. ≈ 103°C (decomp.) after recrystallization from diethyl ether. ^{1}H NMR (C_6D_6): $\delta = 4.09$ (dd, $J = 7.5$, 8.5 Hz, 1-H), 3.75 (m, 2-H), 1.91 (dd, $J = 8.5$, 13.5 Hz, 2′-H), 2.08 (m, 3-H), 4.50 (m, 4-H), 4.01 (dd, $J = 6.5$, 10.5 Hz, 5-H), 4.83 (dt, $J = 2$, 6.5 Hz, 6-H), 4.96 (dd, $J = 6.5$, 7.5 Hz, 7-H), 3.17 (m, 8-H), 0.04 (m, 9-H), 0.79 (m, 9′-H), 3.67 (ester-CH_3); Assignment by exhaustive decoupling. ^{13}C{^{1}H} NMR (C_6D_6): $\delta = 26.7$ (C1), 47.9 (C2), 55.1 (C3), 82.6, 88.1, 101.9, 104.3, 105.6 (C4 to C8), 28.9 (C9), 185.5, 50.4 (CO_2CH_3), 209.4, 210.1 (2CO); Assignment by comparison with the non-decoupled spectrum of the compound deuterated in the 1-H and 2-H positions. IR (*n*-hexane): ν(CO) = 2020, 1972; ν(ester-CO) = 1699 cm^{-1}. UV (*n*-hexane): $\lambda = 365$ (sh, $\varepsilon = 1400$), 275 (sh, 6600), 228 (7900), 209 nm (20100). — **6**: Procedure: 0.50 g (1.7 mmol) **2** is irradiated in 150 mL *n*-hexane under carbon monoxide (immersion lamp apparatus made of Solidex glass, mercury lamp Philips HPK 125W), 2.5 h at room temperature. Chromatography on silica gel (pentane with 15% diethyl ether) affords 0.41 g **6** (75%); yellow crystals, m.p. 79–83°C (after recrystallization from *n*-hexane). ^{1}H NMR (C_6D_6): $\delta = 5.57$ (d, $J = 15.8$ Hz, 1-H), 6.61 (dd, $J = 5.5$, 15.8 Hz, 2-H), 1.25–1.55 (m, 5H, 3-H, 4-H), 2.43 (m, 2-H, 5-H), 4.52 (m, 2H, 6-H), 3.41 (s, 3H, ester-CH_3). IR (*n*-hexane): ν(CO) = 2049, 1981, 1977.5; ν(ester-CO) = 1734 cm^{-1}. — **7**: yellow crystals, m.p. = 80–82°C (decomp.). ^{1}H NMR (C_6D_6): $\delta = 1.75$ (dd, $J = 7$, 11.5 Hz, 1-H), 1.51 (ddd, $J = 1.5$, 7, 14 Hz, 2-H), 3.30 (dt, $J = 14$, 11.5 Hz, 2′-H), 2.59 (m, 3-H), 4.24 (t, $J = 9.5$ Hz, 4-H), 3.90 (t, $J \approx 9$ Hz, 5-H), 4.28 (dd, $J = 4$, 8 Hz, 6-H), 5.74 (dd, $J = 4$, 10.5 Hz, 7-H), 5.35 (dt, $J = 10.5$, ≈ 8 Hz, 8-H), 1.91 (m, 9-H), 1.61 (m, 9′-H), 1.20 (m, 10-H), 0.79 (m, 10′-H), 3.57 (s, 3H, ester-CH_3); Assignment by exhaustive decoupling. ^{13}C{^{1}H} NMR (C_7D_8): $\delta = 25.9$, 33.6, 38.5, 39.3, 49.4, 50.2, 70.8/89.8/92.6 (η^3-allyl group), 131.2/131.7 (C7/C8), 180.8 (ester-CO), 204.7/211.3/213.6 (CO). IR (*n*-hexane): ν(CO) = 2063.5, 2009.5, 1991; ν(ester-CO) = 1709 cm^{-1}. — **8**: yellow crystals, m.p. ≈ 104°C (decomp.). ^{1}H NMR (C_6D_6): $\delta = 2.12$ (dd, $J = 6$, 14 Hz, 1-H), 2.47 (m, 2-H), 3.17 (ddd, $J \approx 11$, 12.5, 14 Hz, 2′-H), 2.49 (m, 3-H), 4.84 (t, $J \approx 9$ Hz, 4-H), 3.84 (t, $J \approx 9$ Hz, 5-H), 4.41 (dd, $J = 6$, 9 Hz, 6-H), 5.38 (dd, $J = 6$, 12 Hz, 7-H), 5.51 (dd, $J = 5.5$, 12 Hz, 8-H), 5.24 (ddd, $J \approx 1$, 5.5, 12.5 Hz, 9-H), 5.56 (dd, $J = 10$, 12.5 Hz, 10-H), 3.55 (s, 3H, ester-CH_3); Assignment by exhaustive decoupling. IR (*n*-hexane): ν(CO) = 2064, 2010.5, 1991.5; ν(ester-CO) = 1709 cm^{-1}. — **9**; yellow crystals, m.p. = 57–58°C. ^{1}H NMR (C_6D_6): $\delta = 1.9$–2.0 (4H, 1-H), 1.38 (4H, 2-H), 1.62 (2H, 3-H), 2.59 (2H, 4-H), 4.47 (2H, 5-H), 3.27 (s, 6H, ester-CH_3). ^{13}C NMR (C_6D_6): $\delta = 32.8/26.9$ [t, ^1J(C–H) = 127 Hz, C1/C2], 39.2 (d, $J = 122$ Hz, C3), 67.2 (d, $J = 160$ Hz, C4), 85.1 (d, $J = 172$ Hz, C5), 173.0 (ester-CO), 51.0 (q, $J = 147$ Hz, ester-CH_3), 212.6 (CO). IR (*n*-hexane): ν(CO) = 2049, 1980.5; ν(ester-CO) = 1748 cm^{-1}. — **10**: yellow crystals, m.p. = 39–42°C. ^{1}H NMR (C_6D_6): $\delta = 1.82$ (2H, 1-H), 1.06 (2H, 2-H), 0.77 (1H, 3-H), 1.19/1.57 (2H/2H, 4-H/4′-H), 2.53 (2H, 5-H), 6.36 (2H, 6-H), 3.29 (3H; ester-CH_3). IR (*n*-hexane): ν(CO) = 2047, 1978; ν(ester-CO) = 1750 cm^{-1}.

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[8] An adduct of type **2**, a derivative of dimethyl maleate, is known: R. E. Davis, T. A. Dodds, T.-H. Hseu, J. C. Wagnon, T. Devon, J. Tancrede, J. S. McKennis, R. Pettit, *J. Am. Chem. Soc. 96* (1974) 7562.

Bioelektrochemische Membranelektroden. By *J. G. Schindler* and *M. M. Schindler*. Verlag Walter de Gruyter, Berlin 1983. xi, 340 pp, bound, DM 180.00.

The astonishing developments in the field of bioelectrochemical membrane electrodes is certainly a result of the enormous practical importance which these bioanalogous sensors are gaining in analytical biochemistry, diagnostic clinical chemistry, for biotechnological process control, and for reaction control. A (German language) summary of the fundamental principles, of the various possible applications, and of further developments of electrochemical measuring systems will, therefore, be welcome, particularly to clinical medical practitioners, biochemists, biophysicists, and process engineers.

The functional principles of bioelectrochemical membrane electrodes, such as the membrane concept, ionic selectivity, membrane-immobilized enzymes, streamline form for flow measuring sensors are copied from nature. The construction of highly specific electrochemical sensors is often bioanalogous down to the smallest detail. This is true not only for the measuring systems for the determination of the activities of metal and nonmetal ions and of dissolved gases (e.g. O_2 and CO_2), but also for biodetectors for the highly specific determination of ionic and nonionic cell metabolites.

Bioelectrochemical measuring sensors include a large number of enzyme electrodes, which are employed as the sensitive elements of gas and ion sensors. Immobilized microorganisms, cell organelles such as mitochondria, and cell tissue are employed as enzyme carriers. Highly selective immune reactions are the functional basis of immune electrodes; hormone-receptor reactions are also exploited electroanalytically in membrane electrodes.

The authors explain the bioanalytically important topic of bioelectrochemical electrodes in seven chapters. After an introduction to ion-selective measurement circuits and some physicochemical principles, quantitative electrode characteristics are discussed. Further sections cover structure and binding, electrically neutral ionophoric antibiotics and synthetic carriers (including chiroselective transport molecules), ion-selective carrier membrane systems (transport principle, membrane production), ion-selective carrier membrane electrodes (derivation, continuous flow sensors, dip electrodes), gas-sensitive electrodes (potentiometric and polarographic measuring cells), and finally membrane electrodes with sensitized detectors.

The book is clearly written and reflects the competence of the authors and their experience with bioelectrodes. But chemical thermodynamics is thin ice for them even when they only need to copy it out. The free enthalpy (Gibbs) is naturally "work potential" and not as asserted on p. 2 "the amount of heat taken up or evolved". The quantity named after *Loschmidt-Avogadro* is not a number but a constant possessing dimensions. The molar free enthalpy of reaction $\Delta\overline{G}$ is not known "as the chemical potential μ" (p. 4), but rather $\Delta\overline{G} = \Sigma\nu_i\mu_i$ is the change in free enthalpy for one stoichiometric turnover and is given by the sum of the chemical potentials of the reaction partners, whereby the stoichiometric coefficients of the educts are taken as negative.

These inadequacies in the introduction do not, however, detract from the service the authors have performed in providing a good and comprehensible presentation of a complicated topic. The book contains a comprehensive bibliography, including recent publications. It is to be recommended to beginner and expert alike as a general orientation guide.

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NMR and Chemistry. An Introduction to the Fourier Transform-Multinuclear Era. 2nd Edit. By *J. W. Akitt*. Chapman and Hall, London—New York 1983. xiii, 263 pp, paperback, £ 7.95.

This introduction to modern NMR methods is aimed mainly at students of chemistry and related sciences and at NMR spectroscopists in industry.

The first half of the book comprises six chapters which contain a vivid presentation of the fundamentals of high resolution NMR spectroscopy of dissolved compounds. The basic physical background is dealt with in Chapter 1. The following chapters are devoted to the important NMR parameters, chemical shift (Chapter 2), spin-spin coupling (Chapter 3), and relaxation (Chapter 4). It is particularly pleasing that these chapters do not just refer to examples with protons and carbon-13, but also touch on the NMR properties of other nuclei such as ^{11}B, ^{15}N, ^{17}O, ^{19}F, and ^{31}P. The third chapter on the analysis of spin systems is also a successful introduction to spectral interpretation and gets by largely without formulas. The chapter on relaxation is satisfying since all the important phenomena are clearly presented, although the treatment of exchange phenomena and instrumental details at this juncture may confuse some readers, since the modern spectrometer system is not treated until the fifth chapter. The sixth chapter discusses the nature of the samples and the problems of the standardization of spectra.

In the second half of the book the author deals with more complex NMR techniques and introduces examples of multinuclear NMR methods. Many of the double resonance methods described in Chapter 7 are already outdated as a result of the rapid development of pulse spectroscopy. A more detailed treatment of ^{13}C NMR spectroscopy would have been desirable here. It is pleasing that the most recent NMR techniques are mentioned (Chapter 8). The short presentation of solid and in vivo NMR methods is particularly successful. The examples chosen to illustrate the application of two dimensional NMR spectroscopy are less fortunate; there is no mention of shift correlation diagrams, which are of great practical importance because the bonding of the C and H atoms in the organic skeleton can be derived from them without any prior information. Immediate chemical applications are discussed in the last chapter. In addition to ^{1}H and ^{13}C NMR, the chemical relevance of ^{7}Li, ^{23}Na, ^{11}B, ^{27}Al, ^{15}N, ^{31}P, ^{17}O and ^{19}F NMR spectroscopy is demonstrated on the basis of examples. The appendix contains 18 short exercises together with their solutions, a reference list that is, however, too short, and a list of contents.

This book will be of immense value to those seeking an insight into high resolution NMR spectroscopy. Its strength lies in the clear presentation of NMR phenomena. On the other hand, very little comparison material, which is of such importance for the NMR spectroscopist, is given. This reasonably priced book can be highly recom-

mended to undergraduate and postgraduate students who come into contact with NMR spectroscopy.

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New Books

The following books have been received by the editor. All the publications listed are available through W & P Buchversand für Wissenschaft und Praxis, Boschstrasse 12, D-6940 Weinheim (Federal Republic of Germany). Tel. (06201) 606-0, Telex 465516 vchwh d, Telefax (06201) 602328.

Proceedings of the 7th International Conference on the Origins of Life. Edited by *K. Dose, A. W. Schwarz,* and *W. H.-P. Thiemann.* D. Reidel Publishing Company, Dordrecht 1984. 856 pp., bound, HFl. 285.00.—ISBN 90-277-1694-3

Studies in Physical and Theoretical Chemistry. Vol. 33: Inorganic Electronic Spectroscopy. 2nd edition. By *A. B. P. Lever.* Elsevier, Amsterdam 1984. xvi, 862 pp., bound, HFl. 295.00.—ISBN 0-444-42389-3

Gmelin. Handbuch der Anorganischen Chemie. A publication of the Gmelin-Institut für Anorganische Chemie der Max-Planck-Gesellschaft zur Förderung der Wissenschaften e.V. 8th edition. **W—Tungsten. Supplement Vol. B 6: Anhydrous Tungstates of Group IV A to VI B Metals.** Springer-Verlag, Berlin 1984. xx, 397 pp., bound, DM 1329.00.—ISBN 3-540-93506-1; **Sc, Y, La—Lu—Rare Earth Elements. Part A 8: Minerals (Silicates)—Deposits—Mineral Index.** Springer-Verlag, Berlin 1984. xv, 413 pp., bound, DM 1391.00.—ISBN 3-540-93505-3

Bacterial Endotoxin. Chemical, Biological and Clinical Aspects. Edited by *J. Y. Homma, S. Kanegasaki, O. Lüderitz, T. Shiba,* and *O. Westphal.* Verlag Chemie, Weinheim 1984. ix, 420 pp., bound, DM 118.00.—ISBN 3-527-26164-8

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Wasser und Wasseruntersuchung. 2nd revised and supplemented edition. **Methodik, Theorie und Praxis chemischer, chemisch-physikalischer und bakteriologischer Untersuchungsverfahren.** By *L. A. Hütter.* Diesterweg/Salle-Sauerländer, Frankfurt 1984. viii, 344 pp., paperback, DM 48.00.—ISBN 3-425-05075-3

Studies in Physical and Theoretical Chemistry. Vol. 34: Electrochemistry: The Interfacing Science. Proceedings of the Sixth Australian Electrochemistry Conference, Geelong, Victoria, 19—22 February 1984. Edited by *D. A. J. Rand.* Elsevier, Amsterdam 1984. x, 482 pp., bound, HFl. 295.00.—ISBN 0-444-42304-4

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Radwaste Immobilization by Structural Modification—the Crystallochemical Properties of SYNROC, a Titanate Ceramic

By Timothy J. White,* Robert L. Segall, and Peter S. Turner

New studies utilizing electron microscopic techniques have revealed the immobilization of radionuclides in crystalline ceramic waste forms to be not merely a question of substituting waste elements into the appropriate crystallographic sites of a host matrix. Rather than entering the ceramic as a "continuous" solid solution it has been found that the incorporation of highly radioactive waste elements is commonly accompanied by structural modification. This may take the form of cation ordering, crystallographic shear, or twinning on a unit cell scale. Such mechanisms considerably enhance the capacity of a ceramic to immobilize (simulated) radwaste and impart to it the flexibility to respond to inevitable variations in wastestream composition.

1. Introduction

One of the major challenges confronting the nuclear power industry is to provide an enduring solution to the problem of high level waste (HLW) disposal which is both satisfying from a scientific viewpoint and convincing to the layman. The technological and environmental difficulties associated with radioactive refuse have long been recognized. In 1953 *Hatch*[1] showed remarkable prescience by outlining the likely hazards associated with the containment of spent fuel rods and recognizing the political and social responsibilities of a world embarking upon the generation of electricity by nuclear fission. It was he who coined the expression, now a cliche, "ultimate disposal" and described preliminary research associated with several disposal techniques that are under consideration today.

Currently, there is a broadly based consensus that securement of HLW is achieved most effectively by the use of nested multibarriers.[2] The barriers may be divided into two categories. The first is the immobilization barrier. Primarily, this refers to the material which has been produced by solidification of liquid waste. This matrix should be in a form that is mechanically sound and exhibits stability in the presence of groundwater. The barrier may include a corrosion resistant cannister in which the solidified waste has been placed. This "package" is then deposited in an (inaccessible) repository which can take the form of a salt dome, deep-sea clay formation, disused mine or deep bore hole; these and their surroundings constitute the geological barrier.

At present, the nuclear power establishment favors the incorporation of radwaste in borosilicate glass. The major advantage of the glass matrix is that it is "amorphous", hence the process of metamictization (or radiation induced disorder) is eliminated. However, glasses have a maximum waste load capacity of about 10 wt%, since it is difficult to maintain homogeneity during preparation, and annealing due to self-irradiation may cause devitrification.[3,4] In addition, doubts have been expressed with regard to the stability of glass under repository conditions which admit ground water.[5]

For these reasons, considerable effort is being expended to develop alternative or second generation crystalline

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waste forms whose hydrothermal stability exceeds that of glass, and in addition possess the ability to effectively immobilize similar or greater waste loadings without undergoing deleterious structural change leading to inadequate leach resistance.[6] To this end, three approaches are receiving significant attention: a glass-(titanosilicate) ceramic the principal constituent of which is the mineral sphene ($CaSiTiO_5$);[7a] an alumina waste form which may be tailored to suit a variety of wastestreams;[7b] and SYNROC (*syn*thetic *rock*) a titanate ceramic based on several naturally occurring minerals.[7c]

In this article we explore the crystallochemical properties of SYNROC[8] and describe for the first time some unexpected structural characteristics which impart to the ceramic the flexibility to incorporate a great diversity of wastestream compositions and loadings.

2. The SYNROC Process

It is not the purpose of this paper to describe the techniques of SYNROC manufacture; this has been documented extensively elsewhere.[9, 10] However, some aspects of the fabrication which bear directly upon the microcrystalline properties of the ceramic are worthy of mention. At present, the favored preparative route—the Sandia process[11]—involves the hydrolysis of titanium tetraisopropoxide and zirconium tetra-*n*-butoxide in the presence of NaOH to yield a "sodium titanate—sodium zirconate" powder which behaves as a cation exchanger for an aluminum, barium and calcium nitrate solution. Simulated waste (see Table 1), also as a nitrate solution, is subsequently added to this precursor material. The slurry is dried and calcined under reducing atmosphere, then hot pressed with 2 wt.-% titanium metal added to control the redox potential. The most significant feature of this fabrication process, which distinguishes it from those employed for other ceramic waste forms, is the maintenance of low oxygen potential during manufacture. The reducing conditions ensure that molybdenum is reduced to metal, thus preventing the formation of molybdates which are highly susceptible to leaching. In addition, considerable quantities of Ti^{3+} are produced; as will be shown, this profoundly influences the crystal chemistry of the system because of its ability to substitute for Zr^{4+} (due to its size) and Al^{3+} (as a result of its valence).

Table 1. Typical composition (wt% oxide) of simulated waste (for 20 wt% loaded SYNROC) as compared to high level waste calcine.

Fission Products			Actinoids		
Rb_2O, Cs_2O	as Cs_2O	8.0	NpO_2, U_3O_8, PuO_2	as UO_2	5.4
SrO		2.6			
BaO		3.8	Am_2O_3, Cm_2O_3	as Gd_2O_3	0.5
Y_2O_3		1.5			
La_2O_3, Ce_2O_3	as Ce_2O_3	11.3			
Pr_6O_{11}, Nd_2O_3, Pm_2O_3	as Nd_2O_3	15.0	Processing Contaminants		
Sm_2O_3		2.3	Fe_2O_3		3.7
Eu_2O_3, Gd_2O_3	as Gd_2O_3	0.8	Cr_2O_3		0.8
ZrO_2		12.1	NiO		0.3
MoO_2		12.7	P_2O_5		1.6
TeO_2		1.8			
Tc_2O_7, RuO_2, Rh_2O_3, PdO, Ag_2O, CdO	as Ag_2O	15.8			

3. The Phase Assemblage of SYNROC

Studies of the partition behavior of SYNROC phases have to date relied primarily on electron microprobe data. In order to grow crystals sufficiently large for satisfactory microprobe analyses ($>1\,\mu m$) samples must be hot-pressed at temperatures very close to the solidus ($>1200\,^\circ C$). However, during actual fabrication calcined powders are hot pressed at lower temperatures (1100—1170 °C) yielding a ceramic with grain sizes which are invariably less than 1 μm, many only a few hundred Ångstroms. Consequently, conventional methods of microstructural evaluation, viz. scanning electron microscopy (SEM) and energy dispersive spectroscopy (EDS), are unable to probe individual grains, making it impossible to unequivocally document the elemental partitioning between phases. In any case, the compositions of many SYNROC minerals are very similar, so chemical analyses alone are insufficient for definitive phase and structural identification.

Instead, it is necessary to adopt the more sophisticated technique of combining high resolution transmission electron microscopy (HRTEM), selected area diffraction (SAD), scanning transmission electron microscopy (STEM) and energy dispersive analysis to unequivocally characterize the waste form. Specimens were prepared for examination by crushing under ethanol and mounting on holey carbon films. (The more drastic preparative method of ion-beam milling was avoided since there is some evidence to suggest that structural alteration and elemental migration may result.[13])

The constituent phases of SYNROC are conveniently placed in six crystallographic categories: these are fluorite derivatives; perovskites; rutile; hollandite; magnetoplumbite/β-alumina types, and alloys. The relevant crystallographic data and approximate proportions of these phases in SYNROC are summarized in Tables 2 and 3, respectively. Their compositions are given in Figure 1.

4. Fluorite Superstructures

Fluorite (CaF_2) itself is cubic with $a = 5.463$ Å.[14] However, many nonstoichiometric derivatives containing a variety of altervalent ions are known; they are especially likely to form where the cations are relatively large, i.e. when r_{cation}/r_{anion} is about unity.[15] The effective ionic radii of the lanthanoids and actinoids are quite large[16] and so it is not surprising that several fluorite phases are observed in waste-loaded SYNROC. Most significantly, each fluorite structure may be derived from the others by the application of simple crystallographic operations on topographically similar portions of the structures. The relative abundance of these phases is determined by radwaste composition and loading.

Table 2. Unit cell parameters for SYNROC phases.

Phase Name/ Structure Type	System [a]	Cell Parameters						Ref.
		a [Å]	b [Å]	c [Å]	α [°]	β [°]	γ [°]	
Fluorite derivatives								
Zirconolite	m	12.611	7.311	11.444	90	100.52	90	[18]
Zirkelite[b]	tr	12.62	7.29	16.89	90	90	90	[22]
Pyrochlore[b]	c	12.61	7.26	17.84	90	90	90	[22]
Polymignyte[b]	o	2×12.37	7.28	17.41	90	90	90	[22]
Perovskite	o	5.37	7.64	5.44	90	90	90	[26]
Perovskite-Polytype	h	5.4	5.4	22.1	90	90	120	this work
Rutile	te	4.58	4.58	2.95	90	90	90	[30]
Hollandite[c]	te	10.039	10.039	2.943	90	90	90	[34]
$BaTi_2Ti_6O_{16}$[d]	m	14.209	9.981	2.971	90	90	133.5	[37]
Magnetoplumbite (e.g. $CaAl_{12}O_{19}$)	h	5.576	5.576	21.97	90	90	120	[41]
β-Alumina (e.g. $RbAl_{11}O_{17}$)	h	5.597	5.597	22.877	90	90	120	[41]

[a] m: monoclinic, tr: trigonal, c: cubic, o: orthorhombic, h: hexagonal, te: tetragonal. [b] Non-standard C-centered cells. [c] Dimension of subcell axes. [d] Non-standard axial setting.

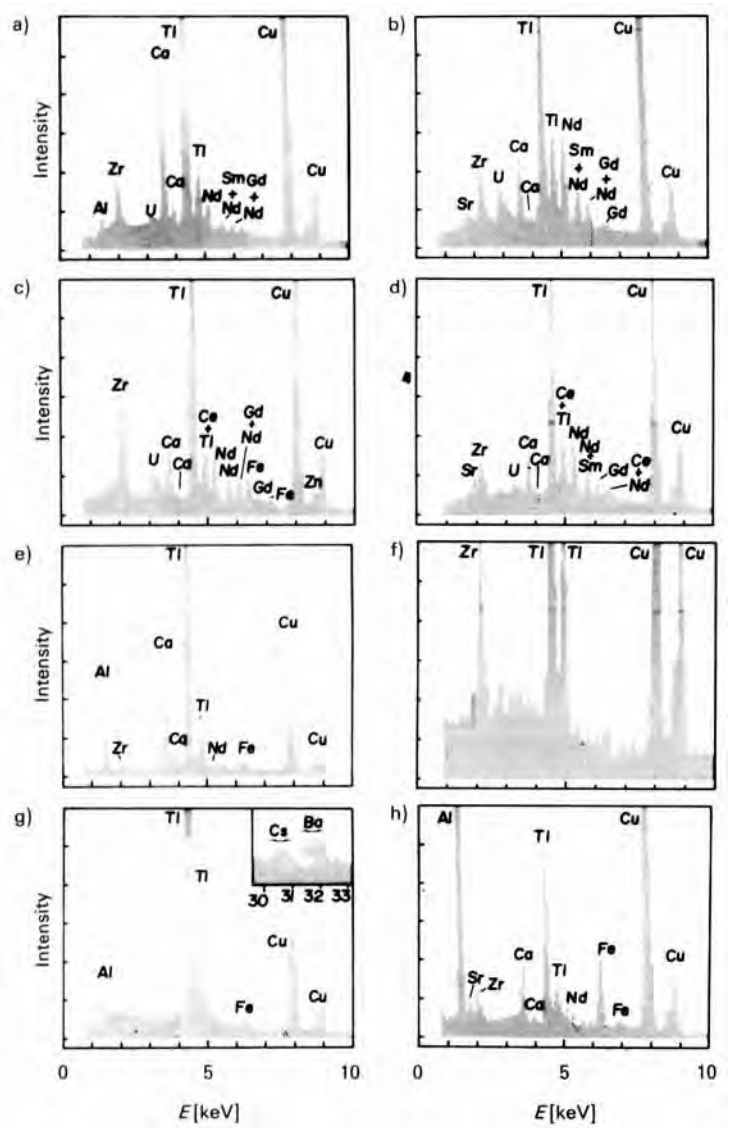


Fig. 1. Energy dispersive X-ray analyses for the major minerals found in SYNROC. (a) zirconolite-zirkelite intergrowth, (b) pyrochlore, (c) polymignyte, (d) perovskite, (e) perovskite polytype, (f) rutile, (g) hollandite, (h) magnetoplumbite. (Background copper peaks are present in all spectra.)

Table 3. Approximate constitution of phases [wt%] for the SYNROC C variant. Other SYNROC formulations contain the same phases in different proportions.

Fluorite Phases	30%
Hollandite Phases	30%
Perovskite Phases	15%
Rutile	15%
Magnetoplumbite	$\leqslant$ 5%
Alloy	$\leqslant$ 5%

4.1. Zirconolite

In 1964 *Pyatenko* and *Pudovkina*[17] showed zirconolite, nominally $CaZrTi_2O_7$, to be an anion-deficient superstructure derived from a fluorite-type substructure. Each unit cell of zirconolite consists of eight fluorite subcells ($8\times Ca_4F_8$) and contains $Ca_8Zr_8Ti_{16}O_{56}\square_8$, where $\square$ represents an oxygen vacancy. The (111) fluorite = (001) zirconolite metal planes are retained, but are occupied in an ordered fashion. However, the exact nature of the cation ordering over the subcell, crucial to our understanding of radwaste partitioning behavior, has only recently been determined.[18] It is useful to regard zirconolite in a formal way as a layer structure[18,19] in which planes of TiO_6 octahedra alternate with sheets of CaO_8/ZrO_7 polyhedra. The former are arranged in rings of three and six in the so-called hexagonal tungsten bronze type motif (Fig. 2). The larger cations are sandwiched between these layers and occur in strings of distorted Ca–O cubes (coordination number, CN = 8) or Zr–O monocapped octahedra (CN = 7). The interstice within the six-membered octahedral ring is occupied in a complicated manner. Ideally, a titanium atom would reside at the center of the ring in heavily distorted cubic coordination. However, such a polyhedron would be structurally unstable because of the large Ti–O bond lengths required. In accordance with Born theory[20] the cation moves slightly off-center such that the titanium atom is randomly located in either of two trigonal bipyramids (CN = 5).

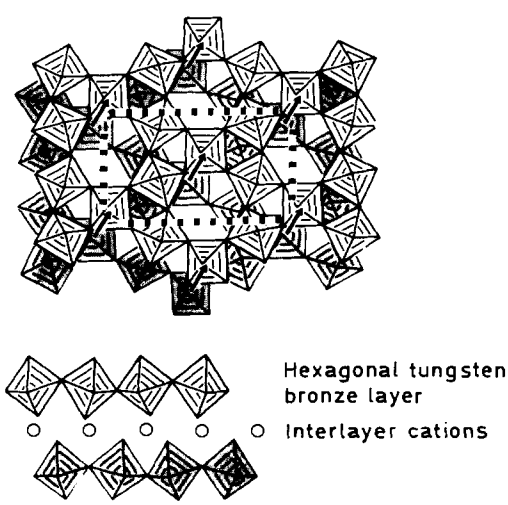


Fig. 2. Two hexagonal tungsten bronze layers as they occur in zirconolite. The upper (unshaded) is offset from the lower (shaded) by an interlayer displacement vector (arrowed). Large radionuclides are inserted between the layers. ■ ■ ■ delineates the unit cell repeat in (001).

In Figure 2 two adjacent hexagonal tungsten bronze layers in zirconolite are illustrated. The upper layer is staggered with respect to the lower (shaded); this offset is emphasized by arrows in the diagram. A third layer (not shown) would lie directly over the lowermost layer; thus, when considered sequentially, the displacement between layer pairs would be indicated by antiparallel arrows. This relationship between hexagonal tungsten bronze layers is conveniently represented by plotting the interlayer displacements upon the $a-b$ basal plane (Fig. 3). The double headed arrows, (placed at the corners of the unit cell and the C-center), indicate schematically the alternation in the direction of layer stagger (Fig. 3a). All the other fluorite structures may be derived from zirconolite by varying the pattern of layer displacement, and, as we shall see, this facilitates the incorporation of a variety of waste elements at a number of concentrations (cf. Section 10). Some other interlayer stacking sequences are shown in Figures 3b–f.

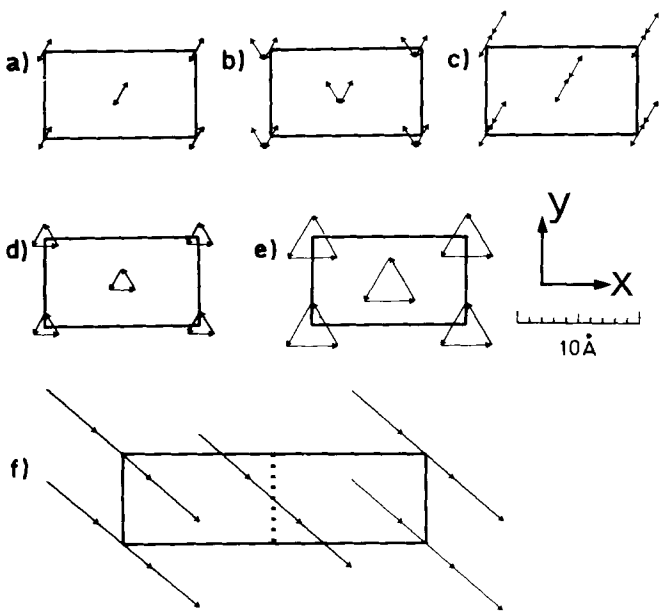


Fig. 3. Displacement vector diagrams for the fluorite derivatives plotted on the common a-b plane. (a) zirconolite, (b) zirconolite with t-type twin, (c) zirconolite with m-type twin, (d) zirkelite, (e) pyrochlore, (f) polymignyte.

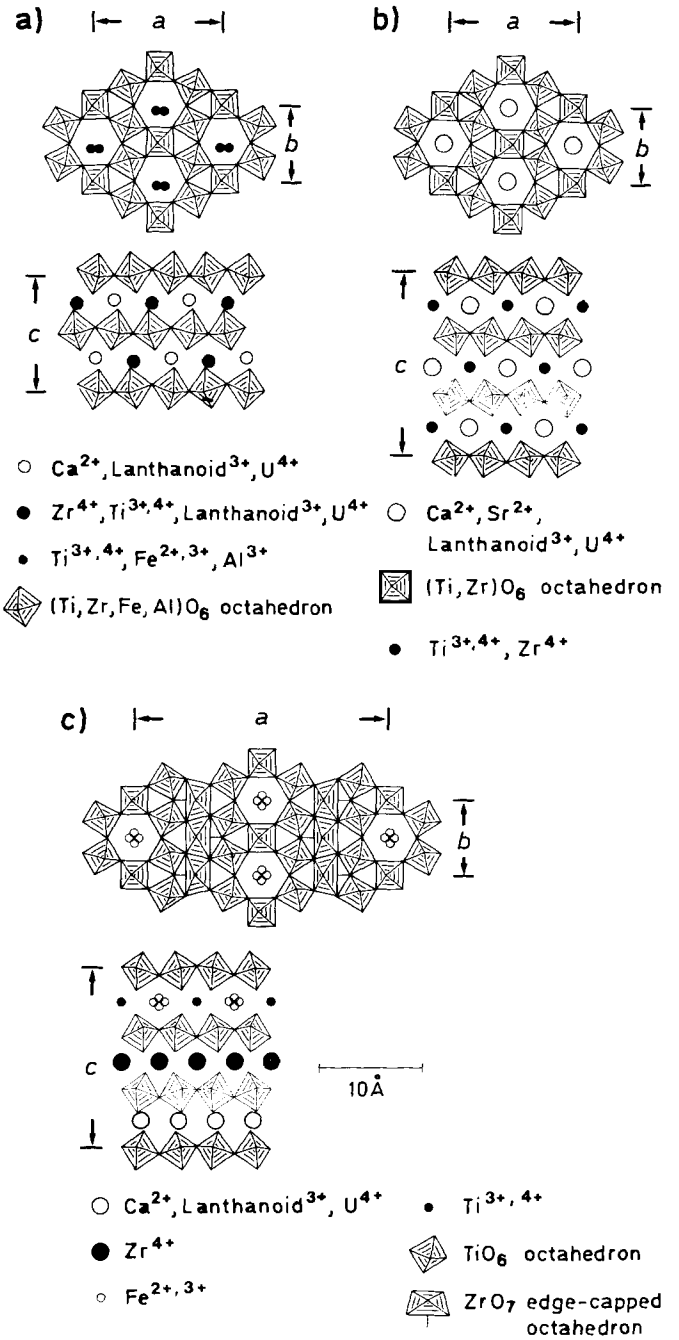


Fig. 4. Crystallochemical partitioning in (a) zirconolite and zirkelite, (b) pyrochlore, (c) polymignyte. In zirconolite-zirkelite and polymignyte the large interstice formed by the six-membered octahedral ring is filled by cations which are randomly distributed over two and four sites respectively. In pyrochlore the interstice is filled by large lanthanoids, actinoids, or Sr.

The partitioning behavior of zirconolite is quite complex (Fig. 4a). TiO_6 octahedra will accept Zr^{4+}, $Fe^{2+,3+}$, and Al^{3+}, while the smaller TiO_5 trigonal bipyramids will only accommodate the latter two of these. Trivalent lanthanoid ions and Th^{4+} are preferentially partitioned into Ca-sites whilst Zr^{4+} is replaced by U^{4+} and small, heavy trivalent lanthanoid ions.[12] The incorporation of these elements in zirconolite was confirmed by EDS (Fig. 1a).

At low concentrations the replacements are quite straightforward and radwaste is immobilized as a dilute substitutional solid solution. However, at modest concentrations—at the level of only 2.4 at% for neodymium[21]—isomorphic substitution no longer plays the primary role and the zirconolite structure is modified in a manner which greatly enhances the maximum concentration of "dissolved" radwaste. Initially, structural modification takes the form of polysynthetic (i.e. frequent) twinning on a unit cell scale. Displacement vector diagrams for the simplest twins are shown in Figure 3b,c. In t-type twins the zirconolite domains are related by rotations at 120° (i.e. a $t$riad rotation), whilst for m-type twins a 360° or $m$onad rotation is operating. Figure 5 is a typical high resolution electron micrograph of a twinned zirconolite crystal in SYNROC; different lattice periodicities result from the change in orientation across the twin boundaries.

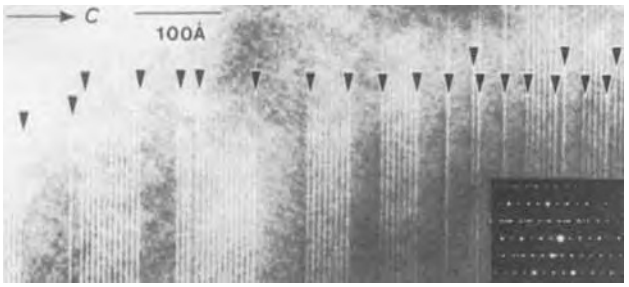


Fig. 5. High-resolution electron micrograph of SYNROC zirconolite. The frequent insertion of twin boundaries (arrowed) on the scale of a few tens of Angströms facilitates the incorporation of radionuclides. Each twin boundary can be considered as a narrow lamellar intergrowth of zirkelite, a phase stabilized by high actinoid concentrations.

4.2. Zirkelite

As the concentration of radwaste increases so does the frequency of twinning. It is not impossible for twinning to become perfectly regular and new ordered structure types produced.[21] One of these, zirkelite, has recently been analyzed using single crystal X-ray diffraction by *Mazzi* and *Munno*[22] and shown to be mimetically twinned zirconolite; mimetic twinning, as distinct from polysynthetic twinning, is perfectly regular.[23] *Mazzi* and *Munno*'s erudite interpretation of their diffraction data should not be underestimated. For many years, zirkelite and zirconolite were regarded as isotypic (i.e. structurally identical) as metamictization due to self-irradiation made diffraction studies equivocal. In the final analysis, the correct diffracted intensities could only be obtained by subtracting reflections due to other closely related species. Zirkelite was shown to have trigonal symmetry; however, the cell dimensions of the more useful C-centered unit cell are preferred and are given in Table 2. The sequence of layer displacements for zirkelite is shown in Figure 3d. Clearly, the insertion of three *t* type boundaries in zirconolite will yield a single unit cell of zirkelite. It is now obvious that the twin boundaries in zirconolite are usually very thin lamellar intergrowths of zirkelite. This is in complete agreement with other experiments which show zirkelite to have a greater capacity to incorporate actinoids than zirconolite provided that secondary cations such as Fe, Al or Mg are present.[12,21] Thus, the coherent intergrowth of zirconolite and zirkelite on a unit cell scale permits the incorporation of larger quantities of simulated radwaste (particularly the actinoids), than would be possible if simple cationic replacement was functioning alone.

4.3. Pyrochlore

The structure of pyrochlore, having the general stoichiometry (Ca, lanthanoids, actinoids)$_2$Ti$_2$O$_7$, has been extensively studied for many years.[24] It is cubic ($a = 10.1$ Å), but in the context of this discussion a direct comparison with other fluorite-related structures is facilitated by adopting the C-centered setting (Table 2). In this instance the interstices of the hexagonal tungsten bronze layers are occupied by large trivalent lanthanoid ions or tetravalent actinoid ions (Fig. 4b) in eightfold oxygen coordination. The sequence of interlayer displacements is identical to that found in zirkelite (Fig. 3e), but the offset between the layers is twice as great. In this manner CaO_8 cubes similar to those of zirkelite are retained, but the distorted monocapped octahedra are replaced by perfect (Ti,Zr)O_6 polyhedra, thus changing the interlayer cation coordination numbers from 8 plus 7 to 8 plus 6.

Pyrochlore occurs in SYNROC containing high waste loadings (i.e. >20 wt%). In crystallochemical terms this means a material with a relatively high Ca/Zr ratio, and a low concentration of Ca with respect to lanthanoids (Fig. 1a, b). The effect of doubling the interlayer displacement is to produce a fluorite derivative which has a greater capacity to immobilize lanthanoid fission fragments. In addition, pyrochlore may incorporate Sr^{2+}, U^{4+} and Th^{4+}; the partitioning behavior is summarized in Figures 4b and 1b.

4.4. Polymignyte

In a prototype SYNROC formulation containing 40 wt% simulated waste, yet another fluorite superstructure appears. The unit cell parameters of polymignyte, which is orthorhombic,[22] are given in Table 2. The octahedral motif of its layer cations is shown in Figure 4c. Clearly, large sections are still of the hexagonal tungsten bronze type, but they have been modified by crystallographic shear to yield a new type of layer interstice—an edge-capped octahedron.

This phase is favored when the concentration of Ca and Zr are simultaneously depleted relative to the amount of lanthanoids and actinoids. Iron (a processing contaminant), is a necessary constituent of this phase (Fig. 1c) being distributed statistically over four sites (two tetrahedral and two trigonal bipyramidal) which are situated around the center of the 6-membered octahedral ring.[22] These changes in the topology of the hexagonal tungsten bronze layers result in four different types of interlayer cation site. Two of them are not dissimilar to those found in zirconolite; however, in this instance the Zr-site is apparently devoid of any waste elements and the Ca-site accommodates all the U^{4+}. TiO_6 octahedra occur as in pyrochlore, and for the first time statistically occupied sites appear in the interlayer region. The interlayer stacking sequence for polymignyte is shown in Figure 3f.

Thus, zirconolite may be regarded as the structural aristotype of a group of minerals composed of (modified) hexagonal tungsten bronze layers. Providing altervalent cations are available (usually as processing contaminants) to ensure electrostatic charge balance, these layers can be stacked in a number of orientations which permit the incorporation of lanthanoids and actinoids at variable concentrations.

5. Perovskite and Related Structures

Perovskite has the composition $CaTiO_3$. Although initially thought to be cubic it was soon recognized to possess lower symmetry.[25] Subsequent X-ray crystallographic studies revealed it to be orthorhombic[26] (Table 2). The TiO_6 octahedral array of perovskite is derived from the

well known ReO_3 type (Fig. 6a); Ca atoms fill the large interstices between the octahedra and enter twelve coordinate cuboctahedral sites.

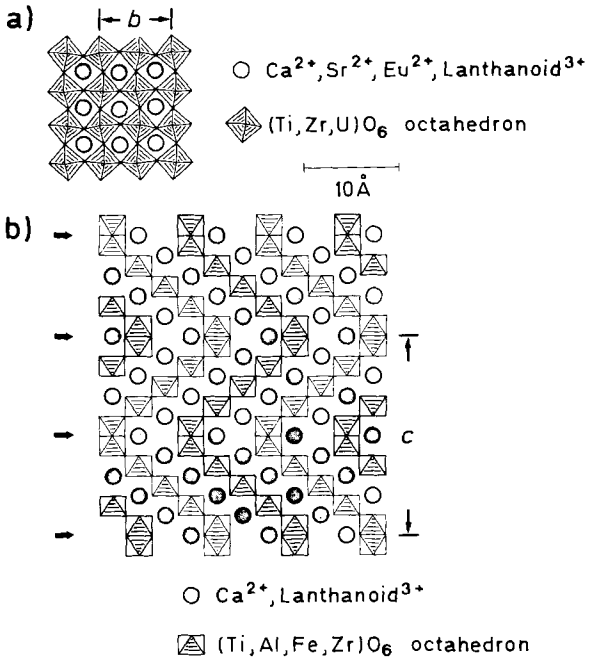


Fig. 6. (a) Octahedral array, projected down [101], and elemental partitioning in perovskite. (b) A drawing (idealized to cubic closest packing) of the most common perovskite polytype. This twinned arrangement of perovskite blocks accompanies the incorporation of neodymium and iron. Arrows indicate twin boundaries.

This mineral is the major host for Sr^{2+} and Eu^{2+}, and acts as a secondary host for trivalent lanthanoid ions; these replace Ca^{2+}. U^{4+} is also immobilized and it occupies the octahedral position.[27] The presence of these simulated waste elements was confirmed by EDS analyses (Fig. 1d). A large number of experiments have shown that radwaste generally enters perovskite by isomorphic substitution.[28]

In a special case, apparently when the local concentration of Nd and Fe are correct (see Fig. 1e), the perovskite grains begin to twin mimetically on the (approximately) close-packed atom planes. In this manner perovskite polytypes are produced. Figure 6b shows the most common structure (idealized to perfect cubic-closest-packing). Occasionally, disorder arising from variations in the width of the perovskite portion of the structure has been observed (Fig. 7).

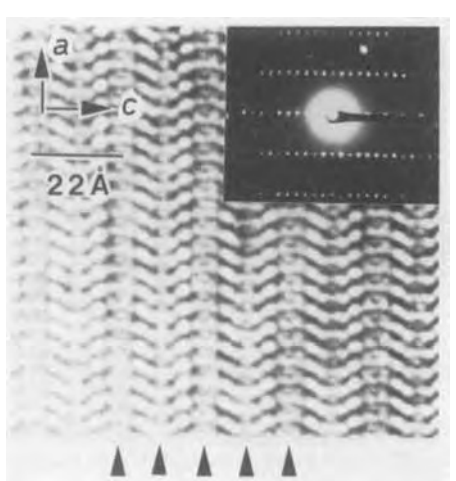


Fig. 7. High resolution electron micrograph of the perovskite polytype. Arrows indicate the same twin boundaries as those shown schematically in Figure 6b.

Infrequently, complex perovskite superstructures similar to those reported by *Nanot* et al. (1981)[29] are observed in 40 wt% waste loaded SYNROC; these phases are stabilized by high neodymium concentrations.

6. Rutile

The structure of rutile (Fig. 8a) was first determined by *Vegard* in 1916.[30] It is rather simple, being composed of TiO_6 octahedral strings that are corner connected to form tunnels one-octahedron wide. However, it has received considerable attention from crystal chemists because of its ability to accommodate nonstoichiometry by the introduction of crystallographic shear planes. At their simplest, these shear planes have the form $(hkl)_r = p(121)_r + q(011)_r$, where $1 \leqslant p/q \geqslant \infty$. This gives rise to an infinite number of crystallographic shear planes which are said to "swing" between $(121)_r$ and $(011)_r$.[31] The reducing conditions employed during SYNROC manufacture ensure that rutile invariably contains a variety of "swinging" shear planes due to the incorporation of Ti^{3+}. For all practical purposes radionuclides do not enter rutile, its major role being to buffer the redox conditions. A small amount of Zr^{4+}, typically 2 wt%[10] (Fig. 1e) does replace Ti and its stoichiometry is best regarded as $(Ti^{3+,4+}, Zr^{4+})_n O_{2n-1}$.

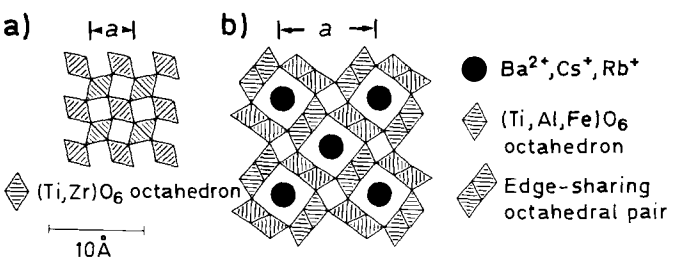


Fig. 8. Octahedral arrangement, shown along the short unit cell edge, of (a) rutile and (b) hollandite. The small octahedral tunnels of hollandite cannot accommodate simulated waste, but the larger incorporate Cs and Rb.

7. Hollandite

The structure of hollandite, *sensu stricto* $BaMn_8O_{16}$ was first determined by *Bystrom* and *Bystrom* in 1950[32] and shown to be tetragonal (Table 2). SYNROC hollandite has the ideal formula $Ba(Al^{3+},Ti^{3+})_2Ti_6O_{16}$.[33] Its structure is closely allied to that of rutile. Hollandite contains tunnels both one and two octahedra in width (Fig. 8b). The smaller of these are empty as in rutile, but the larger are occupied by Ba^{2+} which may be replaced by the radionuclides Cs^+ and Rb^+ (provided suitable altervalent cations are present). Evidence for the partitioning of the former element into hollandite is given in Figure 1g.

More recent structural refinements have shown that cation ordering along the tunnels is quite complex. The exact crystallographic positions and degree of filling of the tunnels is controlled by interactions between the occupants and the valence of the surrounding octahedrally coordinated cations.[34] These ordering effects in SYNROC hollandite are readily observed by selected area electron diffraction.[35] This is illustrated in Figure 9; stronger reflections arise due to the substructure defined by *Bystrom* and *Bystrom*, whilst weaker diffuse reflections (arrowed) are indicative of ordering along the tunnels. An extensive transmission electron microscopic study of SYNROC hollandite doped with Cs and Rb has shown that the incorporation of higher concentrations of monovalent species leads to longer range ordering sequences in the tunnel direction (Fig. 10).[36] It has been shown elsewhere[34] that the small cationic displacements, which produce these (incommensurate) superstructure reflections, yield a slightly larger cation acceptor site which is more suitable for the incorporation of Cs.

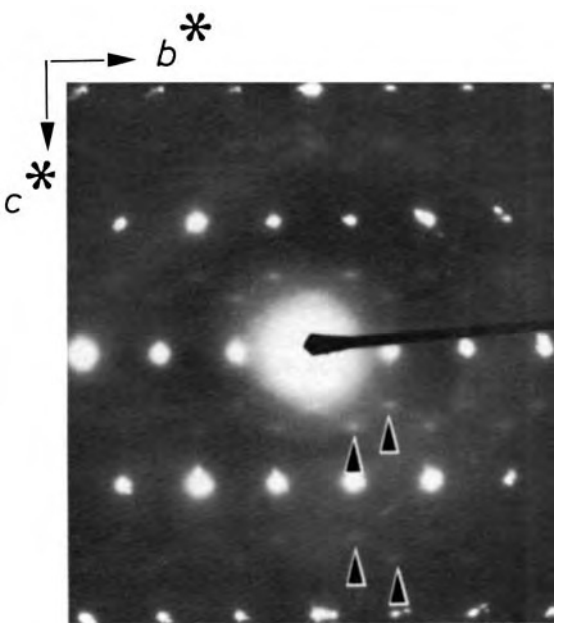


Fig. 9. Selected area electron diffraction pattern of hollandite. Diffuse reflections (arrowed) are indicative of cation ordering along c^*, the tunnel direction.

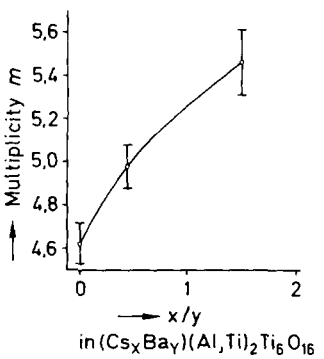


Fig. 10. The number of subcell units per supercell, or the multiplicity (m) of hollandite crystals increases as the Cs/Ba ratio is raised. That is, higher waste loadings lead to (increasingly) long range cation ordering sequences along the large hollandite tunnels. Values of m were determined from selected area electron diffraction patterns like that shown in Figure 9.

The titanium end member (*viz.* $BaTi_2Ti_6O_{16}$) has monoclinic symmetry and a doubled (pseudotetragonal) cell edge[37] (Table 2). This phase, however, has never been found in SYNROC; presumably the structure is destabilized by the presence of Fe and Al. Very occasionally "faulting" normal to the tunnel direction has been observed in a SYNROC variant (designated SYNROC E), which largely consists of rutile (80 percent by weight). This may be the result of intergrowth between the $BaAl_2Ti_6O_{16}$ and $BaTi_8O_{16}$ end members, and would certainly provide a means of incorporating some of the excess Ti^{3+}. It has been suggested that other hollandite derivatives may occur in SYNROC,[38,39] and indeed small ("defect") quantities of a number of structural variants have been recognized. One of these, $Ba_2Ti_9O_{20}$, may be of concern as it appears to be unable to take up Cs, and instead coexists with a highly soluble phase of approximate stoichiometry $Cs_2Ti_4O_9$.[40] However, the examination of many SYNROC preparations by selected area electron diffraction has failed to produce any evidence in support of the existence of single crystal $Ba_2Ti_9O_{20}$; it seems likely that this phase is not stable under the strongly reducing conditions. Nonetheless, some of the more complex defects in hollandite may contain elements of the $Ba_2Ti_9O_{20}$ structure. (Some crystallites in the SYNROC E formulation mentioned above yield diffraction patterns consistent with the $Cs_2Ti_4O_9$ phase of *Bursill* and *Kwiatkowska*.[40])

8. Magnetoplumbite and β-Alumina Structures

The structure of magnetoplumbite (Fig. 11) and β-alumina[41] are very closely related, both belonging to the same space group and having the ideal stoichiometries $AB_{12}O_{19}$ and $AB_{11}O_{17}$, respectively. They are mixed hexagonal-close-packed (h) cubic-close-packed (c) structures with the stacking sequence $(h^2c^3)^2$. Each cubic-close packed block is of the spinel type. These units are related by mirror planes at which large A atoms (Sr^{2+}, trivalent lanthanoid ions) and the appropriate number of B cations ($Ti^{3+,4+}$, Al^{3+}, $Fe^{2+,3+}$) commensurate with charge balance are inserted. The elemental contents of a magnetoplumbite crystal are given in Figure 1h. In β-alumina, the B atoms of the

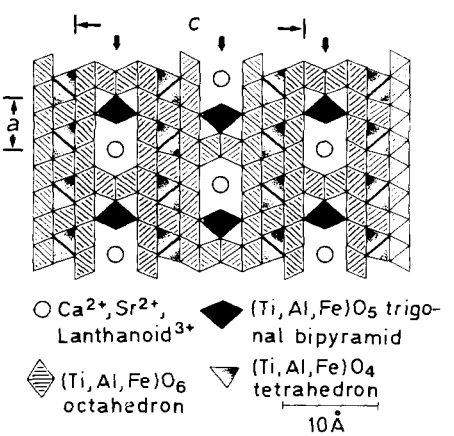


Fig. 11. Polyhedral arrangement in magnetoplumbite; mirror planes are arrowed.

inter-spinel region occupy tetrahedra, while in magnetoplumbite, octahedra and trigonal bipyramids are filled. In each instance AO_{12} twinned-cuboctahedra are present. The structures have been regarded as intergrowths between spinel and perovskite;[42] however, such a description is not convincing.

Magnetoplumbite has been extensively studied by *Morgan* et al.[7] as a possible host for a wide variety of radionuclides; it will accept most radwaste elements with the exception of the actinoids and possibly Cs. Only relatively small quantities of this phase are found in SYNROC as it provides a means of consuming residual Al^{3+} discarded from hollandite due to incorporation of Ti^{3+} produced during hot pressing.[33] This phase can be removed entirely, without deleterious effect on the performance of the ceramic, by eliminating the aluminum content of the formulation.[33]

Stacking faults in magnetoplumbite and β-alumina are well known and may arise from changes in the width of the spinel blocks[7] or from the insertion of antiphase boundaries.[7,43] These faults, which form in response to local variations in the concentration of radwaste species, should be regarded as structural intergrowths rather than "defects".

9. Other Phases

Fabrication under reducing conditions ensures that several of the waste constituents are (partially) reduced to metal; these include Tc, Ru, Rh, Pd, Cd, Fe, Ni, Mo and Ti. *Dosch* et al.[11] tentatively identified three intermetallic compounds in their experiments—a body-centered-cubic Mo-rich phase (≥80% Mo), Mo_4Ru_3 and Pd_4Te. However, the compositions of these alloys were quite variable, and their structures are unlikely to be as simple as the stoichiometries suggest.

In a ceramic as complex as fully waste-loaded SYNROC there exists the possibility for the formation of minor phases. It is perhaps surprising that these are rarely observed and probably account for less than 2 wt% of the bulk; the commonest additional phase is a Ca,Fe-titanate whose diffraction patterns are consistent with those of $CaTi_2O_4$. The only element whose crystallographic location has not been established is the processing contaminant phosphorus. Independent experiments[44] have shown the phosphate $Ca_3(PO_4)_2$ to be compatible with other SYNROC minerals, but the present study failed to identify this phase.

10. Concluding Remarks

The careful characterization of SYNROC by transmission electron microscopy has revealed the uptake of radwaste to be not only a question of inserting radionuclides into the appropriate crystallographic sites of a host matrix. We have shown the phenomenon of structural modification to very often accompany the incorporation of substantial levels of waste.

The fluorite oxides exhibit the greatest diversity of structural modification, engineered simply by varying the offset between successive hexagonal tungsten bronze layers. At low waste-loadings (< 10 wt%), zirconolite predominates. However, even at these levels, not all the waste may be accommodated directly into the "perfect" structure. Some of the elements, primarily the lanthanoids and actinoids, modify their crystallographic environment by causing zirconolite crystals to twin. The twin boundaries, rather than being regarded as crystalline defects are more rationally considered as thin lamellae of the closely related structure zirkelite. This mineral is known to be stabilized by high actinoid concentrations. If the waste is rich in lanthanoids or a 20 wt% loading is used, then pyrochlore coexists with zirconolite. At still higher waste-loadings (40 wt%) polymignyte becomes the dominant phase—zirconolite is seldom observed. It should be remarked that, with the exception of Rb, Cs, Sr, and P, all the radwaste (not reduced to metal) may be accommodated in fluorite phases. Perovskite and its polytypes are present to ensure the immobilization of Sr^{2+}, whilst hollandite and small quantities of some incompletely identified variants, which intergrow with the parent structure, take up Cs^+ and Rb^+; in both instances the incorporation of higher radwaste concentrations promotes long-range cation ordering. Little work has been done on the alloy structures, but they must also be quite complex.

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The Glycine Receptor of Rat Spinal Cord: Exploring the Site of Action of the Plant Alkaloid Strychnine**

By Heinrich Betz*

The amino acid glycine is a major neurotransmitter in the spinal cord of all vertebrates and is involved in the control of various motor and sensory functions. By binding to specific receptors of the neuronal plasma membrane, glycine produces an increase in chloride permeability and thus a hyperpolarization, i.e., an inhibition of glycine-sensitive neurons. This inhibitory action of glycine is reversibly blocked by the plant alkaloid strychnine. We have used strychnine for the biochemical characterization and isolation of the glycine receptor of rat spinal cord. Our results show that the glycine receptor is a large membrane protein which contains three different polypeptides. Based on the currently available data we propose a structural model of the glycine receptor and discuss its relation to other proteins of the neuronal membrane that are involved in the transmission of nerve impulses.

1. Introduction

Numerous investigations over the last two decades suggest that, besides their metabolic function, amino acids serve an important role in the transmission of nerve impulses between neurons. For a long time it has been known that aromatic amino acids are the precursors for the synthesis of catecholamines and thus are important in the metabolism of signal substances (neurotransmitters) in the brain. Only recently, however, was it realized that unmodified amino acids also can serve as neurotransmitters.[1] Today, several acidic and neutral amino acids (Table 1) are generally accepted as neurotransmitters at many synapses (interneuronal communication sites) in the central nervous system. There, the amino acids are concentrated in specialized intracellular organelles, the synaptic vesicles. Upon excitation, they are released onto the plasma membrane of connecting "postsynaptic" neurons, where they bind to highly specific receptors and thus produce various responses. Acidic amino acids, such as glutamate or aspartate, excite and neutral amino acids, e.g., γ-aminobutyric

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acid (GABA) and glycine, inhibit neuronal firing. Table 1 lists the amino acids that are currently considered to function as neurotransmitters or neuromodulators.

Table 1. Amino acid neurotransmitters.

Excitatory (increasing sodium conductance):
L-glutamate, L-aspartate, L-homocysteic acid [a]
Inhibitory (increasing chloride conductance):
glycine, GABA, taurine [a], β-alanine [a]

[a] Neurotransmitter function debated.

All the amino acid neurotransmitters listed in Table 1 produce selective alterations in the ion permeability of the neuronal cell membrane. Glutamate and aspartate increase the conductivity for Na^+, i.e., the influx of extracellular Na^+ into the negatively charged cytosol of the neuron. The resulting depolarization of the membrane's resting potential leads to an excitation of the nerve cell. GABA and glycine, in contrast, increase the chloride permeability: the influx of extracellular Cl^- produces a hyperpolarization of the plasma membrane, i.e., the neuron is inhibited.

The molecular structure of the plasma membrane proteins responsible for these conductance changes has only been poorly explored. In analogy with other receptor systems, amino acid receptors are thought to contain ion channels capable of assuming different protein conformations (Fig. 1). According to this model, the binding of an amino acid (or, more generally, an activator or "agonist") to the receptor induces the transition to an open, conducting conformation of the ion channel. Competitive receptor blockers ("antagonists") inhibit this conformational change by occupying the agonist binding site without activating the receptor: antagonists cannot produce the corresponding conformational alteration of the membrane protein. In other words, amino acid receptors are considered as bifunctional regulatory ("allosteric") proteins which mediate both neurotransmitter binding and ion transport. It should be noted here that the receptor activation depicted in Figure 1 implies a high molecular amplification of the primary signal: the binding of one or a few agonist molecules results within 1—5 ms in the flux of ca. 10^2—10^6 ions through the open channel of the activated receptor.

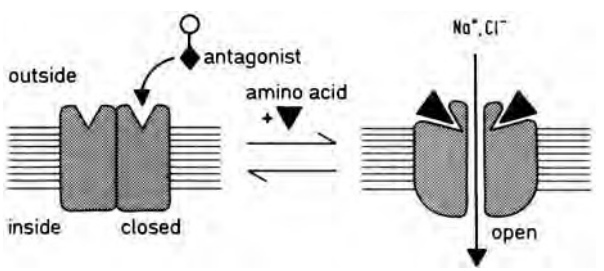


Fig. 1. Schematic representation of the closed and open conformations of an amino acid receptor.

So far, the biochemical analysis of amino acid receptors of the central nervous system has been hampered by their low concentration in the brain: a complete purification requires purification factors of ca. 10^4—10^6. However, the development of highly sensitive analytical techniques during the past three years has changed this situation. Today, the structural and functional analysis of these membrane proteins has become possible at the molecular level.

This review describes the efforts of our group to elucidate the molecular structure of an inhibitory amino acid receptor, the glycine receptor of rat spinal cord. Our results show that this chemically gated chloride channel has a complex structure which resembles that of other neuronal ion channels.

2. Strychnine—a Tool for Analyzing the Glycine Receptor

The alkaloid strychnine from *Strychnos nux vomica* has a rich history in natural products chemistry. The structural analysis of this alkaloid (Fig. 2) culminated in 1962 in its total synthesis by *Woodward*'s laboratory. In medicine, strychnine has long been popular as a stimulant and tonic. Higher doses of this alkaloid produce characteristic symptoms of poisoning which may cause pain and convulsions leading to death. Today, strychnine is still in use as a rat poison.

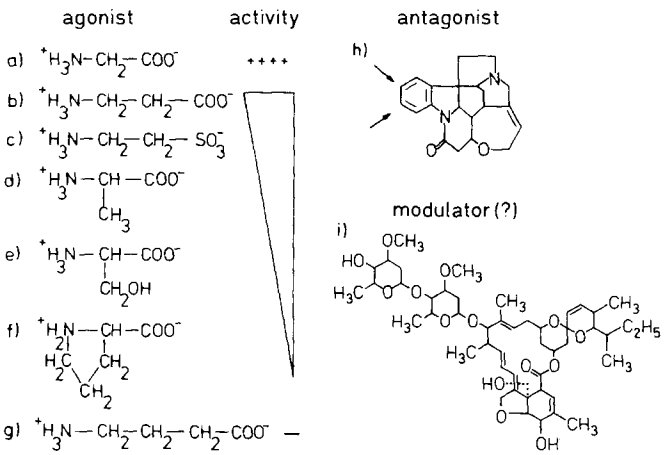


Fig. 2. Structure of glycine receptor agonists and antagonists. a) glycine; b) β-alanine; c) taurine; d) alanine; e) serine; f) proline; g) GABA; h) strychnine (the arrows indicate positions 2 and 3, which are suitable for substitution); i) avermectin B1a.

In the early 1950s strychnine was shown to disinhibit neurotransmission in the spinal cord. Meanwhile, it has been established that the toxic effects of strychnine result from a selective inhibition of the glycine receptor.[2] Strychnine binds with high affinity to this receptor (equilibrium dissociation constant ca. 10^{-8} M; see Table 2). It is thus a typical receptor antagonist. In 1973 *Young* and *Snyder*[3,4] demonstrated the existence of high-affinity binding sites for tritiated strychnine in membrane fractions of rat spinal cord. This binding was blocked by an excess of glycine and other amino acids that activate the glycine receptor.[3] Obviously these strychnine binding sites were located on the glycine receptor protein. The determination of these pharmacologically "specific" strychnine binding sites has since been used to localize and quantify the glycine receptor by a simple radioligand binding assay.[3-5]

Table 2. Equilibrium dissociation constants K_D of natural glycine receptor ligands.

Ligand	K_D [M] [a]
strychnine	9×10^{-9}
glycine	6×10^{-6}
β-alanine	5×10^{-6}
taurine	1×10^{-5}
GABA	$> 10^{-3}$

[a] The values are taken from [12] and were determined using glycine receptor purified by affinity chromatography.

3. Molecular Pharmacology of the Glycine Receptor

Not only glycine but also other amino acids inhibit neuronal firing in the central nervous system. Electrophysiological investigations have shown that β-alanine and taurine are efficient agonists of the glycine receptor. L-Alanine, serine, and proline, in contrast, have only weak agonist activity.[2-5] The binding affinities of the amino acid agonists are about 1000-times lower than that of strychnine (Table 2). GABA, which, together with glycine, is the most important inhibitory amino acid transmitter in the central nervous system, binds to a separate receptor system which is also coupled to a chloride channel.[6]

The structural formulas presented in Figure 2 show that the ionic groups of glycinergic agonists cannot be separated by more than two C atoms without destroying their activity. Side chains also inactivate their potency (Table 3). The stereoselectivity of asymmetric glycine receptor agonists is low.

Table 3. Inhibition of [^{3}H]strychnine binding to the glycine receptor by amino acids. [^{3}H]Strychnine binding to membrane-bound glycine receptor was determined in the presence of 20 mM amino acid as described in [9] (F. Pfeiffer, unpublished experiments).

Amino acid	Inhibition [%]
glycine	86.3
β-alanine	79.5
L-alanine	52.9
D-alanine	63.0
L-proline	49.0
D-proline	47.4
L-α-aminobutyric acid	<5
D-α-aminobutyric acid	16.8
L-valine	22.5
D-valine	<5

Strychnine (Fig. 2) has little structural similarity with the amino acid agonists. It is still a matter of debate whether strychnine binds to the glycine binding site of the receptor or to another site which is allosterically coupled with the former.[4] Strychnine tolerates only limited chemical modification without losing its biological activity. Substitutions in the aromatic ring system, in particular, lead to active derivatives, some of which are naturally occurring, such as brucine and other *Strychnos* compounds. The oxygen-containing seven-membered ring of strychnine can be opened without significantly impairing biological activity. In contrast, opening of the heterocyclic six-membered ring to give, for example, strychnic acid causes inactivation. Similarly, bulky substituents outside the aromatic ring system result in inactivation (Table 4). The biological activity of the different strychnine analogues does not correlate with their lipophilicity. Therefore, strychnine has been postulated to bind as a protonated base to the glycine receptor.[7]

Table 4. Biological activity and equilibrium dissociation constants K_D of receptor binding of strychnine and its derivatives.

Compounds	Biological activity [a] LD_{50} [μmol/kg]	K_D [M] [b]
strychnine	0.4	$\approx 10^{-8}$
2-aminostrychnine, 2-nitrostrychnine, 3-aminostrychnine, brucine (2-dimethylaminostrychnine), 2,3-dihydroxystrychnine, 2,3-diacetamidostrychnine, etc. (substitution in the aromatic ring system)	0.4–10	$\approx 10^{-8}$–$2.5 \cdot 10^{-7}$
21,22-dihydroxystrychnine, isostrychnine, bromodeoxyisostrychnine, etc. (substitution in the oxygen-containing seven-membered ring)	5–40	$\approx 10^{-7}$–10^{-6}
strychnic acid (9,10-secobrucin-10-ate), etc. (opening of the heterocyclic ring containing the keto function)	>50	$> 10^{-6}$

[a] LD_{50} was determined using mice [7]. [b] K_D was determined by competition experiments with [^{3}H]strychnine [7]; D. Graham, unpublished.

Figure 2 also shows a compound which is active at glycine and GABA receptors, avermectin B1a. This macrocyclic lactone, which is used as an antihelminthic agent, potentiates neurotransmission at inhibitory GABA synapses and thus causes paralysis of annelids.[8] At the isolated glycine receptor, avermectin B1a is an extremely efficient antagonist of strychnine binding.[9] Its in-vivo effect on spinal cord neurons has not, however, been investigated. In any case, this lactone represents a new class of active agents for the glycine receptor, and the elucidation of its mechanism of binding is thus of considerable interest.

4. Solubilization and Photoaffinity Labeling of the Glycine Receptor

The biochemical investigation of membrane-bound proteins requires their solubilization from the lipid bilayer of the membrane. This is usually achieved by generating micellar suspensions of the membrane components with suitable detergent mixtures. Our biochemical experiments thus began with attempts to solubilize the glycine receptor. This receptor can be efficiently solubilized with ionic and nonionic detergents (e.g., Triton X-100, sodium cholate) from membrane fractions of rat spinal cord.[10] The native (i.e., strychnine- and amino-acid-binding) conformation of the receptor, however, was only maintained in the presence of excess phospholipid in the detergent buffer. With such soluble glycine receptor preparations, a preliminary biochemical characterization of this membrane protein could be achieved. By classical methods of biochemistry, the glycine

receptor was shown to behave as a large glycoprotein with a molecular weight of about 250000 daltons.

The first identification of a subunit of the glycine receptor was based on photoaffinity labeling with tritium-labeled strychnine.[11] In the late seventies, several groups showed that photolabile low-molecular-weight compounds could be irreversibly bound to their high-affinity protein binding sites by illumination with ultraviolet (UV) light. Strychnine is light-sensitive; we therefore suspected that this alkaloid could serve as a natural photoaffinity ligand. In initial experiments, membranes from rat spinal cord were irradiated with UV light in the presence of [^{3}H]strychnine. The membrane proteins then were separated according to their molecular weight by gel electrophoresis, and the incorporated radioactivity was detected by fluorography. These experiments revealed a polypeptide that was covalently labeled with [^{3}H]strychnine; a comparison with marker proteins of known size revealed a molecular weight of 48000 daltons.[11] The labeling of this polypeptide is pharmacologically specific and occurs at or close to the high-affinity strychnine binding site of the glycine receptor.[12] The exact mechanism of this UV-induced incorporation of strychnine into the glycine receptor is not known. Kinetic studies suggest a photoactivation not only of strychnine, but also of aromatic amino acids (tyrosine) in the binding region of the 48000-dalton polypeptide.[12]

Photoaffinity labeling with [^{3}H]strychnine was also used for exploring the topology of the 48000-dalton polypeptide in the neuronal plasma membrane. Upon incubation of photoaffinity-labeled membrane vesicles of rat spinal cord with the protease trypsin, the radioactive 48000-dalton polypeptide was degraded into smaller peptides, and a final major product with an apparent molecular weight of 37000 daltons accumulated. This result indicates that the strychnine-binding subunit of the glycine receptor has a protease-accessible extracellular region of at least 11000 daltons.[12] Surprisingly, even extensive proteolytic digestion did not remove the radiolabel from the membrane fractions. Therefore, we suspect that the strychnine binding site of the glycine receptor is located at a domain of the

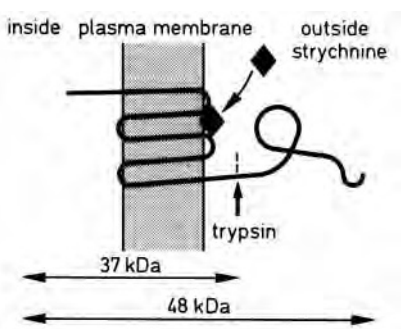


Fig. 3. Topology of the 48000-dalton polypeptide in the neuronal plasma membrane. The number of transmembrane domains is not known; five have been assumed here.

48000-dalton polypeptide which is protected from proteolytic cleavage by the hydrophobic environment of the lipid membrane (Fig. 3).

5. Affinity Chromatography and Biochemical Characterization of the Glycine Receptor

The solubilized glycine receptor was purified by affinity chromatography. A biologically active derivative of strychnine, 2-aminostrychnine (cf. Table 4), was coupled to an agarose support via a long hydrophilic spacer. Upon incubation with detergent extracts of spinal cord membranes, this aminostrychnine—agarose bound more than 90% of the soluble glycine receptor. After extensive washing with buffers of high ionic strength, about 20% of the bound receptor molecules could be recovered by elution with the competing agonist glycine (Fig. 4).[13] This simple procedure resulted in a 2000-fold purification of the glycine receptor in one step. Currently, one purification yields about

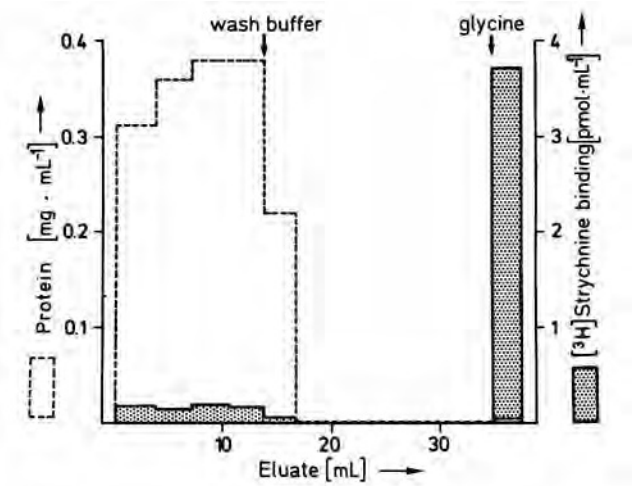


Fig. 4. Affinity chromatogram of the glycine receptor. A detergent extract of rat spinal cord membranes was pumped through an aminostrychnine-agarose column, and the column was then washed with detergent buffer. Under these conditions, 80–90% of the strychnine binding sites, but < 1% of the protein is adsorbed to the column. Subsequently, strychnine binding sites, i.e., glycine receptor, were eluted with glycine. Note the low protein content of the strychnine eluate (corresponding to a 1500-fold purification of the receptor).

25–50 μg of highly purified glycine receptor. Polyacrylamide gel electrophoresis in the presence of the denaturing detergent sodium dodecyl sulphate separated the purified glycine receptor into three polypeptides with molecular weights of 48000, 58000, and 93000 daltons.[13] The native receptor had a molecular weight of about 250000 daltons (Section 4). Using photoaffinity labeling, the 48000-dalton polypeptide of the purified glycine receptor preparations was shown to be identical with the strychnine binding subunit of the glycine receptor previously identified in membrane fractions.[13] The function of the two other receptor polypeptides is not known. These polypeptides are probably associated with the 48000-dalton subunit and form a heteropolymer which functions as the chloride ion channel.[14] This idea is also supported by structural investigations of the glycine receptor of pig spinal cord[15] and by reconstitution experiments using affinity-purified glycine receptor. Using methods developed for other receptor proteins,[16] the purified glycine receptor was incorporated into phospholipid vesicles by removal of the detergent, and these vesicles subsequently were used to form planar

lipid bilayers. The addition of glycine to these planar membranes produced an increase of membrane conductance which exhibited several characteristics of the typical glycine response.[17] These experiments indicate that the isolated glycine receptor contains all components required for ion translocation.

A model based on the currently available data is given in Figure 5. According to this model, the glycine receptor contains two copies of the 48000-dalton and one copy each of the 58000- and 93000-dalton subunits. The binding of two glycine molecules to specific binding sites on the 48000-dalton polypeptide induces a conformational change of the receptor and thus the opening of a chloride ion channel formed by all (or only the 93000-dalton) subunits. This model is compatible with the available electrophysiological and biochemical data. It should, however, be emphasized that many of its features, in particular the exact stoichiometry and topology of the subunits, have to be verified by additional experiments.

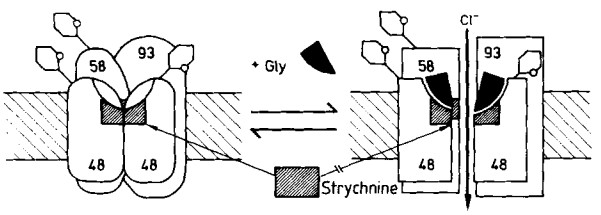


Fig. 5. A model of the glycine receptor. Here, it is assumed that the binding of glycine to the receptor alters the conformation of all receptor polypeptides via allosteric interactions, and thus opens the chloride channel. The numbers are the molecular weights [kDa] of the peptides. The carbohydrate side chains present on the 48- and 58-kilodalton polypeptides are schematically shown.

In order to produce new ligands for the further characterization of the glycine receptor, we have produced monoclonal (i.e., determinant-specific) antibodies against the glycine receptor protein by using the hybridoma technology of *Köhler* and *Milstein*.[18] Currently, nine monoclonal antibodies are available. Some of these antibodies bind to the 48000-dalton and others to the 93000-dalton subunit of the receptor.[19] Surprisingly, two of our monoclonal antibodies recognize not only one but two subunits of the glycine receptor. The subunits of this receptor therefore can be assumed to contain common antigenic determinants, probably homologous peptide structures. Peptide maps produced with different proteolytic enzymes also suggest chemical similarities between the glycine receptor polypeptides, in particular the small ones.[19] These results suggest that all subunits of the glycine receptor may be derived from a common ancestor receptor polypeptide. A divergent evolution of individual receptor polypeptides from a homopolymeric ancestor membrane protein is well established for another neurotransmitter receptor, the nicotinic acetylcholine receptor from the electric organ of fish.[20]

6. Conclusions and Perspectives

Our investigations of the glycine receptor demonstrate that the membrane proteins involved in neurotransmission are amenable to biochemical analysis provided high-affinity ligands such as strychnine are available. Suitable affinity chromatographic techniques allow the purification of these rare (<0.1—0.01% of total cell protein) membrane proteins. Today, the glycine receptor is one of the biochemically well-characterized neurotransmitter receptors of the central nervous system. This membrane glycoprotein has a native molecular weight of 250000 daltons and contains three different polypeptides. Photoaffinity labeling and reconstitution experiments showed that the purified receptor oligomer contains not only the ligand binding site but also the chloride channel of this allosteric membrane protein. We are, however, still far from a true understanding of its structure and function as a chemo-electrical signal transducer. Here, only detailed pharmacological and structural investigations can advance our knowledge. For the organic chemist, a detailed analysis of the structure-function relationship of glycinergic agonists and antagonists and their discrimination from GABA receptor ligands appears particularly appealing. The currently available data are unfortunately rather poor. At present we have only limited information on the topology of the agonist binding site of the glycine receptor; it is certain, however, that closely spaced cationic and anionic groups are required. In addition, there are restrictions on side-chain substitutions of the agonist.

The further analysis of the receptor protein requires the identification of the amino acids involved in strychnine binding via affinity ligands or specific antibodies, as well as the determination of the complete primary structure of the 48000-dalton subunit. Since only limited amounts of highly purified receptor protein are available, the latter goal must be based on gene cloning methods. Our current efforts therefore concentrate in part on the isolation of the messenger ribonucleic acid (mRNA) of this and the other glycine receptor polypeptides. This requires their amplification as complementary deoxyribonucleic acid (cDNA) in bacteria and the determination of their informational content by base sequencing. If successful, this approach may allow the expression of individual receptor polypeptides in bacteria and even of the functional heteropolymeric protein in eucaryotic cells. Specific chemical mutagenesis of the DNA should then allow the modification of individual receptor regions and thus lead to a dissection of functionally important receptor domains, such as the ligand binding region and the ion channel. Refinement of these techniques may in addition help to develop a precise structural pharmacology of the glycine receptor. This receptor definitely has considerable potential for the application of new pharmacological agents, since it is known to control not only the motor neuronal pathways, but also many sensory neuronal pathways. Efficient glycine receptor agonists and modulators thus have considerable promise as potential anticonvulsive and analgesic drugs. Furthermore, glycine receptor studies may open new possibilities for applied medicine; this protein has been suggested to induce autoimmune reactions in degenerative spinal cord diseases. A detailed analysis of receptor structure and metabolism should illuminate the pathogenesis of these syndromes.

It may be noted here that the molecular structure of the glycine receptor emerging from these studies is similar to

that of other ion-channel proteins in the electrically excitable plasma membrane. Table 5 summarizes the molecular weights and, where known, the subunit composition of the currently investigated chemically and voltage-gated ion channels. All these membrane proteins are large glycoproteins with a total molecular weight of about 250000 to 300000 daltons. In the case of the voltage-dependent sodium channel responsible for the propagation of nerve impulses, this molecular mass is located on one large glycopeptide. The nicotinic acetylcholine receptor and the glycine receptor, in contrast, contain subunits with mean molecular weights of about 50000 daltons. Several other neuroreceptors, like the GABA receptor and the nicotinic acetylcholine receptor of the central nervous system, also fit into the latter scheme; these proteins consist of polypeptides of 50000–60000 daltons and have native molecular weights of about 250000–300000 daltons (Table 5). It has therefore been proposed that the evolution of these channel proteins followed a common organizational principle.[21] Recently discovered structural homologies between the individual subunits of the nicotinic acetylcholine receptor[22] and probably also the glycine receptor[19] support this idea. Whether the different receptor proteins and ion channels of the neuronal membrane are all related, i.e., members of a large gene family, is unknown. The primary structure data that will become available during the coming years should clarify the picture.

Table 5. Molecular properties of neuronal ion channels.

	Molecular weight of native protein [kDa]	Molecular weight of subunits [kDa]	Composition of subunits
nicotinic acetylcholine receptor			
skeletal muscle, electroplax [22, 23]	≈270	40, 50, 60, 65	$\alpha_2 \beta \gamma \delta$
central nervous system [24]	≈300	57	?
glycine receptor [13]	≈250	48, 58, 93	$\alpha_2 \beta \gamma$?
GABA receptor [25]	220–350	50–53, 57	?
voltage-dependent sodium channel			
electroplax [26]	270–300	≈260	α ?
skeletal muscle, central nervous system [27, 28]	≈310	270, 37–47	$\alpha \beta \beta'$

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The 3′-End of tRNA and Its Role in Protein Biosynthesis**

By Stanislav Chládek and Mathias Sprinzl*

In the course of protein biosynthesis, the 3′-ends of aminoacyl-tRNA (aa-tRNA) and peptidyl-tRNA specifically interact with macromolecules of the protein biosynthesis machinery. The 3′-end of tRNA consists of an invariant C-C-A single strand. Interaction of the aminoacyl-tRNA 3′-end with elongation factor Tu (EF-Tu) containing bound GTP is necessary for the formation of the aa-tRNA·EF-Tu·GTP complex and, after the complex binds to the ribosome, for the GTP hydrolysis. This process is followed by the specific binding of the aminoacyl-tRNA 3′-end to the aminoacyl (A) site of the ribosome. In this review, a model is proposed that involves Watson-Crick base pairing of the C-C sequence of the aminoacyl-tRNA 3′-end with a specific G-G sequence of the ribosomal 23S RNA. Similarly, peptidyl-tRNA binds with its 3′-end to the peptidyl (P) site of the ribosome. This binding may also involve Watson-Crick base pairing of the C-C-A sequence with a complementary sequence of 23S RNA. It is proposed that peptide bond formation is catalyzed by a functional site of the 23S RNA located near the 3′-ends of aminoacyl-tRNA and peptidyl-tRNA. A model is suggested in which two loops of the 23S RNA, brought into close proximity via folding, are involved both in binding the 3′-ends of the tRNAs and in catalyzing peptide bond formation. This model presumes a dynamic structure for ribosomal RNA, which is modulated by interaction with elongation factors and ribosomal proteins.

1. Introduction[***]

The biosynthesis of proteins, a central process in the living cell, is one of the most intensively studied topics of molecular biology. Several aspects are a focus of current interest: the regulation of protein synthesis at the translational level,[3] the processing and transport of newly synthesized proteins,[4,5] and the fidelity of protein synthesis.[6] Nevertheless, the basic questions remaining to be answered concern the mechanism of translation and the structure and function of the protein synthesis apparatus.

The most important step in protein biosynthesis, from a chemical point of view, is the formation of the peptide bond. This reaction, which is accomplished on the ribosome, takes place via the transfer of an activated peptidyl residue from peptidyl-tRNA to the amino group of aminoacyl-tRNA. The correct reading of the mRNA during translation is of utmost importance since, once the peptide bond is formed, it is energetically unfavorable for the translational apparatus to correct any errors. Since extremely few errors are observed,[6] the correction steps must take place prior to peptide bond formation. The tRNA adaptor molecule plays a central role in this process since it must, on the one hand, faithfully recognize the appropriate codon of the mRNA and, on the other hand, transfer the aminoacyl residue onto the growing peptide chain. Although recognition of tRNA by the protein biosynthesis apparatus cannot be a simple matter, two areas of the tRNA molecule are of a special significance for the translational process: the anticodon region, which specifically interacts with the mRNA codon, and the 3′-end, where the chemical reactions take place.

The 3′-end of tRNA consists of the single stranded invariant C-C-A^{76} sequence,[2] which is connected to the helix of the aminoacyl stem by an unpaired nucleotide, usually a purine nucleotide (Fig. 1). The C-C-A sequence of tRNA is not involved in tertiary interactions with other regions of the molecule. Thus, the 3′-end of tRNA should presumably be available for interactions with the components of the protein synthesis apparatus.

The aminoacyl residue is attached to the 2′(3′)-hydroxyl group of the terminal adenosine residue of tRNA via an ester linkage. Thus, the C-C-A terminus of the charged tRNA, by virtue of its specific interactions with the ribosomal components, can assist in the binding of the aminoacyl residue to the appropriate site on the ribosome.

The C-C-A sequence of tRNA has an ordered structure, which is stabilized by stacking interactions in the aminoacyl stem. This structure is probably recognized by the en-

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[**] This review was written during a sabbatical stay of *S. C.* at the Laboratorium für Biochemie der Universität Bayreuth.

[***] Standard abbreviations for nucleotide and amino acids according to the CBN recommendations (see [1, 2]): N, nebularin (purine riboside); F, formycin; Ade, adenine; Gua, guanine; Cyt, cytosine; Ura, uracil; Hyp, hypoxanthine. aa-tRNA, aminoacyl transfer ribonucleic acid; mRNA, messenger ribonucleic acid; EF, elongation factor; IF, initiation factor. tRNA nucleotides are numbered using the standard system with yeast $tRNA^{Phe}$ as a reference: the 3′-terminal adenine is 76 [2]; tRNA-C-C-A, native tRNA with the terminal C-C-A sequence; tRNA-C-C-2′dA, tRNA in which the terminal nucleotide is 2′-deoxyadenosine; tRNA-C-C-3′NH_2A, tRNA in which the terminal nucleotide is 3′-amino-3′-deoxyadenosine (similar abbreviations for other isomeric derivatives); $tRNA^{Phe}$, tRNA specific for phenylalanine (similarly for other amino acids); $tRNA_{ox\text{-}red}$, tRNA in which the 2′,3′ bond of the 3′-terminal ribose was cleaved by oxidation and the dialdehyde reduced to the diol (Fig. 8); tRNA-U-C-A, tRNA in which cytidine 74 was replaced by uridine (similarly for other derivatives); f, formyl; Ac, acetyl; GMPPCP, guanylyl 5′-methylenediphosphonate; pA, adenosine 5′-phosphate; MepA, adenosine 5′-methylphosphate; AppA, diadenosine-5′,5′-diphosphate; Nps, *o*-nitrophenylsulfenyl; A site, acceptor site on the ribosome; P site, peptidyl site on the ribosome; A′ site, acceptor site of peptidyl transferase; P′ site, peptidyl site of peptidyl transferase.

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zymes of the protein biosynthesis apparatus. 3′-Terminal adenosine is involved in the stack, and relatively small structural changes, e.g., aminoacylation, may lead to a perturbation of this ordered structure.[7,8] It is assumed that even small changes in the physical environment of the C-C-A sequence of tRNA can also modulate its structure. Thus, the 3′-end of tRNA can serve as a mobile instrument, capable of accommodating different partners of the translational machinery.

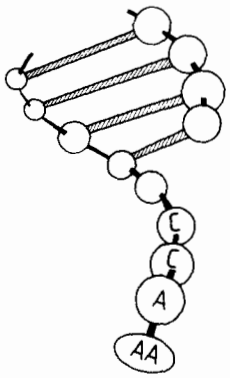


Fig. 1. Schematic drawing of the structure of the 3′-end of aa-tRNA. The last four nucleotides do not interact with the rest of the tRNA molecule; they are probably stacked on top of one another. AA = aminoacyl residue.

This article will focus on the role of the 3′-end of tRNA in protein biosynthesis. The discussion of the molecular mechanism of recognition of the 3′-end of tRNA will be based primarily on chemical results. This will hopefully lead to further stimulation of interest in this important topic and, in addition, aid efforts in understanding the events that lead to the synthesis of proteins on ribosomes.

Some aspects of this topic were recently reviewed.[9–15] The overall mechanism of protein biosynthesis has recently been discussed by several authors[16–18] and the structure of ribosomes has been reviewed by *Wittmann*.[19]

2. Properties of the Aminoacyl Ester Bond

2.1. Chemical Properties of the Aminoacyl Ester Bond

The ester bond of aa-tRNA is an activated, energy-rich bond. The free energy of hydrolysis of aa-tRNA is approximately equal to the free energy of hydrolysis of ATP.[20] The attachment site of the aminoacyl residue is the oxygen atom in the 2′- or 3′-position of the terminal adenosine of tRNA. The esterification of tRNA with the amino acid is catalyzed by a specific aminoacyl-tRNA synthetase. A simplified reaction scheme is depicted in Figure 2. In the first reaction, the amino acid is activated via formation of the aminoacyl adenylate from the amino acid and ATP in the presence of the enzyme. Pyrophosphate, which is also formed, is hydrolyzed in a further enzymatic reaction to inorganic phosphate. This coupled reaction shifts the equilibrium of the amino acid activation in the direction of the aminoacyl adenylate product. The transfer of the aminoacyl residue from aminoacyl adenylate to the 3′-terminal adenosine of the tRNA is accomplished in the second reaction, which again is catalyzed by aminoacyl-tRNA synthetase. In principle, either the 2′- or 3′-hydroxyl group of the terminal adenosine can function as an acceptor of the aminoacyl residue. However, the aminoacyl-tRNA synthetases are specific for only one hydroxyl group.[14,21] It is remarkable that the overall error rate for both reactions, i.e., activation and transfer of the aminoacyl residue, is very low. This high fidelity is achieved by an enzymatic proofreading mechanism.[22–24]

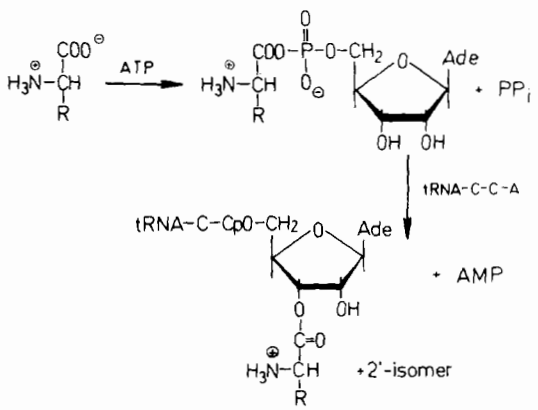


Fig. 2. Enzymatic aminoacylation of tRNA. Both steps are catalyzed by the appropriate specific aa-tRNA synthetase.

Assuming that only the pure 2′- or 3′-isomer of aa-tRNA is formed in the enzymatic reaction, two spontaneous, competing reactions can take place: a) hydrolysis with the formation of a free amino acid and uncharged tRNA and b) transacylation between the vicinal *cis*-hydroxyl groups of the 3′-terminal adenosine, resulting in the formation of an equilibrium mixture of 2′- and 3′-*O*-aminoacyl esters of tRNA (Fig. 3). Both chemical processes have been studied intensively. The hydrolysis of the aminoacyl residue of aa-

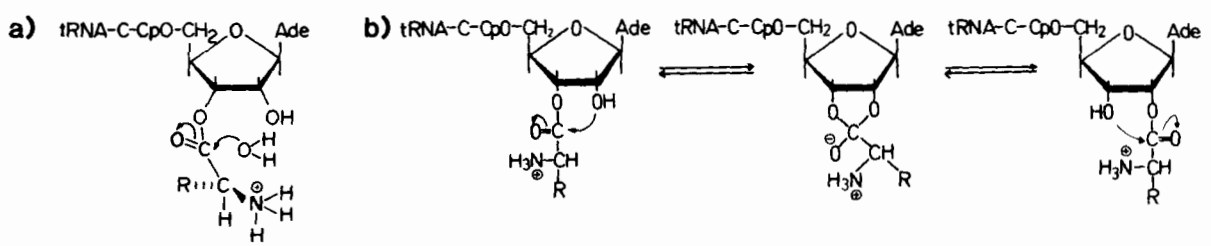


Fig. 3. a) Hydrolysis of the aminoacyl residue of aa-tRNA. b) Transacylation between 2′- and 3′-hydroxyl groups of aa-tRNA. The formation of the ortho acid intermediate is facilitated by the protonated α-amino group of the aminoacyl residue.

tRNA is facilitated by the presence of the neighboring 3′(2′)-hydroxyl group.[25] However, this effect has been often overestimated. The aminoacyl residue of native aa-tRNA terminating with adenosine hydrolyzes only about three times faster than that of aa-tRNA terminating with deoxyadenosine.[26] The 2′(3′)-hydroxyl group of the ribose residue is a poor leaving group for hydrolysis ($pK = 12.5$), but still more acidic than, e.g., ethanol ($pK = 16$). This property of the ribose hydroxyl groups is due to the electron withdrawing effect of the endocyclic oxygen of ribose. Indeed, it is known that aa-tRNA hydrolyzes about 30 times faster than aminoacyl alkyl esters. This difference can be attributed mainly to the pK difference of 3.5 for these particular leaving groups, which corresponds to a factor of ten in their rates of hydrolysis, and only to a much lesser extent (factor of 3) to the effect of the neighboring hydroxyl group.[27]

Aminoacyl-pyrimidine or -purine nucleotides and aa-tRNAs with the same aminoacyl residue have very similar rates of hydrolysis,[28,29] indicating that neither the terminal nucleobase nor the polynucleotide chain of aa-tRNA influences significantly the reactivity of the ester bond. On the other hand, there are significant differences in the rates of alkaline hydrolysis of aa-tRNAs incorporating different amino acids.[30]

The rate constants for the hydrolysis of methyl esters of amino acids can be correlated with the Taft substituent constants σ.[31] There are, however, two notable exceptions to this correlation, namely, valine and isoleucine esters, wherein the chain branching adjacent to the reaction center leads to steric hindrance which slows the rate of hydrolysis. The main factor facilitating the nucleophilic attack on the carbonyl group of the aminoacyl ester is the inductive ($-I$) effect of the protonated α-amino group. For instance, Val-tRNA with a positively charged α-amino group hydrolyzes 90 times faster than the neutral form of the same aa-tRNA.[27] The absence of a protonated α-amino group also explains the high stability of *N*-acylaminoacyl-tRNA[27] or phenyllactyl-tRNA[32] toward alkaline hydrolysis. Since the pK values of the α-amino group of aa-tRNA are in the range between 7 and 8,[33] the rate of hydrolysis at physiological pH will depend principally on the degree of protonation of the particular amino group and the differences in the rates will be largest in the physiological range (pH 7–8).

The rate of transacylation of 2′(3′)-*O*-aminoacyl esters of adenosine and adenosine 5′-phosphate was recently measured by the NMR saturation transfer method.[34] The rate constants for transformation of a 2′-*O*-aminoacyl adenosine into the 3′-derivative in aqueous buffer at pH 7.3 and 37 °C were estimated to be 3–11 s^{-1} for the 2′→3′ transacylation and 1–4 s^{-1} for the 3′→2′ transacylation. The rate of transacylation also depends primarily on the protonation of the α-amino group. The protonated aminoacyl residue migrates about 100 times faster than the unprotonated one. This is due to the inductive effect of the protonated amino group and presumably to its ability to stabilize the intermediate orthoester structure by ionic interactions (Fig. 3b). The 5′-phosphate group of the terminal adenosine and the charged functional groups of amino acids such as lysine or glutamic acid do not significantly influence the rate of transacylation. Moreover, the structures of the terminal C-C-A sequence of aa-tRNA and other structural elements of the polynucleotide chain apparently do not affect appreciably the rate of transacylation.

The overall rate of protein biosynthesis in *E. coli* corresponds to the incorporation of 15–20 amino acid residues per second.[35] Thus, the rates of spontaneous 2′⇄3′ transacylation are slow compared to the overall rate of biosynthesis. Therefore, it is conceivable that an enzymatic activity is present in the cell which catalyzes the transacylation of the aa-tRNA to give the required 2′- or 3′-isomer.[36]

2.2. Conformation of the Aminoacyl Residue

There is little information about the structure of the aminoacyl residue in aa-tRNA and its possible interactions with the polynucleotide chain of tRNA. The physicochemical studies of this problem are limited by the instability of the ester linkage of aa-tRNA and the relatively large amount of material needed for such studies. Crystallization of aa-tRNA has not yet been possible. Therefore, a crystallographic structural analysis was made only with puromycin, the stable analogue of 3′-*O*-aminoacyl adenosine[37] (cf. caption to Fig. 14). The results have not indicated any direct interaction between the aminoacyl side chain and the adenine moiety. On the other hand, some structural changes in the polynucleotide chain were detected upon aminoacylation of tRNA.[38,39] The nature of the changes is however unknown. Crystallization of stable aa-tRNA analogues[9] and high-resolution NMR studies of such compounds would be invaluable in the study of this problem.

3. Analogues of Aminoacyl-tRNA

Several aspects of the function of the 3′-end of tRNA have been clarified using analogues. Two types of analogues are used: tRNA species with modified units incorporated at a precise site of the 3′-end, and 3′-terminal fragments of aa- or peptidyl-tRNA, which may also contain modified units.

3.1. Modified Aminoacyl- and Peptidyl-tRNAs

The incorporation of modified nucleotides into the 3′-end of tRNA can be accomplished by a combination of chemical and enzymatic methods. Some synthetic nucleoside 5′-triphosphates are substrates for ATP (CTP): tRNA nucleotidyl transferase and can be incorporated into shortened tRNAs, thus replacing the natural CMP and AMP residues in the C-C-A sequence[40] (Fig. 4). This approach was used for the preparation of tRNAs **1** and **2** with terminal deoxyadenosine,[14,21] which were then converted into aa-tRNAs. In such tRNAs 2′(3′)-isomerization cannot take

$$\text{tRNA-N-C}^{74} + \text{C*TP} + \text{ATP} \longrightarrow \text{tRNA-N-C-C*-A} + 2\,\text{PP}_i$$
$$\text{tRNA-N-C-C}^{75} + \text{A*TP} \longrightarrow \text{tRNA-N-C-C-A*} + \text{PP}_i$$

Fig. 4. Enzymatic incorporation of ATP or CTP analogues into truncated tRNAs using ATP (CTP): tRNA nucleotidyl transferase. C* and A* are modified cytidine and adenosine units. N signifies any nucleotide.

place because the neighboring OH group on the terminal adenosine is absent. tRNA derivatives containing a 2′-amino-2′-deoxyadenosine **4** or a 3′-amino-3′-deoxyadenosine **3** on the 3′-end were prepared in an analogous way[40,41] (Fig. 5). Similarly, the natural cytidine unit at position 74 or 75 can be replaced by a modified nucleotide if an analogue of CTP is employed. The truncated tRNAs required for such syntheses (tRNA-N[73], tRNA-N-C[74], or tRNA-N-C-C[75]) are obtained by partial degradation of native tRNA-N-C-C-A[76] with snake venom phosphodiesterase[42] or polynucleotide phosphorylase.[43] The stepwise degradation of nucleotides via periodate oxidation, β-elimination, and phosphatase treatment has been especially used for the large scale preparation of truncated tRNAs. The disadvantage of this chemical method is the deactivation of some tRNA species during periodate treatment.[40]

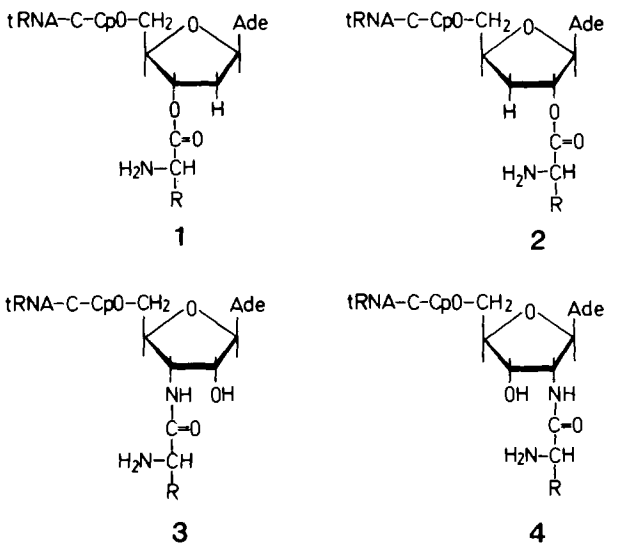


Fig. 5. Structures of non-isomerizable analogues of aa-tRNA: aa-tRNA-C-C-2′dA **1**, aa-tRNA-C-C-3′dA **2**, aa-tRNA-C-C-3′NH_2A **3**, and aa-tRNA-C-C-2′NH_2A **4**.

More recently, tRNAs modified on the 3′-end were prepared via incorporation of oligonucleotides using RNA-ligase (Fig. 6). In this reaction, truncated tRNAs are used as

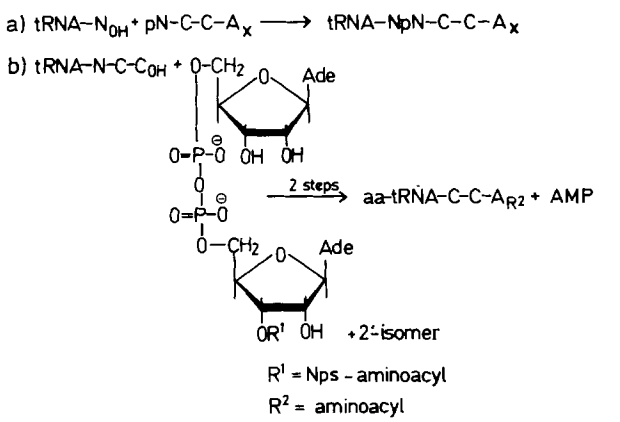


Fig. 6. Enzymatic synthesis of modified aa-tRNAs using RNA ligases. The truncated tRNA may either react with the 3′-blocked tetranucleotide donor (a) or the extension is achieved via the reaction with AppA derivatized with an *N*-protected amino acid (b). After the condensation, catalyzed by RNA ligase, the *o*-nitrophenylsulfenyl (Nps) group is selectively removed (according to [48]). N signifies any nucleoside.

acceptors;[44] donor molecules are either 5′-phosphorylated oligoribonucleotides[45–47] protected at the 3′-hydroxyl group or derivatives of diadenosine-5,5′-diphosphate (AppA-X), where X is a substituent on the 3′- or 2′-hydroxyl group of the donor adenosine residue.[48]

3.2. 3′-Terminal Fragments of Aminoacyl- and Peptidyl-tRNA

These fragments are nucleosides or oligoribonucleotides of various lengths and can be prepared by specific enzymatic cleavage of aa-tRNAs. The method is obviously limited to the sequences that occur in native tRNAs.[49] Chemical synthesis can provide analogues with any sequence, including those in which various functions, e.g., aminoacyl and carbohydrate moieties, are modified.[50]

4. Definition of the Partial Reactions of Protein Biosynthesis; Assays for these Steps

4.1. Definition of the Partial Reactions

For the purpose of our discussion, it will suffice to briefly define the partial reactions of protein biosynthesis in which the 3′-end of the aminoacyl-tRNA is involved. We will use the classical two-site model proposed by Watson[51] some 20 years ago, with a few modifications. The general features of this model are shown in Figure 7. The 70S ribosome has two functionally distinct sites, the acceptor (A) and the donor or peptidyl (D or P) site. The aa-tRNA bound at the A site can accept the peptide from the peptidyl-tRNA bound at the P site. The 3′-terminal CCA sequences of the two tRNAs are in contact with subsites A′ and P′, which are located on the peptidyl transferase center of the ribosome.[52]

In the initiation step, fMet-$tRNA^{fMet}$ (initiator tRNA) is bound to the P site in the presence of initiation factors (complex I). In the elongation cycle, several reactions take place: aa-tRNA (Phe-$tRNA^{Phe}$ in Fig. 7) first interacts specifically with EF-Tu·GTP to form a ternary aa-tRNA·EF-Tu·GTP complex. This complex next binds to the ribosome in a codon-dependent reaction, with the probable formation of the intermediate complex II in which EF-Tu·GTP is still bound to the ribosome, thus preventing reaction between aa-tRNA and peptidyl-tRNA (fMet-$tRNA^{fMet}$). Initially, the aa-tRNA C-C-A end is not properly accommodated on the A′ site (as schematically shown in complex II) and therefore must undergo a small movement to assume the positioning indicated in complex III. This occurs after hydrolysis of GTP and dissociation of EF-Tu·GDP from the ribosomal complex.[53,54] In complex III, the aa-tRNA C-C-A end is positioned on the A site and the peptidyl transferase reaction can take place. This reaction is assumed to be catalyzed by an enzymatic activity, which is an integral part of the 50S subunit of the ribosome; neither external energy nor other protein factors are required (see Section 6). As a result of the transpeptidation reaction, the peptidyl residue (or fMet) is transferred to the α-amino group of aa-tRNA to form complex IV, commonly called the pre-translocation intermediate. The

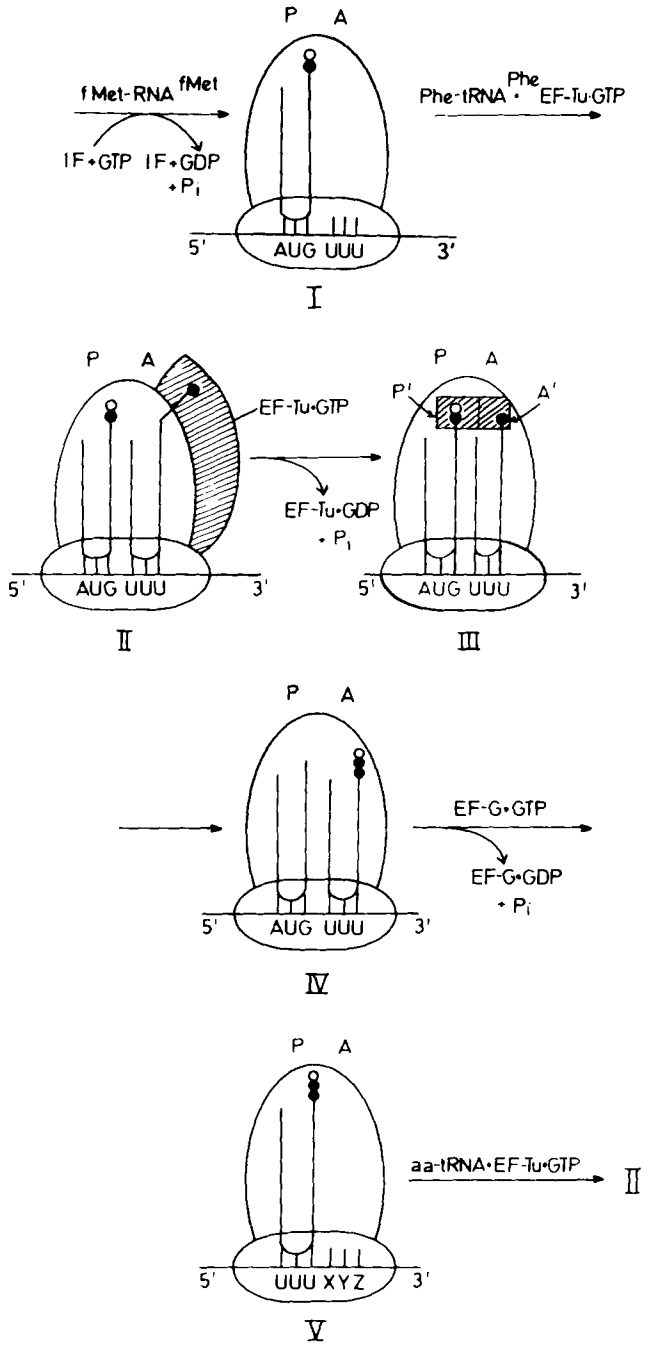


Fig. 7. Schematic drawing of the ribosomal cycle, showing the steps in the peptide chain elongation process (see text). A′ and P′ denote the subsites of the peptidyl transferase, which are parts of the A and P sites. The C-C-A terminal sequences of aa- and peptidyl-tRNA bind to the A′ and P′ sites.

newly formed peptidyl-tRNA is now located on the A site and has to be translocated to the P site in order to participate in another round of the cyclic process. The translocation step involves another protein factor, elongation factor G (EF-G); in the process one molecule of GTP is hydrolyzed. As a result, the deacylated tRNA dissociates from the ribosomal complex and the newly formed peptidyl-tRNA (fMetPhe-tRNA in Fig. 7) shifts together with mRNA to the P site, thereby exposing the next codon, X-Y-Z. When the mRNA nonsense codon (U-A-A, U-G-A, or U-A-G), which does not code for any amino acid, reaches the A site, termination of protein biosynthesis occurs in a process involving releasing factors and the hydrolysis of GTP; the peptide chain is hydrolyzed off, probably with the involvement of peptidyl transferase, and the newly synthesized protein leaves the ribosome.

Recently, *Nierhaus* et al.[55,56] proposed the three-site ribosomal model, which postulates the existence of a third site for the deacylated tRNA (E site, exit site). According to this model, deacylated tRNA is released from the E site during the binding of the ternary aa-tRNA·EF-Tu·GTP complex to the ribosome. After peptide bond formation takes place between the aa-tRNA in the A site and the peptidyl-tRNA in the P site, translocation results in the movement of newly formed peptidyl-tRNA to the P site and deacylated tRNA to the E site. However, for the sake of simplicity, we will base our discussion here on the two-site model, since this simplification does not have any effect on the conclusions stated herein.

4.2. Assay Systems for the Partial Reactions of Protein Biosynthesis

4.2.1. Interaction of aa-tRNA with EF-Tu

Various techniques, including gel filtration, affinity chromatography, and hydrolysis protection experiments, can be used to investigate the ability of aa-tRNA to complex with EF-Tu·GTP.[57-60] The 2′(3′)-*O*-aminoacyl oligonucleotides interact with EF-Tu·GTP only at very high concentrations and do not form a stable ternary complex.[61] The interaction of modified aa-tRNA species with EF-Tu·GTP can also be studied directly via the EF-Tu·GTP- and codon-dependent binding to the ribosomal A site. This assay is usually performed in the presence of deacylated tRNA bound to the P site. The binding of aa-tRNA to the A site and the EF-Tu- and aa-tRNA-dependent GTPase reaction, which accompanies this binding, may be measured simultaneously.[62]

Both aa-tRNA and 2′(3′)-*O*-aminoacyl oligonucleotides can protect EF-Tu·GTP against deactivation by the L-phenylalanine derivative (*S*)-*N*-(1-benzyl-3-chloro-2-oxopropyl)-*p*-toluenesulfonamide,[63] which reacts, in the absence of the aa-tRNA, with an essential cysteine SH group of EF-Tu·GTP.[11] The resultant blocking of the SH group can be used as an indirect binding assay.

A most convenient method for the study of the interaction of 2′(3′)-*O*-aminoacyl oligonucleotides with EF-Tu is based on the measurement of the EF-Tu-catalyzed GTPase activity induced by these oligonucleotides. In the simplest assay, the EF-Tu·GTPase is activated by the antibiotic kirromycin and further stimulated by a 2′(3′)-*O*-aminoacyl oligonucleotide.[54,64] The degree of stimulation is a measure of the extent of interaction between EF-Tu·GTP and the oligonucleotide. In a second assay, the activity of the EF-Tu·GTPase is measured in the presence of 70S ribosomes. 2′(3′)-*O*-Aminoacyl oligonucleotides promote this reaction[65] in the presence of deacylated tRNA and mRNA.[66]

4.2.2. Binding of aa-tRNA to the Ribosomal A and P Sites

The studies of the enzymatic binding of modified aa-tRNAs reveal an affinity of some of these substrates for

both EF-Tu and ribosomes. Certain modified aa-tRNAs that do not interact with EF-Tu·GTP, such as Phe-tRNA-C-C-A-3′NH_2,[57] may still bind to the ribosomal A site nonenzymatically under appropriate ionic conditions (usually higher $Mg^{2\oplus}$ concentration) and in the presence of mRNA.[67] The presence of the deacylated, correctly coded tRNA at the P site stimulates the binding of aa-tRNA to the A site.[68] The enzymatic binding of peptidyl-tRNA to the P site can be achieved via translocation in the presence of EF-G and GTP, or, for fMet-$tRNA^{fMet}$, in the presence of initiation factors and GTP. Under appropriate ionic conditions, peptidyl-tRNA will also bind nonenzymatically to the P site.[69]

The aa- and peptidyl-tRNAs can also be studied as acceptors and donors in the peptidyl transferase reaction. The formation of the peptide can be measured and the peptide can be identified chromatographically. A similar approach can also be applied to the studies of tRNA fragments. In typical systems, oligolysyl-tRNA, AcPhe-$tRNA^{Phe}$, or fMet-$tRNA^{fMet}$ are used as the donor molecules in the presence of an appropriate mRNA.[70,71]

In order to study 2′(3′)-*O*-(*N*-acylaminoacyl)oligonucleotides as potential donors in the peptidyl transferase reaction with aa-tRNA or puromycin as acceptors, the presence of ethanol and a buffer of higher ionic strength is required. However, no mRNA is necessary in this so-called "fragment reaction,"[72] and, under these conditions, the 50S subunit can replace the 70S ribosome. It was originally postulated that ethanol may promote the interaction of the substrates with their binding sites.[73] However, other authors[74,75] have suggested conformational changes of ribosomal binding sites induced by the organic solvent. Whatever role ethanol plays in the fragment assay, it does not appear to change the specificity of the peptidyl transferase reaction.[76,77]

Compounds such as C-C-A-Phe bind to the A′ site of the 70S ribosome in the presence of ethanol and high $Mg^{2\oplus}$ concentrations[78] or even without alcohol in the presence of $tRNA^{Phe}$ and poly(U).[79] Analogously, compounds such as U-A-C-C-A(AcLeu) bind to the P′ site under the conditions of the fragment reaction.[80]

Using the fragments that are derived from the C-C-A terminus of aa- or peptidyl-tRNA, it is possible to isolate and study in detail the interaction of the C-C-A terminus with the peptidyl transferase center or with the active site of EF-Tu independently of its interaction with other parts of the tRNA. It is remarkable that the results obtained with fragments are in good agreement with those with intact tRNAs.[62,81]

5. Interaction of the 3′-End of Aminoacyl-tRNA with Components of the Protein Biosynthesis Apparatus

It is important to consider at this point the interactions of the 3′-end of aa-tRNA with (a) initiation factors and the ribosome during initiation, (b) elongation factor Tu during the enzymatic binding of aa-tRNA to the ribosome, and (c) the peptidyl transferase acceptor and donor sites.

5.1. Interaction with Initiation Factors

Very little is known about the interaction of the 3′-end of initiator tRNA, fMet-$tRNA^{fMet}$, with initiation factors.[82] It is obvious that the initiation factors recognize structural features in the tRNA molecule that differ between the initiator tRNA and the other elongator tRNAs.[83] The ribosomal site to which fMet-$tRNA^{fMet}$ binds, in a process requiring IF-2 and IF-3, is probably the P site, since the bound fMet-$tRNA^{fMet}$ is reactive toward puromycin. Both this site and IF-2 distinguish between formylated and unformylated species (see Section 5.3.1). Modification of the C-C-A terminus of tRNA influences its binding to the ribosome. Thus, AcPhe-$tRNA^{Phe}_{ox\text{-}red}$ **5b** (Fig. 8), in which the 2′,3′ bond of the terminal ribose moiety is cleaved, does not bind to the P site in the initiation-factor-dependent process.[84] Moreover, fMet-$tRNA^{fMet}$-U-C-A binds very poorly to the ribosomal P site in the presence of initiation factors.[85] This is the only indication to date of the role of nucleotide 74 in binding to the P′ site.

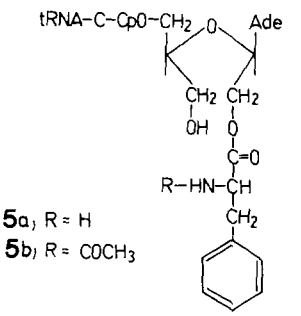


Fig. 8. Phe-$tRNA^{Phe}_{ox\text{-}red}$ **5a** and AcPhe-$tRNA^{Phe}_{ox\text{-}red}$ **5b**.

$tRNA^{fMet}$ is enzymatically aminoacylated at the 2′-OH of the terminal ribose.[14] However, the formylation of methionine, which is required for initiation, proceeds specifically only if the methionine is bound to the 3′-position of the terminal ribose. Thus, the transacylation of methionine in Met-$tRNA^{fMet}$ must take place before the formylation. Furthermore, only the 3′-isomer of fMet-tRNA can participate in the initiation process in the presence of initiation factors, mRNA, and the 70S ribosome.[86]

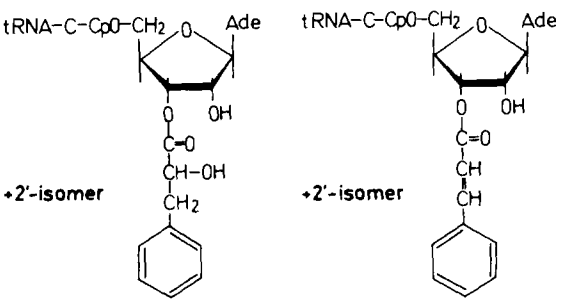
5.2. Interaction with Elongation Factor Tu

The ternary aa-tRNA·EF-Tu·GTP complex is a true intermediate of the enzymatic binding of aa-tRNA to the ribosome as was shown using aa-tRNA species chemically crosslinked to EF-Tu·GTP.[87] The aa-tRNA C-C-A terminus plays a crucial role in the formation of the ternary complex and its subsequent binding to the ribosome, which is accompanied by hydrolysis of GTP.[88-91] The double stranded acceptor stem, which is immediately adjacent to the C-C-A sequence of aa-tRNA, is especially involved in EF-Tu recognition.[92] This could be demonstrated in experiments in which the pC residue of the 5′-end of Met-$tRNA^{fMet}$, which is a poor substrate for EF-Tu·GTP, was chemically transformed to a pU residue. The

tRNA so modified is recognized by EF-Tu, apparently because a completely base-paired stem is formed via the modification. The absence of this important structural feature in bacterial $tRNA^{fMet}$ molecules explains the very weak interaction of the Met-$tRNA^{fMet}$ with EF-Tu·GTP.

5.2.1. *The Aminoacyl Moiety*

The amino acid residue of aa-tRNA is of considerable importance for binding to EF-Tu; only a weak interaction has been observed between deacylated tRNA and EF-Tu·GTP.[11,63,93] The amino group of the aminoacyl residue is apparently directly involved in binding to the protein, since it is protected against chemical acylation while aa-tRNA is complexed with EF-Tu·GTP.[94] The replacement of the aa-tRNA aminoacyl group with either a phenyllactoyl[95] or a cinnamoyl[96] group (**6** and **7**, respectively; Fig. 9) leads to a lowering of the efficiency of binding to EF-Tu by a factor of 300. Thus, the ester function of these analogues still contributes appreciably to the interaction with EF-Tu·GTP.



6 7

Fig. 9. Phenyllactoyl- and cinnamoyl-tRNAs, **6** and **7**, respectively.

It was postulated that the tRNA 5′-phosphate group forms an intramolecular salt bridge with the α-amino group of the aminoacyl residue and that the proposed interaction may be involved in recognition of aa-tRNA by EF-Tu·GTP.[92] However, this hypothesis was found incorrect, since there is little difference between binding of native aa-tRNA and 5′-dephosphorylated aa-tRNA to EF-Tu·GTP.[97] The aminoacyl residue of aa-tRNA in the ternary complex is protected against hydrolysis; this again demonstrates that this moiety is bound to the enzyme.[59,60]

EF-Tu interacts preferentially with L-aminoacyl-tRNA; the derivatives of D-amino acids are bound much more weakly.[66,98,99] However, this specificity is not absolute. For instance, EF-Tu can functionally interact with achiral 2′(3′)-*O*-aminoacyl oligonucleotides **8a** and **8b** (Fig. 10). These analogues contain a second substituent on the α-carbon (α-aminoisobutyric acid and cycloleucine).[54,66] This finding indicates a certain degree of flexibility in the interaction of the amino acid with EF-Tu.

The amino acid side chain also influences the strength of the interaction of intact aa-tRNA with EF-Tu·GTP.[60,100,101] The activity of aminoacylated fragments, e.g., 2′(3′)-*O*-aminoacyl nucleosides and oligonucleotides, as promoters of EF-Tu·GTPase likewise depends on the structure of the amino acid side chain.[63,66,91] It was therefore suggested[60] that EF-Tu possesses a binding site for the side chain; the interaction is strongest with basic and aromatic amino acids. The pocket for binding of the amino acid side chain of aa-tRNA was previously postulated to exist on the peptidyl transferase A′ site.[71] If a corresponding pocket exists on EF-Tu, it would provide for specificity with respect to the attachment of the aminoacyl residue to the 2′- or 3′-hydroxyl groups (Fig. 11) and only one isomer should interact with the enzyme. If the amino groups of the two isomers are assumed to interact with the same binding site on the protein, then the respective side chains would point in different directions. However, this model is incompatible with the finding that EF-Tu does not have a great preference for either 2′- or 3′-aa-tRNAs.[57,102]

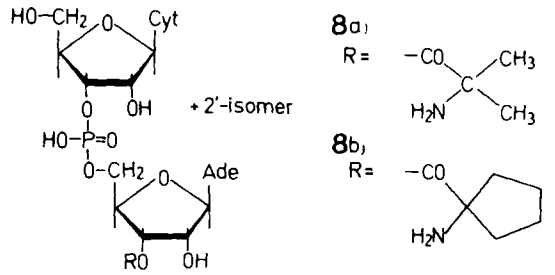


Fig. 10. Structures of 2′(3′)-*O*-(α-aminoisobutyryl) and cycloleucyl derivatives of C-A, **8a** and **8b**, respectively. Cycloleucine is 1-amino-1-carboxycyclopentane.

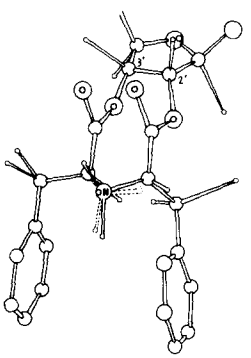


Fig. 11. A perspective view of the probable molecular conformation of 2′- and 3′-*O*-L-aminoacyl derivatives of adenosine at the 3′-end of tRNA (according to [61, 62]). The aminoacyl residues are attached to both the 2′- and 3′-positions in order to show the spatial relationship of the α-amino groups and side chains.

An alternative explanation for the role of the amino acid side chain of aa-tRNA in the ternary complex formation may be the requirement of a protonated α-amino group for the interaction of EF-Tu with aa-tRNA. The degree of protonation of the α-amino group should depend on the nature of an amino acid side chain. This assumption derives support from the observation that the pK values for the protonation of the amino groups of aminoacyl esters depend on the structure of the side chain.[33]

5.2.2. *The Carbohydrate Moiety*

EF-Tu seems to be very sensitive to modifications in the ribose moiety of the 3′-terminal adenosine. Thus, the "deoxy analogues" of aa-tRNA **1** and **2** bind more weakly to EF-Tu than the corresponding unmodified aa-tRNA.[57, 102] Low or no activity in promotion of the EF-Tu·GTPase was also observed with 2′(3′)-*O*-aminoacyl derivatives of C-A in which the 3′(2′)-hydroxyl group was replaced by either methoxy or hydrogen.[54, 66] Also, the oxidation of the *cis*-diol grouping destroys the ability of Phe-$tRNA^{Phe}_{ox\text{-}red}$ **5a** to bind to EF-Tu·GTP.[62, 103] Presumably, such chemical modification unfavorably influences the base stacking of the 3′-end of tRNA. The derivatives **3** and **4** with a 3′- and 2′-aminoacylamido linkage, respectively, do not interact with EF-Tu·GTP as observed for aa-tRNA and for fragments thereof.[57, 66] This can probably be attributed to the rigidity of the acylamido bond relative to the ester bond;[57] apparently, the aminoacylamido derivatives cannot be properly accommodated by the enzyme. It is also possible that EF-Tu recognizes the "intermediate" ortho acid structure of aa-tRNA (Fig. 12). The formation of this structure is not possible either with analogues **3** and **4** or with the deoxy compounds **1** and **2**. An alternative explanation for the decreased activity of deoxy derivatives **1** and **2** may reside in the requirement of the enzyme to bind the 2′- or 3′-hydroxyl group of the terminal ribose. The conformation of the ribose ring and the consequent orientation of the aminoacyl residue must also be taken into consideration in explaining the interaction of aa-tRNA derivatives with EF-Tu·GTP.

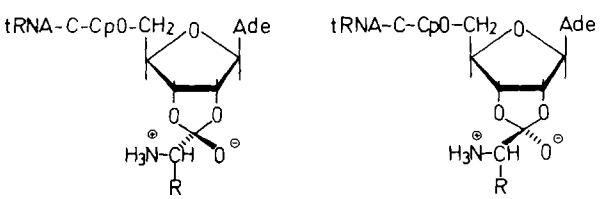


Fig. 12. The hypothetical ortho acid structure of aa-tRNA (both diastereoisomers are shown, cf. Fig. 3).

5.2.3. *The C-C-A Sequence of aa-tRNA*

There is convincing evidence that the 3′-terminal C-C-A sequence of aa-tRNA is involved in the interaction with EF-Tu. This sequence is protected against nuclease attack in the ternary complex, but, at the same time, is available for base pairing with a complementary oligonucleotide.[104, 105] Phe-$tRNA^{Phe}$-C-C-C-A reacts weakly with EF-Tu·GTP, showing that the length of the 3′-terminal sequence is also of importance for the interaction.[106] The activity of 2′(3′)-*O*-aminoacyl oligonucleotides as promoters of EF-Tu·GTPase increases with the chain length in the order A-Phe < C-A-Phe < C-C-A-Phe.[54, 63, 64, 66, 91] aa-tRNA-C-U-A (with uridine replacing cytidine in position 75 of tRNA) interacts only weakly with EF-Tu·GTP. This modification probably disturbs the base stacking of the aa-tRNA 3′-end.[92] No significant impairment of the interaction of EF-Tu·GTP occurs with aa-tRNA in which cytidine 75 is replaced by an alkylated 2-thiocytidine (Fig. 13).[107]

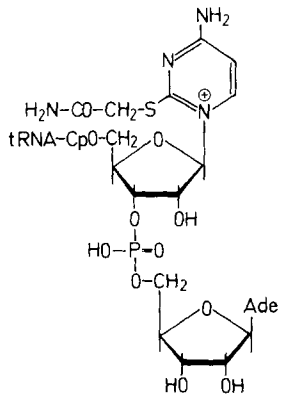


Fig. 13. Structure of the modified tRNA in which the cytidine residue 75 is replaced with 2-thiocytidine carbamoylmethylated at position 2 by iodoacetamide.

Collectively, these findings indicate that EF-Tu probably does not interact directly with the bases of the C-C-A end, but recognizes instead the overall spatial structure of the stacked C-C-A end. This stacked structure does not change appreciably when aa-tRNA is bound to EF-Tu·GTP in the ternary complex.[46] This model may subsequently prove to be an oversimplification, since U-Phe cannot substitute for A-Phe as a promoter of EF-Tu·GTPase. Thus, some base recognition, at least for the terminal adenosine, is implied.[66]

5.2.4. *EF-Tu·GTPase and Transacylation of aa-tRNA*

The ternary aa-tRNA·EF-Tu·GTP complex serves as a vehicle for the codon-dependent binding of aa-tRNA to the A site of the ribosome. This binding step is accompanied by the hydrolysis of one molecule of GTP, which results in the dissociation of EF-Tu·GDP from the ribosome and the subsequent accommodation of aa-tRNA on the A′ site. It is known that the GTPase activity resides on EF-Tu;[108] moreover, the C-C-A terminal sequence of aa-tRNA interacts with EF-Tu during the GTPase reaction.[54] Thus, the C-C-A·EF-Tu interaction persists after the ternary complex binds to the ribosome.[65]

Both isomers—the 2′- and the 3′-aminoacyl-tRNA—can be bound to the A site in the EF-Tu-dependent process.[109] If the transacylation of the 2′-aminoacyl residue to the 3′-position is hindered (cf. **1** and **2**), however, aa-tRNA can be easily displaced from the ribosomal A site.[62, 109] In this respect, Phe-tRNA-C-C-3′dA behaves similarly to natural Phe-tRNA-C-C-A bound enzymatically in the presence of the nonhydrolyzable GTP analogue GMPPCP. In the latter case, since GTP hydrolysis cannot occur and EF-Tu does not dissociate from the ribosome, the C-C-A end of aa-tRNA is probably not properly accommodated by the peptidyl transferase A′ site.[53] Presumably, the 2′-aa-tRNA, in contrast to the 3′-aa-tRNA, cannot be properly bound to the A′-site. As a result of the GTP hydrolysis (which is promoted by both aa-tRNA isomers)[109] and consequent EF-Tu·GDP dissociation, isomerization of the

aminoacyl residue occurs, producing a uniform population of 3′-aa-tRNA. Only the 3′-aa-tRNA binds firmly to the A site (since its C-C-A terminal sequence binds correctly to the A′ site of the peptidyl transferase center) and reacts in the next elongation step as an acceptor.[14, 110] However, this hypothesis still requires direct experimental confirmation. At least part of the aa-tRNA population must be bound to EF-Tu as the 2′-isomer, since EF-Tu accepts both isomers. Therefore, transacylation must take place on the ribosome prior to peptide bond formation. Whether this reaction is enzyme catalyzed is still unknown.[34]

The EF-Tu·GTPase activity can also be stimulated by parts of the tRNA molecule other than the C-C-A sequence.[91, 111] It is not known, however, whether these effects are due to interactions of other portions of aa-tRNA with EF-Tu or due to stabilization of the conformation of the C-C-A end by the rest of the aa-tRNA. The GTPase activity of EF-Tu is normally dormant and is activated only after the ternary complex binds to the ribosome in response to an appropriate codon. Several domains of the ribosome as well as the tRNA and the elongation factor Tu are probably involved in the delicate interplay that leads to GTPase activity. Although the exact structures of the EF-Tu active sites are unknown, the GTPase site is distinct from the C-C-A binding site.[112, 113] Thus, it is tempting to speculate that EF-Tu·GTPase is triggered by a specific interaction of the incoming ternary complex with specific ribosomal domains.[114, 115] At the same time, the aa-tRNA C-C-A sequence must be bound to the EF-Tu site in order to effect the conformational changes in EF-Tu that are required to induce the GTPase reaction.

5.3. Interaction with the Peptidyl Transferase Acceptor and Donor Sites

5.3.1. The α-Amino Group and the N-Acyl-α-amino Group of the aa-tRNA

The α-amino group of the acceptor substrate is required not only for the synthesis of peptide bonds, but also for binding of the aa-tRNA to the A′ site.[116, 117] It can, to a certain degree, be replaced by an OH or SH group.[118, 119]

The binding of substrates to the P′ site requires that the amino group be acylated. Thus, e.g., C-A-C-C-A(AcLeu) binds preferentially to the P′ site,[80] whereas C-A-C-C-A-Phe interacts preferentially with the A′ site.[117] Both the formyl and the acetyl groups are recognized by the P′ site, but they can be replaced in in-vitro experiments by practically any acyl group, in accord with the obvious necessity for the ribosome to accommodate the growing peptide chain of peptidyl-tRNA. It follows, therefore, that the P′ site of the peptidyl transferase must recognize at least two functional groups, the carbonyl group of the first C-terminal peptide bond and that of the ester bond in the peptidyl-tRNA.

5.3.2. The Carbonyl Group

There is an obligatory requirement for the ester carbonyl group of aa-tRNA in the binding to the A′ site. Thus, compounds **9**—**11** (Fig. 14) do not act as acceptors in the peptidyl transferase reaction.[120, 121] Compound **12** (Fig. 15), which has an ortho ester group in lieu of a carbonyl group, is inactive as an acceptor substrate.[81] Thus, the A′ site appears to recognize the definitive spatial arrangement of the α-amino and carbonyl groups while the P′ site recognizes the positions of at least two carbonyl groups at the C-terminus of the peptidyl residue of the peptidyl-tRNA.

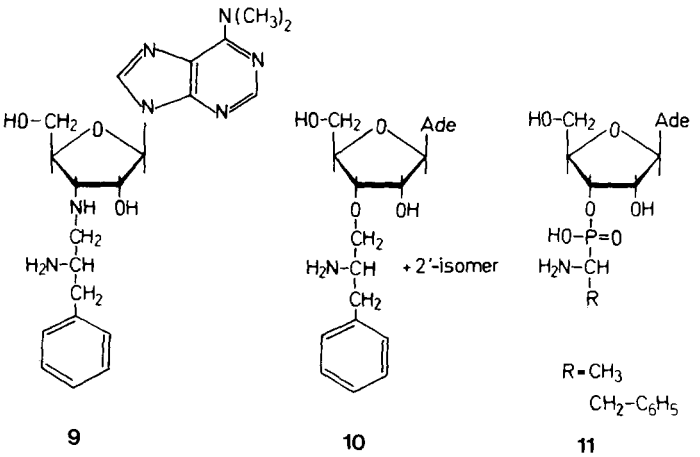


Fig. 14. Puromycin analogue **9** in which the carbonyl group of the aminoacyl residue is replaced by $>CH_2$ and the *p*-methoxy group by H; the analogues **10** and **11** of 2′(3′)-*O*-L-phenylalanyl adenosine in which the carbonyl group is replaced by $>CH_2$ and $>P(O)OH$, respectively.

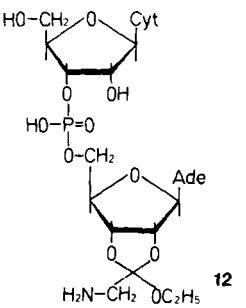


Fig. 15. 2′,3′-Ortho ester derivative **12** of C-A.

5.3.3. The Amino Acid Side Chain

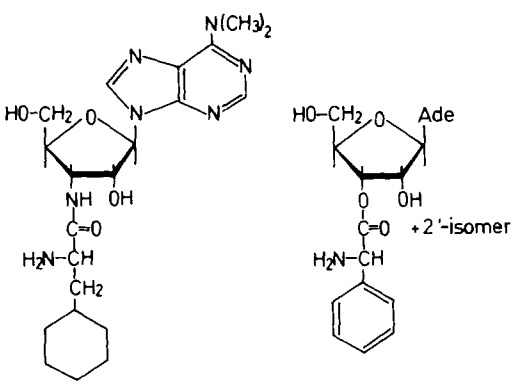
Enzymes that show stereospecificity toward substrates usually recognize them at least at three loci.[122] If this principle is applied to the binding of aa-tRNA to the A′ site of the peptidyl transferase, then, in addition to the α-amino group and the carbonyl group, the third locus is very probably the side chain of the amino acid. *Rychlík* et al.[71] originally suggested the existence of a binding locus for the side chain of an amino acid within the A′ site in order to explain the different acceptor activities of 2′(3′)-*O*-aminoacyl adenosines in the peptidyl transferase reaction. It was also observed, by other researchers,[81, 123–126] that derivatives of aromatic amino acids are the strongest acceptor substrates and derivatives of glycine or proline the weakest.[*] Similar conclusions can also be drawn from the ob-

[*] The only exception was the low activity of the tryptophan analogue of puromycin [127]. This experiment, however, is lacking an independent verification.

servations of *Lessard* and *Pestka*,[78] who studied the binding of various 2′(3′)-*O*-aminoacyl derivatives of C-C-A to the A′ site. Although the effects of the side chain are most pronounced with fragments, they are also recognizable with tRNA.[128] The side chains of all amino acids must be oriented in the same direction on the A′ site in order to account for the stereospecificity of the peptidyl transferase reaction;[81] presumably, this involves an interaction with a "protein pocket." The high binding affinity of aromatic amino acids may, however, be due to fortuitous lipophilic interactions rather than to a specific binding site.

The donor activity of various fragments was also observed to be dependent on the nature of the amino acid side chain.[129–132] However, this dependence is distinct from that of their acceptor activity. Whereas, the best acceptors are derived from phenylalanine, the derivatives of AcPhe are, by contrast, usually poor donors. The highest donor activity was observed with derivatives of fMet and AcLeu. These findings indicate that different ribosomal functionalities are involved in the interaction with the amino acid side chains at the acceptor and donor sites.

The C-A derivatives of achiral amino acids such as α-aminoisobutyric acid **8a** and cycloleucine **8b** are not acceptors.[132] These amino acids have a second α-substituent, which apparently precludes proper binding to the acceptor site. On the other hand, nonproductive binding to the A′ site is possible, and these compounds therefore function as inhibitors. It is not known whether the same phenomenon holds for the P′ site.



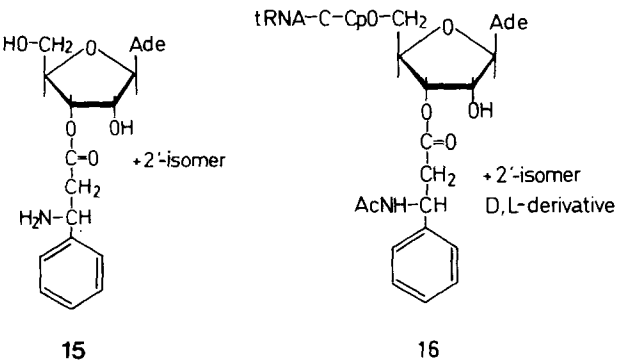
13 14

Fig. 16. Analogues of puromycin and 2′(3′)-*O*-L-phenylalanyl adenosine. In compound **13** the aromatic ring of puromycin is replaced by the cyclohexyl group; compound **14** incorporates L-phenylglycine.

The cyclohexyl analogue **13** of puromycin (Fig. 16) is active as an acceptor,[134] which agrees with the general model presented here, since this alicyclic residue is lipophilic and should interact rather strongly with the A′ site. Several model derivatives were studied recently to probe the distance of the hydrophobic locus from the α-amino group of the acceptor substrate.[135, 136] Moreover, the 2′(3′)-*O*-L-phenylglycyladenosine **14** is a weaker acceptor than the related A-Phe.[137]

5.3.4. *Stereospecificity*

A series of experiments with fragments and intact tRNAs conclusively shows that peptidyl transferase is stereospecific for both acceptors and donors. Only L-α-aminoacyl derivatives can participate in the peptidyl transferase reaction.[47, 81, 132] It is interesting to note that, e.g., C-A(D-Phe) or C-A(Ac-D-Met), neither of which are substrates for the peptidyl transferase reaction, are inhibitors at the respective sites.[81, 132] Thus, as is the case with the proteolytic enzymes, the stereospecificity is not achieved by preferential binding of one diastereoisomer, but by selective positioning of appropriate functionalities of the substrate (carbonyl group, amino group, and side chain) with respect to the enzyme.[138]



15 16

Fig. 17. Analogues of 2′(3′)-*O*-L-phenylalanyladenosine and AcPhe-tRNA^{Phe}. Compound **15** incorporates L-β-phenylalanine; compound **16** incorporates Ac(DL-β-phenylalanine).

Neither D- nor L-2′(3′)-*O*-(β-phenylalanyl)adenosine **15** (Fig. 16) is an acceptor in the peptidyl transferase reaction.[137] On the other hand, Ac(D,L-β-Phe)-tRNA **16** (Fig. 17) can serve as a donor.[47] It would be of considerable interest to learn whether the P′ site also displays a "reverse stereospecificity" in analogy to chymotrypsin, since *N*-acetyl-D-β-phenylalanine esters are cleaved preferentially by chymotrypsin.[139]

5.3.5. *Isomer Specificity*

The specificity of the A′ site of the peptidyl transferase for 2′(3′)-isomers of aa-tRNA was extensively investigated using both fragments and intact tRNAs. The nonisomerizable aa-tRNA derivatives **1**—**4** were used for these investigations. Since the peptidyl transferase is able to recognize tRNA derivatives with modified sugar residues (see Section 5.3.6), structures in which the 2′⇄3′ transacylation is precluded could serve as models for such studies.

The 3′-aa-tRNAs Lys-tRNA^{Lys}-C-C-2′dA (type **1**) and Phe-tRNA^{Phe}-C-C-3′NH$_2$A (type **3**)[67, 109, 140, 141] are acceptors, whereas Phe-tRNA^{Phe}-C-C-3′dA (type **2**) and Phe-tRNA$^{Phe}_{ox\text{-}red}$ are only weak acceptors.[62] A quantitative comparison with several nonisomerizable 2′(3′)-*O*-aminoacyl derivatives of C-A (**18**—**19**; Fig. 18) was performed by *Bhuta* et al.[81] They concluded that the 3′-aminoacyl derivatives of optically active amino acids are much better acceptors than the 2′-derivatives with K_m values more than 100 times smaller than those of the 2′-derivatives (Table 1).

Completely different results, however, were obtained with the isomeric glycine derivatives **20** and **21** (Fig. 19);

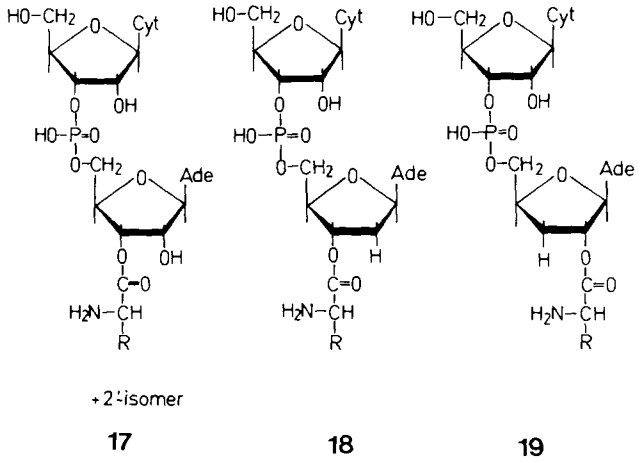


Fig. 18. 2'(3')-*O*-L-Aminoacyl derivatives **17** of C-A; 3'-*O*-L-aminoacyl derivatives **18** of C-2'dA; 2'-*O*-L-aminoacyl derivatives **19** of C-3'dA (R = amino acid side chain; see Table 1).

Table 1. Dependence of the K_m values in the peptidyl transferase reaction on the site of attachment of the amino acid. The fMet-tRNA^{fMet}·A-U-G·70S-ribosome system was used; aminoacyl derivatives of C-A **17**, C-2'dA **18**, and C-3'dA **19** functioned as acceptors [81].

Aminoacyl residues	Michaelis constants K_m [M] 2'(3') **17**	2'-isomer **19**	3'-isomer **18**	$K_m^{2'}/K_m^{3'}$
Phe	1.1×10^{-7}	2×10^{-5}	1.1×10^{-7}	182
Leu	1.0×10^{-6}	$>10^{-3}$	9.5×10^{-6}	> 100
Lys	3.4×10^{-7}	$>10^{-3}$	3.0×10^{-7}	> 1000
Ala	9.0×10^{-7}	$>10^{-3}$	1.0×10^{-5}	> 100
Gly	5.0×10^{-6}	6.4×10^{-5}	4.0×10^{-5}	1.6

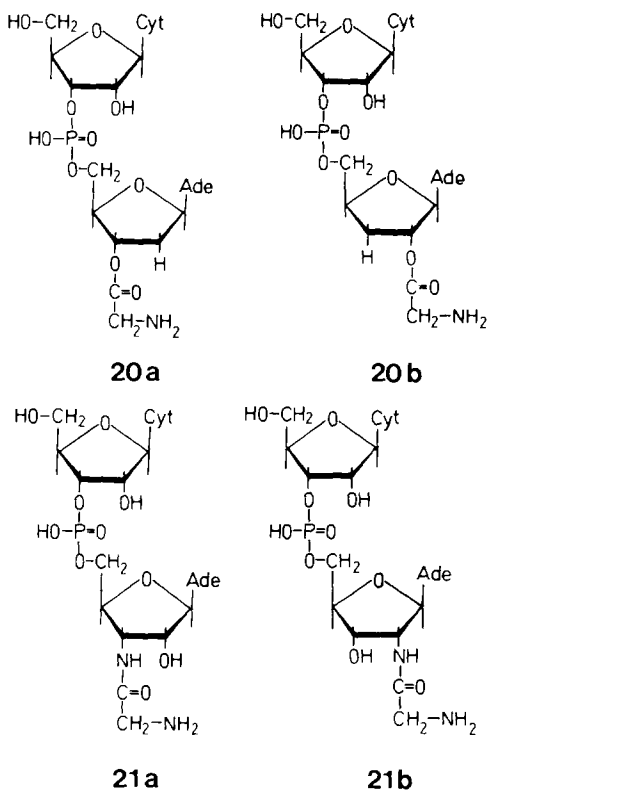


Fig. 19. Nonisomerizable analogues **20** and **21** of C-A-Gly, incorporating a modified adenosine residue.

both the 2'- and 3'-isomers were found to accept the fMet residue from the fMet-tRNA bound to the P site.[81] This is, of course, surprising and the general validity of this finding should be tested by experiments at the tRNA level.

These results can be rationalized using a model which depicts the orientation of the aminoacyl residue on the 3'-end of aa-tRNA (Fig. 11).[61,62] If the reasonable assumption is made that a definite orientation of the α-amino group of the aminoacyl residue is required for the peptidyl transferase reaction, then the side chains of the 2'- and 3'-aminoacyl derivatives extend in different directions. This is the main reason for the selectivity of the A' site with respect to positional isomers. Due to the absence of the side chain in glycine derivatives, this factor is cancelled and both compounds can serve as acceptors.

In all systems investigated, the 2'-aminoacyl derivatives are able to bind to the A' site. However, this binding, like that of D-derivatives, is nonproductive.

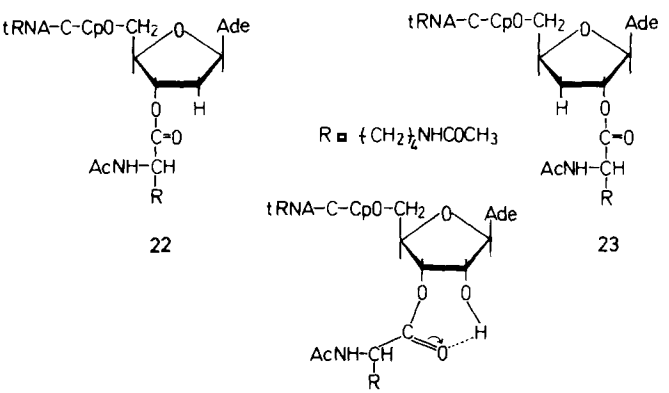


Fig. 20. Nonisomerizable analogues of Ac_2Lys-tRNA^{Lys} in which a hydroxyl group is absent: Ac_2Lys-tRNA^{Lys}-C-C-2'dA **22** and Ac_2Lys-tRNA^{Lys}-C-C-3'dA **23**. The lower structure depicts the activation of the aminoacyl ester bond of peptidyl-tRNA via the hydrogen bond from the neighboring hydroxyl group.

The investigation of the isomer specificity of the P' site proved to be much more difficult than that of the A' site. It was found only recently[109] that Ac_2Lys-tRNA^{Lys}-C-C-2'dA **22** (Fig. 20) can function as a donor substrate, reacting with aa-tRNA bound to the A' site, whereas the 2'-isomer **23** is inactive under the same conditions. Thus, the stereochemical requirements are similar to those of the A' site, although it is not known whether both 2'- and 3'-AcGly esters act as donors (by analogy with the A' site). These findings afford insight into the mechanism of catalysis of the peptide bond, since they show that the activation of the ester carbonyl group via hydrogen bonding with the 2'-OH, which is not possible with derivative **22**, is not an absolute requirement.

5.3.6. The Carbohydrate Moiety

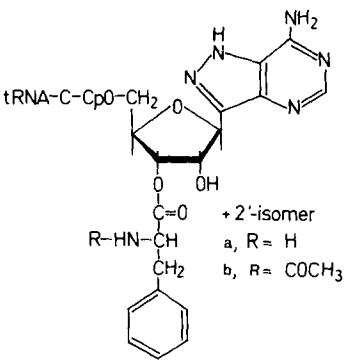
The A' site can recognize a variety of substrates incorporating modified sugar derivatives, e.g., 2'-deoxyribose, 2'-*O*-methylribose, ribose cleaved between C2' and C3', and 3'-amino-3'-deoxyribose.[67,123,142-145] The 2'-aminoacyl

derivatives are in general inhibitors of the A′ site. In this respect, the A′ site is very different from EF-Tu, which is more sensitive to ribose modification. The absence of the 2′-OH group influences the acceptor activity to a greater degree in the case of weak substrates (e.g., those containing glycine) than with the more active acceptors (e.g., those containing phenylalanine).[81] It is interesting to note that 2′dA-Phe is not an acceptor substrate, whereas the dinucleotide C-2′dA-Phe is an excellent acceptor, very similar to C-A-Phe (Table 1). This anomaly can hardly be explained by the existence of a binding locus for 2′-OH only. It is conceivable that a change in pucker of the sugar moiety and a consequent change in orientation of the aminoacyl residue plays a role in the recognition by the peptidyl transferase.[*]

5.3.7. *The Nucleotide Sequence*

The acceptor activity of 2′(3′)-*O*-aminoacyl derivatives of C-A is significantly higher than that of the corresponding adenosine derivatives (the K_m values differ by more than two orders of magnitude).[149] In fact, the observed effect is a consequence of incorporating the Cp residue since it cannot be achieved with other nucleotides.[127, 150] The acceptor activity also increases in the order A-Phe < pA-Phe < MepA-Phe, but the magnitude of increase does not approach that achieved upon incorporation of a Cp residue.[151] On the other hand, the increase of acceptor activity upon attachment of a second Cp residue to form 2′(3′)-*O*-aminoacyl derivatives of C-C-A is not as significant, particularly with highly active substrates. Thus, the acceptor activity of C-A-Phe is similar to that of C-C-A-Phe, whereas, in the case of less active glycine derivatives, the acceptor activity of C-C-A-Gly is much higher than that of C-A-Gly.[79] The second Cp residue also plays a role in binding to the A′ site.[78] Direct interaction of the C-C-A terminus of aa-tRNA with the A′ and P′ sites has been inferred from the observation[152-154] that the C-C-A sequence of the bound aa-tRNA is shielded from chemical or enzymatic attack.

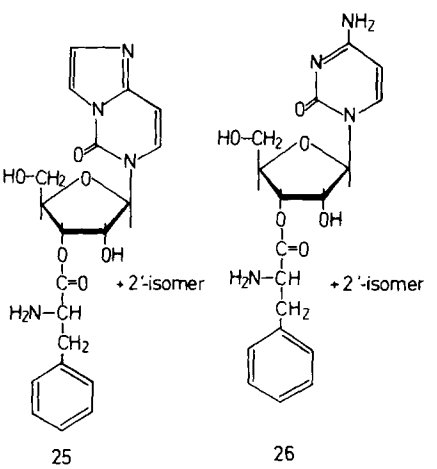
The nucleosides beyond the C-C-A sequence probably do not play an important role in binding to the A′ site, as indicated by the similar binding activities of C-C-A-Phe and C-A-C-C-A-Phe.[78, 79] Detailed studies of the acceptor activity of 2′(3′)-*O*-aminoacyl nucleosides containing modified bases[155, 156] have shown that there is little base specificity for the purine ring of the acceptor; however, G-Phe is inactive. In fact, modifications at the position 6 of the purine may be made, including the introduction of some extremely bulky substituents,[157] providing that they do not significantly influence the electronic configuration of the purine moiety. Interestingly, compounds that cannot form Watson-Crick base pairs, such as puromycin and other 2′(3′)-*O*-phenylalanyl nucleosides, are all acceptors. Therefore, base pairing of the terminal adenosine of tRNA is not required for acceptor activity.[156, 158, 159] The possibility of Hoogsteen pairing from position 7 of the purine ring is also excluded, since 2′(3′)-*O*-phenylalanyl tubercidin (7-deazaadenosine) is an acceptor.[156] The terminal adenosine of tRNA can also be replaced by formycin, since Phe-tRNA^{Phe}-C-C-F **24a** (Fig. 21) functions as an acceptor.[160]



24

Fig. 21. Phe-tRNA^{Phe}-C-C-F **24a** and AcPhe-tRNA^{Phe}-C-C-F **24b**, incorporating formycin as the 3′-terminal nucleotide.

Thus, the A′ site most probably recognizes only the spatial structure of the last nucleobase of tRNA. 2′(3′)-*O*-Phenylalanyl ethenocytidine **25** (Fig. 22) is more active than the



25 26

Fig. 22. 2′(3′)-*O*-L-Phenylalanyl ethenocytidine **25** and 2′(3′)-*O*-L-phenylalanyl cytidine **26**.

corresponding cytidine derivative **26**, since the bicyclic structure of ethenocytidine is apparently more similar to that of the purine ring.[158] Presumably, the terminal adenosine has considerable freedom of motion in intact tRNA.[14] Therefore, it is possible that this nucleoside residue may be accepted in either *syn*- or *anti*-conformation by the enzyme. Model studies with nucleoside analogues **27** and **28** (Fig. 23) have shown that, for the acceptor site, the *anti*-conformation (as in **27**) is preferred.[161]

The acceptor activity of Phe-tRNA^{Phe}-C-C-A modified at cytidine 75 (cf. Fig. 13) was found to be much weaker than that of the unmodified tRNA. The ability of this mod-

[*] There are differences in the sugar conformation of ribose and deoxyribose derivatives. Puromycin is known to be in N-(3′-*endo*) conformation, whereas the 2′-deoxy nucleosides are more likely to exist in S-(2′-*endo*) conformation. The N-conformation is the only one in which stacking with other bases in the C-C-A sequence may occur. Thus, it is tempting to speculate whether the presence of the Cp residue in C-2′dA-Phe may force the N-conformation on the 2′dA moiety of the dinucleoside phosphate [145–148].

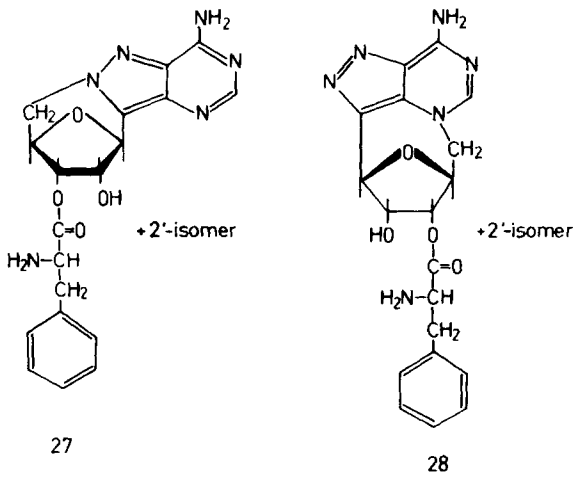


Fig. 23. 2'(3')-*O*-L-Phenylalanyl derivatives of the two cycloformycins. Compound **27** is in an *anti*-conformation and compound **28** in a *syn*-conformation.

ified tRNA to form base pairs from positions 73—75 is also strongly reduced.[107] It is thus obvious that the stacked ordered structure of the C-C-A terminus is extremely important for recognition by the A' site.[162] Accordingly, the 2'-5' dinucleotide **29** (Fig. 24) is not an acceptor, since its stacking geometry is different from that in the natural 3'-5' derivatives.[163]

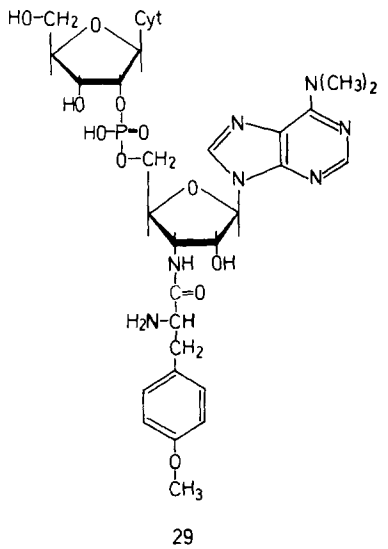


Fig. 24. Cytidylyl (2'-5')-puromycin **29**.

As is the case with aa-tRNA, the terminal C-C-A sequence of peptidyl-tRNA is also involved in specific interactions with the P' site. The donor activity can be detected with 2'(3')-*O*-(*N*-acylaminoacyl) mononucleotides, e.g., pA(fMet) **30a** (Fig. 25), albeit only at very high concentrations of the substrate.[164] The corresponding dinucleotide and, even more so, trinucleotide derivatives are much better donors.[129, 131, 132] Although no quantitative comparisons are available to date, it is apparent that there is a significant increase of donor activity in going from C-A(fMet) to C-C-A(fMet), whereas the effect of joining a cytidine residue to, e.g., pA(fMet) is not as dramatic.[129, 149] As observed for the A' site, there is no significant difference in donor activity between trinucleotide and pentanucleotide derivatives.[129, 131] Therefore, only nucleotides of the C-C-A terminus play an important role in the binding of peptidyl-tRNA to the P' site. AcPhe-tRNA^{Phe}-C-C-F **24b**, in which the 3'-terminal nucleotide is formycin, shows relatively low donor activity as compared to AcPhe-tRNA^{Phe}-C-C-A.[160] This is presumably due to a disruption of base stacking in the modified C-C-A end.[160] The donor activity

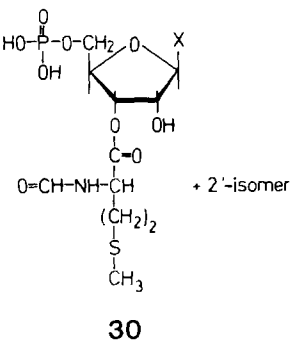


Fig. 25. 2'(3')-*O*-(*N*-Formyl-L-methionyl) nucleoside 5'-phosphate **30a**, X = Ade; **30b**, X = Hyp; **30c**, X = Cyt; **30d**, X = Ura.

of **30** (Fig. 25) decreases in the order X = Ade > Hyp > Gua; derivatives with X = Cyt and Ura are devoid of any activity.[165] Similarly, C-N(AcMet) (N = nebularin) **31** (Fig. 26) is inactive as a donor substrate, whereas C-(8-

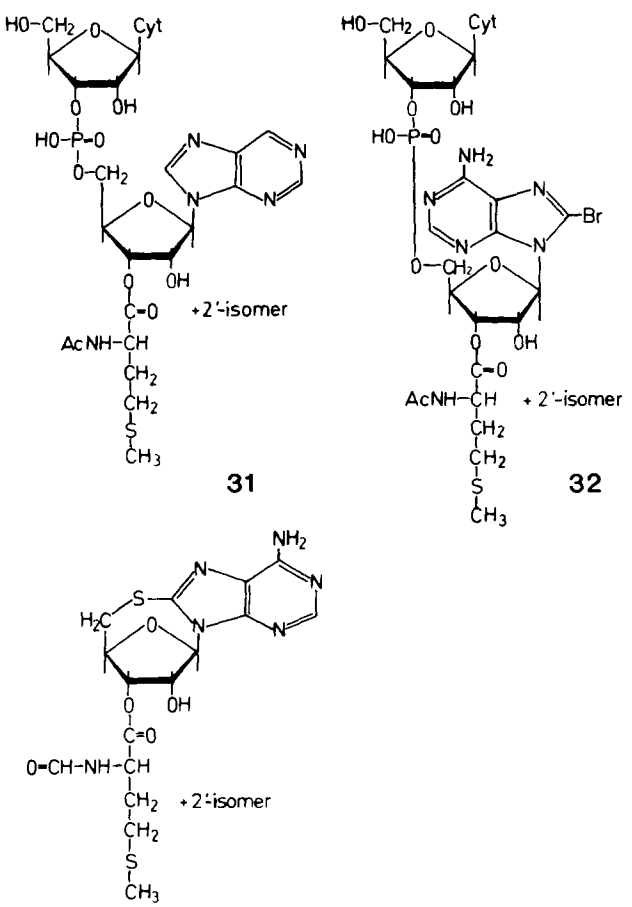


Fig. 26. Cytidylyl(3'-5')2'(3')-*O*-(*N*-acetyl-L-methionyl) purine riboside, C-N(AcMet) **31**; cytidylyl(3'-5')2'(3')-*O*-(*N*-acetyl-L-methionyl)-8-bromoadenosine, C-(8-Br)A(AcMet) **32**; (3')-*O*-(*N*-formyl-L-methionyl)-5', *S*-anhydro-8-mercaptoadenosine **33**.

Br)A(AcMet) **32** is almost as active as the unmodified C-A(AcMet).[132] These findings indicate that the P′ site exhibits greater specificity for the 3′-terminal residues of peptidyl-tRNA than the A′ site exhibits for the corresponding residues of aa-tRNA. C-N(AcMet) **31** cannot form Watson-Crick base pairs from the 3′-terminal residue; C-(8-Br)A (AcMet) **32** is expected to have the 3′-terminal nucleotide in the *syn*-conformation, but is, nonetheless, active as a donor. The latter finding is in agreement with results of other authors,[166] who also detected weak donor activity for p(8-Br)A(fMet) but no donor activity for compound **33**, which exists exclusively in the *anti*-conformation. Although the results with the latter compound have to be interpreted with caution due to the inherently very low activity of "good" peptidyl-nucleosides as donors and due to the lack of similar derivatives in the *syn*-conformation having donor activity, it is possible that the donor site may prefer a *syn*-conformation of the 3′-terminal nucleoside. Thus, peptidyl-tRNA translocation from the A to the P site may be accompanied by a rotation around the glycosidic bond of the 3′-terminal adenosine to give the *syn*-conformation.

Modified AcPhe-tRNA^{Phe}, in which cytidine 75 is alkylated in position 2, is a good donor; the modification has no effect on the rate and yield of the peptidyl transferase reaction, in contrast to its effect on the A′ site.[107] Replacement of cytidine 74 by uridine in fMet-tRNA^{fMet}, yielding fMet-tRNA^{fMet}-U-C-A, leads to the complete deactivation of this substrate as a donor in the puromycin reaction.[85] The extension of the C-C-A end by an additional Cp residue, i.e., AcPhe-tRNA^{Phe}-C-C-C-A, resulted in an approximately 20-fold reduction in the donor activity of aminoacyl derivatives of this modified tRNA relative to those of native Phe-tRNA^{Phe}.[106]

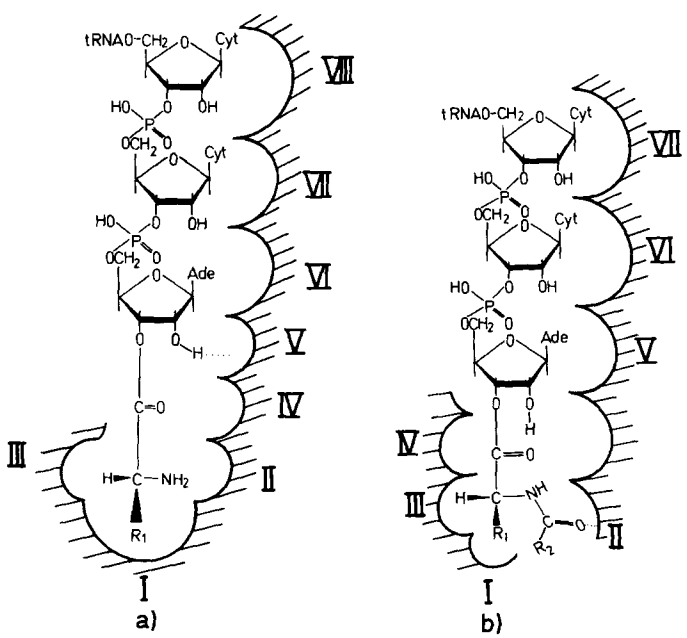


Fig. 27. a) Schematic drawing of the ribosomal A′ site showing the interactions with the 3′-end of aa-tRNA and indicating the peptidyl transferase loci which bind several moieties of the substrate. Binding site III has sufficient space only for α-hydrogen, not for a larger substituent. The loci may not be located on one molecule of a ribosomal component, but rather on one or several ribosomal proteins and a partial sequence of 23S RNA. b) Schematic drawing of the ribosomal P′ site showing the interactions with the 3′-end of peptidyl-tRNA and indicating the loci which bind several moieties of the substrate. The space is allocated for the growing peptide chain. Again, the loci are probably not located on one molecule of the ribosomal component.

It is thus evident that both A′ and P′ sites may have different requirements for the binding of adenosine 76 of tRNA. Furthermore, the results clearly show the existence of binding loci for the C-C sequence at both the A′ and P′ sites. However, despite this structural similarity, these binding sites are not functionally equivalent. The binding behavior of the C-74 and C-75 residues differs not only between the A′ and P′ sites, but also within these respective sites.[77, 107, 149, 167]

These results are summarized, in a very simplified form, in Figure 27.

5.3.8. Cooperative Effects at the Peptidyl Transferase Binding Sites

The ribosome and especially its peptidyl transferase sites have a dynamic structure. Due to the conformational flexibility of the macromolecules forming these sites, cooperative effects may, in principle, be transmitted in several ways, e.g., between the sites, within either the A′ or P′ site, or from different parts of the ribosome. In addition, cooperative effects can be transmitted within the tRNA molecule, e.g., by changing the conformation of the C-C-A end upon binding of a different part of the tRNA to a ribosomal domain.

Bound peptidyl-tRNA (P site) stimulates enzymatic binding of aa-tRNA to the A site.[68] Moreover, peptidyl-tRNA must be the 3′-isomer to provide for this stimulation; the 2′-isomer is inactive.[67] This shows that the correct occupation of the P′ site is specifically involved in this phenomenon. Moreover, the substrate affinity of the A′ site changes in response to the occupation of the P′ site by different molecules. Thus, the acceptor activity of aminoacylated fragments depends on the nature of the donor molecule.[71, 81] Similarly, occupation of the donor site with AcPhe-tRNA^{Phe} may change the affinity of the acceptor site for substrates.[79] Stimulation of the binding of C-A-C-C-A-Phe to the acceptor site by the deacylated tRNA (bound to the P site) is probably an expression of the same phenomenon.[74, 168, 169] Binding of an acceptor to the A′ site on the 50S subunit is also stimulated by tRNA or C-C-A, which interact evidently with the P′ site.[170] The results show an interesting interplay between P′ and A′ sites. Thus, the structure of the A′ site depends on the occupation of particular loci of the P′ site.

Cooperative effects can also be observed within the P′ site. *Černá*[77] has discovered the stimulating effect of pC on the donor activity of pA(fMet) under the conditions of the fragment reaction. The stimulating effect is specific for nucleotides that can form a G·C pair, whereas other nucleotides, such as pA, are inhibitory.[171] This phenomenon is undoubtedly related to the binding of a pC residue to the binding site of the penultimate residue of the peptidyl-tRNA on the P′ site. It is interesting to note that pC inhibits the donor activity of C-A(AcMet).[149] Thus, loci for binding of the second and third residues in the C-C-A ter-

minus of peptidyl-tRNA are not equivalent. Apparently, the binding site for the Cp residue on the A′ site must differ significantly from that on the P′ site, since neither pC nor other cytidine nucleotides show a stimulating effect on the acceptor activity of puromycin or C-A-Lys.[149] In contrast, pC is inhibitory in the latter case.[172]

5.3.9. *Structure of the Peptidyl Transferase*

The body of findings related to the substrate specificities of the A′ and P′ sites, together with the recent structural studies of ribosomes, allow us to draw some conclusions as to the nature of the peptidyl transferase center. The peptidyl transferase is an integral part of the larger ribosomal subunit. To date, it has been impossible to identify a single ribosomal component solely responsible for the binding of substrates or for the enzymatic activity. Affinity labeling studies with reactive derivatives of charged tRNA or other ligands for A′ and P′ sites led to the identification of several ribosomal proteins as well as parts of the 23S RNA in the neighborhood of the peptidyl transferase center. However, these observations do not necessarily imply that these macromolecules form the respective sites.[73]

It is almost certain that the 3′-terminal nucleoside of the A′-site-bound aa-tRNA is not base-paired. The situation with the peptidyl-tRNA may be different. The *N*-acylaminoacyl(peptidyl) moiety most probably binds to a protein. The 3′-terminal adenosine residue may base-pair with an appropriate U residue of ribosomal RNA, since the P′ site, unlike the A′ site, shows considerable specificity for the adenine base of the 3′-end of peptidyl-tRNA.[12, 132, 165] The ability of a donor with a 3′-terminal nucleoside in *syn*-conformation to interact functionally with the P′ site suggests the existence of an asymmetrical base pair between a nucleoside of tRNA in the *syn*-conformation and a nucleoside of ribosomal RNA in the *anti*-conformation.[174]

One of the most interesting results is the stimulating effect observed as a consequence of joining cytidine 3′-phosphate (or cytidine) residues on the activity of either 2′(3′)-*O*-aminoacyl adenosine or 2′(3′)-*O*-(*N*-acylaminoacyl)adenosine 5′-phosphate as acceptors or donors in the peptidyl transferase reaction (see Section 5.3.7). This suggests the possibility of base pairing of the C-C sequence of charged tRNA with an invariant G-G sequence of, most probably, 23S RNA.

Although it has been shown that 23S RNA is capable (unlike 16S RNA) of binding charged tRNA 3′-terminal fragments such as C-A-C-C-A-Leu and C-A-C-C-A(AcLeu),[170] more direct evidence of 23S RNA participation in the peptidyl transferase activity was obtained only recently. For instance, several nucleotide residues of 23S RNA are implicated in resistance to the antibiotics chloramphenicol and erythromycin, which are known to act on the peptidyl transferase center.[175–177] The resistance to these antibiotics derives from a modification of nucleotide residues that are all found clustered in the central loop of domain V of 23S RNA.[178] Thus, this highly conserved region of 23S RNA is likely to constitute part of the peptidyl transferase center (Fig. 28). Moreover, two uridine residues of this loop (2584 and 2585) are also sites of attachment of

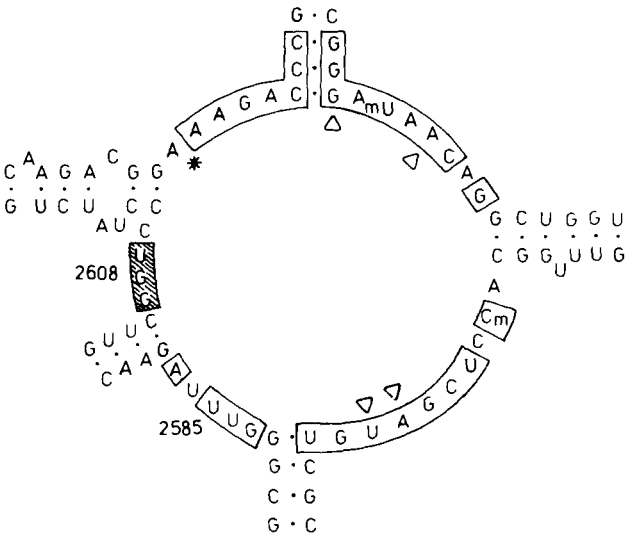


Fig. 28. Secondary structure of a part of *E. coli* 23S RNA, encompassing the central loop of domain V (according to [178, 181]). The conserved nucleotides are boxed; the asterisk denotes the site of erythromycin resistance in *B. stearothermophilus* 23S RNA: the triangles denote the sites of chloramphenicol resistance in mitochondrial RNA [177]. The shaded sequence is proposed to be part of the A′ site which could base-pair with the Pu-C-C^{75} sequence of aa-tRNA. The nucleotides 2584 and 2585 are sites of attack for the photoreactive analogue **34** of peptidyl-tRNA (see Fig. 29) [179].

the photoreactive peptidyl-tRNA analogue **34** (Fig. 29).[179] Since **34** is cleaved by irradiation at the aromatic keto group, the length of the probe is approximately 14 Å from the 3′-terminal adenosine residue. It was suggested that the

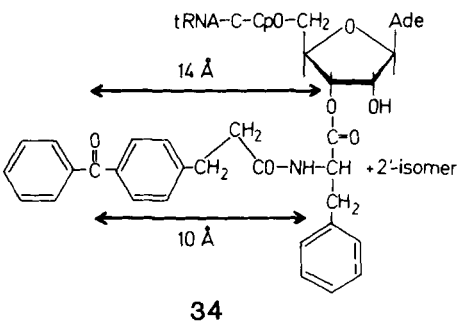


Fig. 29. Structure of the photolabile analogue **34** of Ac-Phe-tRNA^{Phe}. A residue of this compound becomes covalently linked to 23S RNA after photolysis at the site of the aromatic keto group [179].

C-C-A terminus of peptidyl-tRNA forms base-pairs with the highly conserved U-G-G^{809} sequence located in a loop of domain II of the 23S RNA (Fig. 30). The experimental evidence obtained by UV-induced crosslinking of 23S RNA shows that domain II is in close proximity with the central "peptidyl transferase loop" of domain V.[180] If this is the case, where then is the conserved G-G sequence located, which is required for binding of the aa-tRNA 3′-end? Conventional wisdom would place this site at a conserved G-G^{2608} sequence of the central loop of domain V (Fig. 28).[178, 181] There, it is possible to visualize that peptide bond formation between the two species of tRNA, bound in such fashion, is sterically possible. Thus, this sequence would be a part of the A′ site.

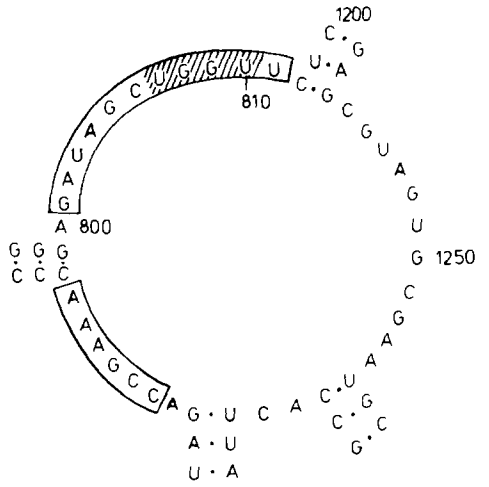


Fig. 30. Secondary structure of the part of *E. coli* 23S RNA (in domain II) which contains the invariant U-G-G-U sequence. This sequence is proposed [179] to be part of the P′ site and interacts via base pairing with the Pu-C-C-A^{76} sequence of peptidyl-tRNA. The conserved nucleotides are boxed; the shaded area denotes part of the A′ site [179].

The vicinity of the antibiotic resistance sites also supports this assignment, since chloramphenicol, for example, is known to inhibit A′ site binding.[182] Residue U^{2605} is possibly also the site of attack of a reactive puromycin analogue.[178, 183] Such a pairing scheme for both tRNA molecules would result in the formation of two coaxial helices; these stabilize the newly formed RNA·RNA hybrids, resulting in precise alignment of both tRNA molecules[178] (Fig. 31). If we allow for the base pairing of residue 73 (usually purine) of both tRNAs with invariant U residues of the 23S RNA (810 and 2609, respectively) (but see also [167]), the coaxial structures would produce two single nucleotide bulges. Such structures may provide recognition sites for the proteins[184] and in this case might modulate the interaction with ribosomal proteins or with elongation and releasing factors.

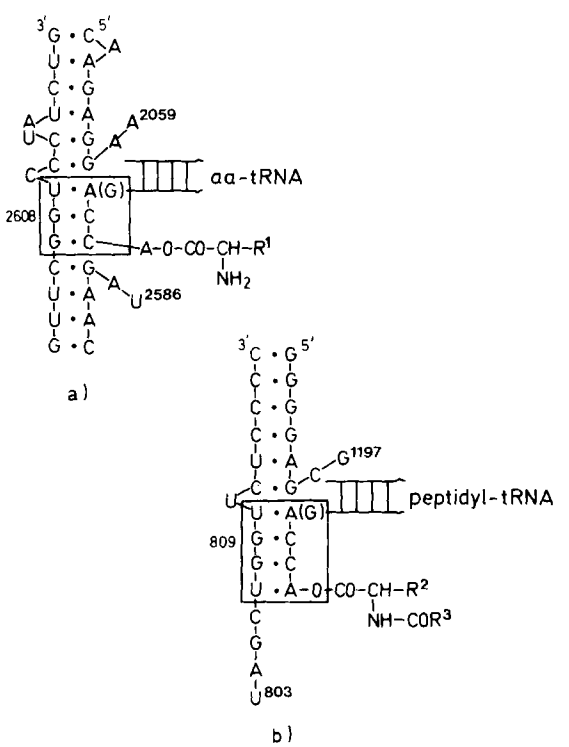


Fig. 31. Models of the coaxial stacking of tRNA with 23S RNA. a) Base-pairing scheme of the aa-tRNA Pu-C-C^{75} sequence with the complementary sequence of 23S RNA (central loop of domain V, cf. Fig. 28) on the A′ site. b) Base pairing of the peptidyl-tRNA Pu-C-C-A^{76} sequence with the complementary sequence of 23S RNA (located in a loop of domain II, cf. Fig. 30) at the P′ site.

5.3.10. *Involvement of the 3′-End of tRNA in Translocation*

Leder[185] postulated that the driving force for the translocation is the product-substrate relation of peptidyl-tRNA and deacylated tRNA in the pre-translocational and post-translocational state, respectively (cf. Fig. 7). Therefore, translocation would be driven, in principle, by the dissociation of the products, peptidyl-tRNA and tRNA, and by the binding of the substrate, peptidyl-tRNA. If this model is correct, the structure of the 3′-terminal adenosine of both peptidyl-tRNA and tRNA should be critical in triggering translocation. Indeed, translocation does not take place if modified peptidyl-tRNA **22** (Fig. 20), lacking the 2′-OH group, is bound to the A site. The EF-G-dependent dissociation of deacylated tRNA from the P site is also inhibited if tRNA-C-C-2′dA is used instead of native tRNA.[186]

These experiments indicate that in the translocation a recognition of the 3′-terminal ribose of both the A′- and the P′-site-bound tRNA is involved. Presumably, translocation is initiated by direct interaction of EF-G with the 2′-OH group of the peptidyl-tRNA and with the *cis*-diol function of the P-site-bound tRNA. Alternatively, a ribosomal protein, which is in contact with the 3′-terminal ribose moieties of both A′- and P′-site-bound tRNAs, may be directly involved in translocation (see also [187]).

During the translocation step, the coaxial helical structures (Fig. 31) would have to be disrupted in order for the newly formed peptidyl-tRNA to move from the A site to the P site. One of the factors that may facilitate such a motion is the acylation of the α-amino group of the newly formed peptidyl-tRNA, now in the A site of the pre-translocation intermediate.[188] An acylated α-amino group does not conform with the specificity of the A′ site, which requires a free α-amino group, and may thus provide a steric impetus for translocation.

6. Catalysis of the Peptidyl Transferase Reaction

Inspite of the fact that the reaction of peptidyl-tRNA with aa-tRNA is thermodynamically favored,[13] there is, to our knowledge, no example of the reaction between the two species in the absence of the ribosome. Peptidyl transferase, which normally catalyzes the synthesis of peptide bonds, is also able, albeit less efficiently, to form ester bonds,[118, 189, 190] thioester bonds,[119] thioamide bonds,[191] and phosphinamide bonds.[192] On the other hand, there is no evidence that peptidyl transferase can cleave peptide bonds. Two other ribosome-mediated reactions appear to involve the peptidyl transferase: the peptide chain termination reaction[193] and the alcoholysis of peptidyl-

tRNA.[194] In these two cases, a molecule of water or ethanol functions as the acceptor substrate.

What then is the nature of peptidyl transferase? Is it an enzymatic activity of a specific ribosomal component or does it work strictly as a template, bringing the "business ends" of two tRNAs into proper juxtaposition to allow spontaneous peptide bond formation? In the following paragraphs we consider both possibilities.

6.1. Peptidyl Transferase as a Template

According to this hypothesis, the peptidyl transferase reaction is simply the aminolysis of the activated ester bond of peptidyl-tRNA by the α-amino group of aa-tRNA via the formation of the tetrahedral intermediate **35** (Fig. 32). The ribosome is not involved catalytically in the reaction. The proposed intermediate is thermodynamically favored, since there is a sufficient energy difference between the activated ester bond of peptidyl-tRNA and the amide bond of the product. It was convincingly argued by *Nierhaus* et al.[195] that the required rates of peptide bond formation, as they are known to occur during protein synthesis, can be achieved if the substrates are properly juxtaposed. The requisite orientation is achieved by the existence of extremely well defined sites for binding of both substrates. According to this model, the functional groups of the ribosomal components do not participate in the peptidyl transferase reaction.

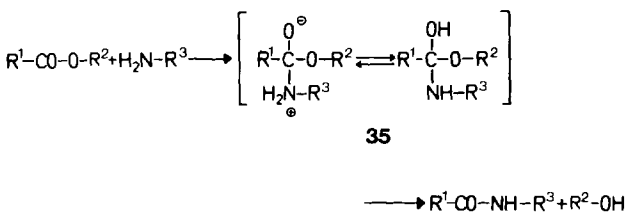


Fig. 32. Peptide bond formation in the peptidyl transferase reaction via a tetrahedral intermediate.

A relevant example of the rapid "uncatalyzed" transacylation reaction is provided by the isomerization of the aminoacyl residue after enzymatic aminoacylation of the accepting 2′-hydroxyl group of tRNA-C-C-3′NH_2A **36** (Fig. 33). The rapid isomerization of the initially formed ester **37** leads subsequently to a stable molecule **3** containing the acylamido bond. This reaction may be considered as a model of "peptide bond formation" via a reactive ester intermediate, which is facilitated by a properly juxtaposed substrate.[14]

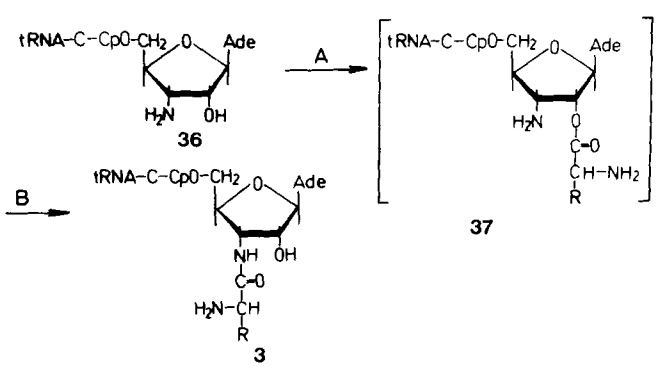


Fig. 33. The formation of the aminoacylamido bond on tRNA-C-C-3′NH_2A **36** involving the ester intermediate **37**. A: 2′-specific enzymatic aminoacylation; B: transacylation to give **3**.

6.2. Peptidyl Transferase as an Enzyme

Although the required rates of peptide bond formation can be achieved by juxtaposition of the 3′-ends of the two tRNA substrates, there are numerous observations that indicate that the ribosome functions as an enzyme for the formation of the peptide bond. The question then arises whether peptidyl transferase could function by a mechanism similar to that of proteolytic enzymes, which are also capable of synthesizing peptide bonds. Members of this class of enzymes, known as serine proteases, all appear to operate by a similar mechanism, involving a serine-histidine-aspartic acid charge relay system and the formation of a covalent acyl-enzyme intermediate. The formation of a covalent substrate-enzyme intermediate in the case of peptidyl transferase is not probable.[195, 196] On the other hand, a mechanism involving the histidine-carboxyl system was postulated for the peptidyl transferase in order to account for the repeated observation that the histidine residue of a ribosomal protein is involved in substrate binding to the A′ site.[197-199] There is no need, however, to postulate the existence of a protease-type charge relay system to explain the putative role of the ribosomal peptidyl transferase in the catalysis, since this mechanism has evolved for an entirely different reaction, i.e., cleavage of the peptide bond.

Before the peptidyl transferase reaction can take place, the α-amino group of aa-tRNA must be deprotonated by an appropriately placed proton-accepting group on the ribosome. Thus, the reaction may be considered to be a "catalyzed" reaction.[200] Moreover, the concerted mechanism of "catalyzed" peptide bond formation, which was originally proposed by *Cheney*,[201] involves the transfer of a peptidyl residue from peptidyl-tRNA to a *deprotonated* amino group of aa-tRNA, followed by a proton transfer with $Mg^{2\oplus}$ participation. It also requires the participation of a suitably oriented ribosomal function to act in "the proton relay" (Fig. 34), which would thus serve as a catalytic site. This mechanism merits serious consideration, since it accounts for the stabilization of the tetrahedral intermediate, which, obviously, is not possible in an "uncatalyzed reaction". Furthermore, this model also provides a rationale for the competitive binding of antibiotics such as lincomycin, chloramphenicol, and erythromycin, which are known to inhibit the peptidyl transferase reaction. According to this model, the antibiotics would be expected to interact directly with the catalytic center and, thereby, obviate the need to postulate allosteric effects. Additionally, the participation of a ribosomal group in the catalysis should facilitate kinetic control of the process, which is necessary in providing for the fidelity of translation.[6, 202]

If the traditional view were to hold, namely, that the enzymatic activity is harbored by a protein, then it would seem rather safe to predict, from an evolutionary point of view, that peptidyl transferase activity should be the prop-

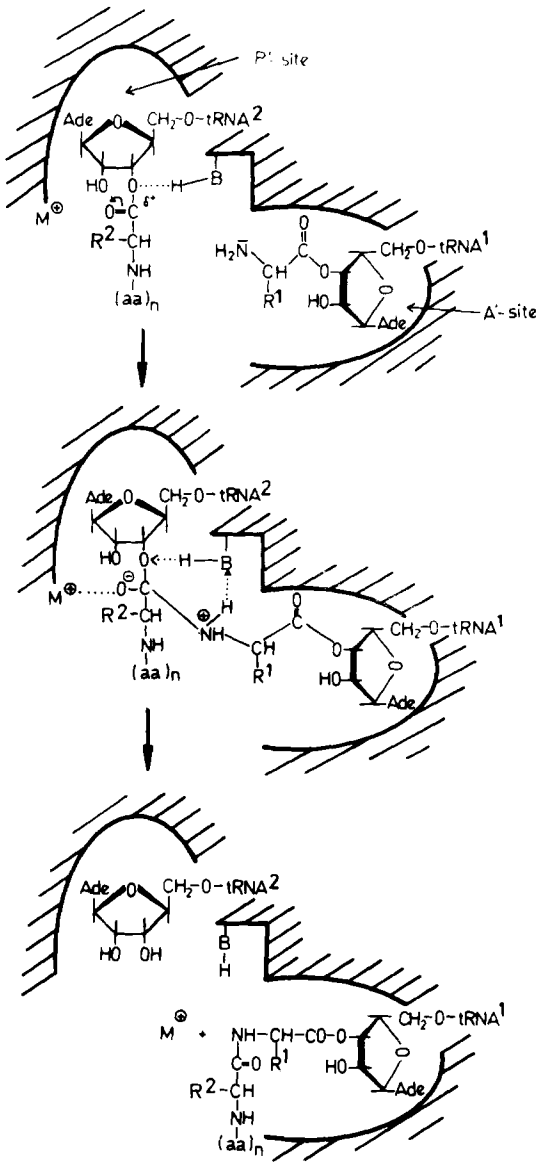


Fig. 34. The mechanism of the enzymatically catalyzed peptide bond synthesis. A metal ion $M^{\oplus}$ and a ribosomal functional group B-H are involved in the reaction. The latter functions as a proton acceptor and proton donor. $tRNA^1$ is aminoacyl-tRNA; $tRNA^2$ is peptidyl-tRNA (redrawn according to [201]).

erty of a single protein. In fact, protein L16 was long regarded as a prime candidate for the peptidyl transferase,[203] but this view is no longer tenable.[204,205] The latest potential candidate for "the peptidyl transferase protein" is the highly conserved protein L2 (see also [187]).

Since the protein synthesizing machinery must have evolved before the existence of proteins themselves, the prebiotic ribosome was most likely composed only of RNA.[206,207] Therefore, the pertinent question arises as to whether RNA alone can catalyze peptide bond formation. A short time ago this view would have been regarded as heretical, since catalytical roles were traditionally reserved for proteins, whereas nucleic acids were believed to have structural functions. This perception has changed dramatically recently. There are, to our knowledge, two examples for the catalytic role of RNA alone in the cleavage and formation of phosphodiester bonds between nucleotides.[208,209] *Garrett* and *Wooley*[200] have recently speculated that the catalysis of peptide bond formation could possibly be mediated by a properly positioned 5'-phosphate group of peptidyl-tRNA, involving a mechanism similar to that shown in Figure 34. It was shown that the rate of poly(Phe) synthesis decreased as a result of the removal of the 5'-phosphate group from tRNA.[97] This effect, however, which was measured for the synthesis of polypeptides de novo, does not seem to be dramatic enough for assigning a crucial catalytic role to this phosphate group. The suggestion of *Garrett* and *Wooley*[200] is also at variance with the donor activity of fragments such as C-C-A(fMet) in the peptidyl transferase reaction, although the fragment reaction apparently proceeds at a slower rate. Since the central loop of the domain V of 23S RNA appears to be a part of the peptidyl transferase center (Section 5.3.9), it seems plausible that some of its functionality, properly oriented, could provide for the catalysis of the peptidyl transferase reaction (or deprotonation of the α-amino group of aa-tRNA).

Indeed, it was recently demonstrated that a complex that forms between 16S and 23S RNA may act as a primitive ribosome, having lower, albeit significant activity in poly(Phe) synthesis.[210] *Burma* et al. have also shown that EF-Tu-dependent binding of $Phe\text{-}tRNA^{Phe}$ to the 16S·23S RNA complex requires the presence of 5S RNA.[210] This RNA binds to the 16S·23S RNA complex only in the presence of the 5S RNA binding proteins (L5, L18, L15/25). Accordingly, these proteins must be included in the experiment. On the other hand, it is very clear that none of these proteins is involved in peptidyl transferase activity. Therefore, peptide-bond-forming activity should most probably be attributed to 23S RNA, specifically to the central loop of domain V, in which most of the single-stranded nucleotides are highly conserved through evolution.[178,181] Furthermore, several mutations leading to ribosomal resistance to chloramphenicol and erythromycin are found in the same region. The binding site of the 3'-end of peptidyl-tRNA in the loop of domain II of 23S RNA is probably the P' site. The binding site of the 3'-end of the aa-tRNA in the peptidyl transferase loop, which includes the catalytic activity, is most likely the A' site. This configuration would provide for the separation of the catalytic activity and acceptor binding from the binding of the donor molecule. This is necessary for the regulation of peptide synthesis, the proofreading mechanism, and the fidelity of the process. Thus, the findings of *Burma* et al.[210] have far-reaching functional implications, showing for the first time that ribosomal RNAs still may retain their primitive protein-synthesizing functions, which, by virtue of evolution, have been much refined by the proteins themselves.

7. Conclusions and Outlook

The data obtained by several approaches make it possible to visualize in considerable detail the nature of the interactions of the 3'-terminal C-C-A end of tRNA with elongation factors and with the A' and P' sites. The most recent and important observations are concerned with the crucial role of 23S RNA in the peptidyl transferase reac-

tion. Since the rRNA story is just beginning to unfold, we are certain to learn more of the direct participation of rRNAs not only in the process of peptide bond formation, but also in other events encompassing overall protein synthesis on the ribosomes.

The interaction of the 3′-end of aa-tRNA with a corresponding site of EF-Tu is of primary importance for the formation of the ternary complex and for the EF-Tu-catalyzed GTP hydrolysis, which is triggered upon binding of the ternary complex to ribosomes. It seems reasonable to assume that the nucleic acid bases of the C-C-A sequence are not directly in contact with EF-Tu while aa-tRNA is complexed to the enzyme. Thus, in the process of the enzymatic binding of aa-tRNA to the ribosome, base moieties of the C-C-A sequence are available for interaction with the ribosomal A′ site. It is not clear whether EF-Tu is indeed nonspecific with respect to the 2′,3′-isomers of the aa-tRNA. Our understanding to date is based on model studies, which may not be fully adequate. The obligatory involvement of the aa-tRNA C-C-A terminal sequence in the process of GTP hydrolysis is, however, clear. Nonetheless, a larger question remains to be answered: how do conformational changes occur in the EF-Tu molecule to bring about GTP hydrolysis by this protein? The question also remains how the binding of other parts of the tRNA, to either EF-Tu or to the ribosome, influences the interaction of the 3′-end of aa-tRNA with the enzyme. Also, it remains to be clarified whether the latter phenomenon is a part of the EF-Tu·GTPase triggering mechanism.

Since the aa-tRNA 3′-end is accommodated at the A′ site upon dissociation of EF-Tu, we do not know whether the process includes, as well, some intermediary interactions. Intermediary configurations of aa-tRNA may allow for proofreading, involving possibly rRNA structure dynamics. A ribosomal protein(s) is required for the precise alignment of the aminoacyl portions of both substrates (aa- and peptidyl-tRNA) for peptide bond formation. Moreover, the protein(s) would be expected to possess binding loci to facilitate proper orientation of both substrates; this must involve, at the very least, the carbonyl group and the side chain of the aminoacyl moieties. Interactions with other moieties of the terminal adenosine unit are also conceivable. On the other hand, the α-amino group of the acceptor and the ester bond of the donor would be expected to be available to hydrogen bond with the catalytic functionality of peptidyl transferase. The acceptor and donor molecules, aa-tRNA and peptidyl-tRNA, react in the form of the 3′-isomer, while the 2′-OH group of the terminal adenosine is not required for this reaction. Gly-tRNA is probably exempt from this rule.

It is likely that the peptidyl transferase reaction is catalyzed by a functionality in the central loop of domain V of 23S RNA. The mechanism of the peptidyl transferase reaction proposed here suggests that the A′ and P′ sites are made up, in part, of the appropriate G-G and U-G-G sequences of 23S RNA, which are located in different domains of the polynucleotide. These sequences are presumably engaged in base-pairing with the C-C and C-C-A sequences of aa- and peptidyl-tRNA. The domains of 23S RNA that form parts of the A′ and P′ sites must be in close proximity for peptide bond formation to occur, but they could be separated during various stages of the ribosomal cycle. Thus, the folding of the 23S RNA chain may provide for the regulation of the protein synthesis, including proofreading.

Even though we do not envision catalysis of the peptidyl transferase reaction being mediated by a ribosomal protein, participation of proteins may not be limited to maintaining the specificity of the reaction and presumably increasing the rate of peptide synthesis. Even if we accept the unorthodox view that the ribosome is an *RNA-driven device*, we cannot deny the apparent role of protein(s) in modulation of RNA structures. Similar roles may be played by elongation and termination factors, which may effect changes in ribosomal configuration.

During the translocation step, interactions of the two tRNAs with ribosomal sites have to be disrupted in order to achieve the movement of tRNA. This might include, among other things, the breaking of at least 5 base pairs between the 3′-ends of each of the tRNAs and 23S RNA. There are indications that another important change in the structure of the tRNA C-C-A terminus may take place during translocation, namely, rotation about the glycosidic bond of the 3′-terminal adenosine. If the 3′-terminal unit of peptidyl-tRNA, bound to the P′ site, is present in a *syn*-conformation, we may expect altered base pairing of this unit as well as an altered stacking arrangement of the whole C-C-A terminus. Such a scheme may explain the different modus of operation of A′ and P′ sites.

Similarly, the termination step must involve structural changes at the peptidyl transferase center in order to allow access of a molecule of water to an otherwise "anhydrous" A′ site. This change could be again modulated by corresponding changes in the 23S-RNA structure with participation of pertinent proteins.

Thus, the dynamic structure of RNA together with specific interactions of the 3′-terminal C-C-A sequences with their respective sites may make possible a virtually foolproof process of protein synthesis.

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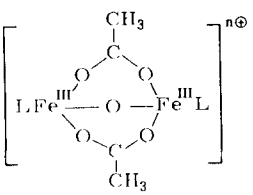
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Reactivity of the $[Fe_2(\mu_2\text{-}O)(\mu\text{-acetato})_2]$ Unit in Methemerythrin Model Compounds towards $N_3^{\ominus}$ and $NCS^{\ominus}$**

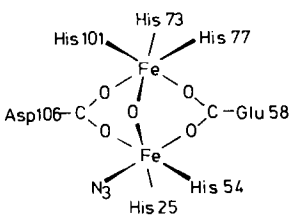
By *Karl Wieghardt,* Klaus Pohl,* and *D. Ventur*

The synthesis and structure of the low-molecular-weight Fe^{III}-complexes **1** and **2**, containing the structural unit $[Fe_2(\mu_2\text{-}O)(\mu\text{-acetato})_2]$ have recently been reported.[1]

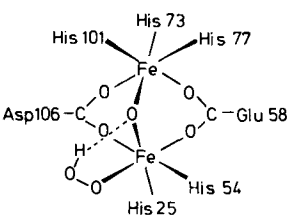


1, L = Tri-1-pyrazolylborate(1-) (n = 0)[1a]
2, L = 1,4,7-Triazacyclononane (n = 2)[1b]
3, L = *N,N',N''*-Trimethyl-1,4,7-triazacyclononane (n = 2)

These complexes, to which the complex **3** presented here also belongs, have proven to be perfect model compounds for the Fe^{III} centers in metazido-[2] and oxyhemerythrin[3] so far as bonding is concerned. Particularly remarkable is the similarity of the electronic spectra in the visible region and of the magnetic properties (antiferromagnetism) of **1**—**3** with those of the methemerythrins.[4]



Metazidohemerythrin

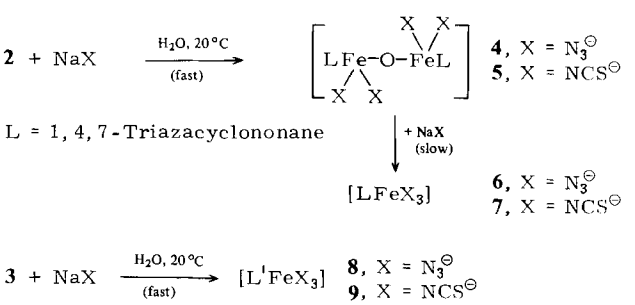


Oxyhemerythrin

The reactivity of the dinuclear structural unit in **1**—**3** is presently the subject of intensive study. The oxo bridge in **1** can be reversibly protonated to the corresponding μ-hydroxo bridge.[5] Furthermore, the μ-carboxylato bridges in **1** and **2** are relatively labile;[6] in **1**, they can be replaced by phosphate diesters.[6b] Aqueous solutions of **2** are stable for only about 2 h at 20°C, after which time an insoluble precipitate slowly forms.[6a] In the presence of excess acetate ions, however, aqueous solutions of **2** and **3** are stable for several hours.

We have investigated the reactivity of **2** and **3** towards $N_3^{\ominus}$ and $NCS^{\ominus}$ in aqueous solution at 20°C. Under these conditions the enzyme deoxyhemerythrin reacts in the presence of $NCS^{\ominus}$, $N_3^{\ominus}$, $CN^{\ominus}$ or $OH^{\ominus}$ and oxygen to give methemerythrin with the intact $[Fe_2(\mu_2\text{-}O)(\mu\text{-carboxylato})_2]$ structural unit with bonding of only *one* of these ligands to *one* Fe^{III} center.[4]

Addition of NaN_3 or NaSCN to freshly prepared aqueous solutions of **2** leads to immediate precipitation of microcrystalline, yellow precipitates of **4** and **5**, respectively. **4** and **5** react with excess $N_3^{\ominus}$ and $NCS^{\ominus}$ very slowly to give red **6** and **7**, respectively. Under the same conditions, **3** immediately furnishes red **8** and **9**, respectively. The formation of **4** and **5** in the presence of sodium acetate proceeds considerably more slowly. With very high concentrations of acetate, $[3\cdot(SCN)_2\cdot 5\,H_2O]$ precipitates out and no substitution reaction takes place at the Fe^{III} center.



4 and **5** are dinuclear, oxo-bridged complexes exhibiting strong antiferromagnetic coupling of the two high-spin Fe^{III} centers (Table 1). The expression for the temperature-dependent susceptibilities (98—293 K) of **2**—**5** were derived from the general, isotropic spin Hamilton operator $H' = -2JS_1\cdot S_2$ for $S_1 = S_2 = 5/2$ ($g = 2.0$, no temperature-independent paramagnetism). The values for J between -76 and $-95\ cm^{-1}$ are typical for oxo-bridged Fe^{III}-complexes. In each case, one band is observed for the ν_{as}(Fe—O—Fe) stretching vibration in the IR spectra of **4** and **5**, at 800 and 810 cm^{-1} respectively; it is shifted to higher wave numbers compared to the corresponding bands of **2** and **3** (and **1**[1a]). This is indicative of a stronger Fe—O bond and an almost linear Fe—O—Fe unit.

6—**9** are monomeric, octahedral Fe^{III}-complexes. The temperature-independent, effective magnetic moment of ca. $5.8\,\mu_B$ (98—293 K) indicates a high-spin d^5-electron configuration of the Fe^{III} centers.

The reactions of **2** and **3** with $N_3^{\ominus}$ and $NCS^{\ominus}$ are different from those of the methemerythrins—despite the very similar coordination and electronic structure of the Fe^{III}

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centers. And, finally, the kinetic lability of the μ-acetato bridge[6] and, of the oxo-bridge in **2** and **3** is *not* observed in methemerythrin under the same conditions.

Table 1. Electron excitation, IR- and magnetic data of the complexes **1**—**9**.

Compound	ν_{as}(Fe–O–Fe) [cm^{-1}]	J[cm^{-1}]	μ_{eff} (293 K) [μ_B]	λ[nm] (ε[L mol^{-1} cm^{-1}]) [a]
1 [1a]	751	−121		262 (6750), 339 (9270), 258 (sh), 457 (110), 492 (920), 528 (sh), 695 (140), 995 (7)
2·I_2·0.5 NaI·3 H_2O [6a]	730	− 84(1)		335 (3679), 373 (sh), 420 (sh), 464 (537), 489 (sh), 506 (398), 543 (sh), 743 (66), 1020 (3.2)
3$(PF_6)_2$	710	− 95(2)		345 (10500), 428 (1000), 475 (1560), 519 (1200), 550 (sh), 734 (120)
4·H_2O	800	− 76(3)		398 (3800)
5	810	− 75(2)		398 (18000), 499 (1000) (sh)
6			5.77	479 (5800)
7			5.87	425 (11500) (sh)), 490 (19000)
8			5.79	500 (4000)
9			5.80	520 (7000)

[a] Molar absorption coefficients; solvent for **3** water, and for **4**—**9** acetone.

Experimental

3$(PF_6)_2$: To a solution of $FeCl_3 \cdot 6 H_2O$ (3.5 g) in ethanol (100 mL) was added 12 mL of 1 M ethanolic solution of *N,N',N''*-trimethyl-1,4,7-triazacyclononane (L'). A yellow precipitate of [L'$FeCl_3$] separated out. After filtration, 0.2 g of this neutral complex was dissolved in 10 mL of a saturated aqueous NH_4OAc solution. 0.25 g of KPF_6 was added to the clear brown solution and the resulting brown precipitate of **3**$(PF_6)_2$ was recovered by filtration (yield 0.2 g (75%)).

4—**7**: A solution of NaN_3 (1 g) or NaSCN (0.2 g), respectively, in H_2O (5 mL) was added at 20°C to a stirred solution of [**2**·I_2·0.5 NaI·3 H_2O] (0.10 g) [1b] in 20 mL H_2O. Ocher-yellow precipitates of **4**·H_2O (0.07 g, 92%) and **5** (0.10 g, 95%) immediately separated out. When the suspensions were stirred for a further 6 h at 20°C, red precipitates of **6** and **7**, respectively, separated out (0.07 g, 95% and 0.08 g, 98%).—All the complexes are sparingly soluble in H_2O, but moderately soluble in acetone or acetonitrile. A molecular weight determination was carried out in the case of **5** (620 ± 30).

8 and **9**: 1 g of NaN_3 or NaSCN was added to 40 mL of an aqueous solution of 0.2 g **3**$(PF_6)_2$. Red precipitates of **8** and **9** immediately separated out (quantitatively). All the compounds gave correct elemental analyses (Fe, C, H, N, S).

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$(Te_2)_2(I_2)$—An Unusual Intercalation Compound**

By *Rüdiger Kniep** and *Heinz-Jürgen Beister*

In a review article on subhalides of tellurium,[1] the existence of a metastable compound Te_3I was reported. We have again synthesized this phase and determined its crystal structure. It is a compound with an unusual layer structure, which can be described as a tellurium intercalate with a phase width related to the intercalated iodine. At maximum iodine content the composition corresponds to the empirical formula Te_2I,[2] at minimum iodine content to an empirical formula $Te_2I_{0.42}$ (sample ca. 30—50 small crystals; 10 mg).

The shiny, black-metallic, air-stable crystals of $(Te_2)_2(I_2)$, **1**, are obtainable by hydrothermal synthesis[3] in concentrated HI.[4] For the structure analysis[5] we used a single, very slightly distorted crystal measuring $0.2 \times 0.07 \times 0.01$ mm^3. Intergrowths and deformations are especially pronounced in this layer-like structured crystalline substance, a factor which has hitherto prevented a satisfactory structure determination.

According to the X-ray structure analysis (Fig. 1), **1** contains planar double layers of tellurium formed from Te_2 units arranged parallel to the c axis. The Te atoms within the double layers thus exhibit a distorted tetragonal-pyramidal (1+4)-coordination with one short (d_1) and four longer bond lengths (d_2). In contrast, a distorted octahedral (2+4)-coordination is observed in the trigonal elemental structure.[6] The bond length d_1 (Te–Te) of 2.713(7) Å is distinctly shorter than that in the trigonal elemental structure ($d_1 = 2.835(2)$ Å)[6] and only slightly longer than the reported Te–Te bond length in Te_3Cl_2 (2.67 Å) with partial double bond character.[1] It may be assumed that the Te_2 units in the compound described here are stabilized by resonance (:$\ddot{T}e$–$\ddot{T}e \leftrightarrow \ddot{T}e = \ddot{T}e \leftrightarrow \ddot{T}e$–$\ddot{T}e$:). The

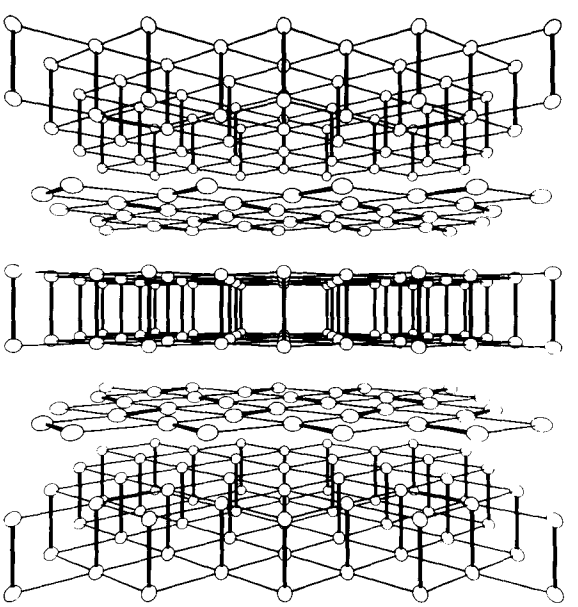


Fig. 1. Perspective representation of the layer sequence ([001]) in **1**. Te_2 pairs and I_2 molecules are accentuated by bolder lines.

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distances d_2 between adjacent Te_2 units within a double layer are 3.323(1) Å and are thus likewise shorter than the intermolecular distances d_2 between the chains of the trigonal elemental structure (3.495(4) Å).[6] The ratio $d_2:d_1$ in the tellurium double layer, with a value of 1.225, is noticeably different from unity, so that little significance attaches to the comparison with a (tetragonal distorted) two-dimensional section of the cubic primitive α-Po structure, which seems reasonable at first glance.

I_2 molecules (I–I 2.866(12) Å) are located between the tellurium double layers; these are arranged via intermolecular contacts (I···I 3.324(14) and 3.841(16) Å) in monomolecular planar layers. The shortest interlayer distance I···Te is 3.812(9) Å. The orientation of the iodine molecules within the layers corresponds to the arrangement of the molecules in the (100) planes of the elemental structure;[7] here, however, the bond length in the I_2 molecule (2.715 Å) is shorter, while the intermolecular contacts (3.496 and 3.972 Å) are longer.

1 can be described as a tellurium intercalate $^2_\infty(Te_2)_2(I_2)$, in which a tellurium modification, previously unknown as an independent phase, is intercalated by elemental iodine. First attempts to obtain a new metastable elemental modification in substance, by thermal decomposition of the compound (as, e.g., in the case of *allo*-germanium[8]), were hitherto unsuccessful, and in each case led to the stable trigonal[6] modification of tellurium.

The crystal investigated by us showed an occupation of the iodine layers of only 88%. This finding can be attributed both to vacant sites within the iodine layers as well as to partial replacement of the iodine molecules by hydrogen iodide from the hydrothermal solution; in the thermal decomposition of **1** the liberation of HI is also detected mass spectroscopically.[9]

The thermal decomposition of **1** begins at ca. 100°C with chiefly elimination of I_2 and formation of small isometric crystals of trigonal tellurium at the ends of the layers of the intercalation compound. With increasing temperature (up to ca. 150 °C), TeI_2[1] is increasingly given off into the gas phase; this likewise leads, in the sense of a chemical transport reaction ($TeI_{2(v)} \rightleftharpoons Te_{(s)} + I_{2(v)}$),[10] to the formation of trigonal tellurium crystals. Under these conditions the crystals grow out parallel from the layers of the intercalation compound with a needle-like habit.

It has been demonstrated mass spectrometrically that solvent molecules are intercalated in the structural assemblage when crystals of **1** are treated with methanol.

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CAS Registry numbers:
$(Te_2)_2(I_2)$, 39449-54-2; GeTe, 12025-39-7; Te, 13494-80-9; I, 7553-56-2.

[1] R. Kniep, A. Rabenau, *Top. Curr. Chem. 111* (1983) 147.
[2] The same composition is also found for the known subhalides Te_2X (X = Cl, Br, I) [1].
[3] A. Rabenau in P. Hartmann: *Crystal Growth—an Introduction*, North-Holland, Amsterdam 1973, p. 198.
[4] Crystal growth: Quartz ampules ca. 14 cm³; 1.5 g of a 1:1 mixture of GeTe and Te; 60% degree of filling with 67% HI; temperature gradient 170→160°C ca. 18 h; duration of cooling ca. 12 h; reaction products: GeI_4, Te, $(Te_2)_2(I_2)$; yield of intercalation compound ca. 50 mg; germanium was not detected in the intercalate; the synthesis can also be accomplished in the presence of arsenic; without these "foreign elements", the compound is not formed; striking is the relatively high hydrogen partial pressure in the ampules on completion of the hydrothermal experiments.
[5] Crystallographic data of **1**: 157 (103) reflections (Syntex $P2_1$, $Mo_{K\alpha}$); $R = 0.079$; Cmmm; $a = 4.464(4)$, $b = 4.924(5)$, $c = 9.037(16)$ Å; $Z = 1$; $\rho_x = 6.39$ g/cm³ (complete occupation of the iodine positions); 6.13 g/cm³ for the observed occupation of 88%. In the space group Cmmm, two oppositely situated sites are present for each iodine atom, which are alternately occupied. The ordered iodine layers described in the text and depicted in Figure 1 follow from the occupation of only one of these sites in each case. This X-ray crystallographically established disorder can, e.g., be attributed to alternating orientation of the iodine molecules in successive layers. Superstructure reflections have not been observed photographically, even with longer exposure times. Further details of the crystal structure investigation are available on request from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2, on quoting the depository number CSD 51279, the names of the authors, and the full citation of the journal.
[6] P. Cherin, P. Unger, *Acta Crystallogr. 23* (1967) 670.
[7] F. van Bolhuis, P. B. Koster, T. Migchelsen, *Acta Crystallogr. 23* (1967) 90.
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[9] HI fraction ca. 5%. It must be taken into account that the measurement was carried out on one sample consisting of many crystals.
[10] J. Burmeister, *Mater. Res. Bull. 6* (1971) 219.

$[Cp_2Ti(PMe_3)_2]$—A Versatile Source of Titanocene Derivatives**

By *Lawrence B. Kool, Marvin D. Rausch,* Helmut G. Alt,* Max Herberhold, Ulf Thewalt,* and *Brigitte Wolf*

Monomeric titanocene, $TiCp_2$ (Cp = η^5-cyclopentadienyl), has so far eluded isolation as a discrete compound, since "in statu nascendi" it immediately reacts to form bi- or multinuclear species.[1] Until now, the best source for titanocene has been $[Cp_2Ti(CO)_2]$ **5**.[2] We now report the synthesis, spectroscopic characterization, and molecular structure of $[Cp_2Ti(PMe_3)_2]$ **1**, which may be considered as trimethylphosphane-stabilized titanocene. **1** is the first bis(trimethylphosphane) complex of a group 4 transition metal to be isolated and fully characterized.[3] It is synthesized in quantitative yield via the reduction of Cp_2TiCl_2 by magnesium in the presence of trimethylphosphane:

$$Cp_2TiCl_2 + Mg + 2\,PMe_3 \xrightarrow{THF} [Cp_2Ti(PMe_3)_2] + MgCl_2$$

1

1 has been characterized by elemental analysis, NMR spectroscopy, and X-ray structural analysis. The analogous zirconium derivative has similarly been obtained via magnesium reduction of the metallocene dichloride.

It was not possible to sublime **1** without decomposition. An intense peak for Cp_2Ti^+ (*m/z* 178) was observed in the EI mass spectrum; in addition, peaks of higher *m/z* appeared, which resulted from formation of binuclear titano-

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[+] X-ray structure analysis.

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cene species. In the ^{1}H-, ^{13}C-, and ^{31}P-NMR spectra, all the expected signals could be assigned.[4]

The X-ray structural analysis[4] of **1** indicates that two crystallographically independent molecules are present in the unit cell: one molecule (containing Ti1) occupies a common position while the other occupies a special position with crystallographic C_2 symmetry. Both molecules possess the same dimensions and conformations within narrow limits. All PMe_3 ligands are so oriented that one C atom always lies almost in the P–Ti–P plane (Fig. 1).

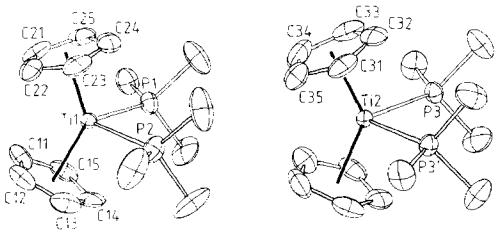


Fig. 1. The two (crystallographically) independent molecules of **1**. Important distances [Å] and angles [°]: Ti1–P1 2.527(3), Ti1–P2 2.524(4), Ti2–P3 2.527(2), Ti1–Z1 2.057(12), Ti1–Z2 2.062(14), Ti2–Z3 2.049(12); Ti–C(Cp) 2.338(13)–2.422(12); P–C(Me) 1.837(19)–1.887(11); P1–Ti1–P2 92.9(1), P3–Ti2–P3′ 91.5(2), Z1–Ti1–Z2 133.2(5), Z3–Ti2–Z3′ 134.3(6). Z1, Z2, Z3: center of gravity of the C11, C21, and C31-containing Cp rings; Z3′: center of gravity of the unnumbered Cp ring.

The Ti–P distances in **1** (2.524(4) and 2.527(3) Å) are in excellent agreement with the recently reported complex **2**.[5] They are, however, shorter than the Ti–P distance in **3** (2.585(1) Å).[6] The Cp_2Ti units in **1**, **2**, and **3** are essentially identical. The P–Ti–P angle in **1** (91.5(2) and 92.9(1)°) is, as expected, larger than in the chelated complex **2** (76.9(2)°).[5]

$[(Me-C_5H_4)_2Ti(dmpe)]$
2, dmpe = 1,2-bis(dimethylphosphino)ethane:

$[Cp_2Ti(PEt_3)(CO)]$ **3**	$[Cp_2Ti(PMe_3)(CO)]$ **4**
$[Cp_2Ti(CO)_2]$ **5**	$[Cp_2Ti(dmpe)]$ **6**
$[Cp_2Ti(SPh)_2]$ **7**	$[Cp_2Ti(PMe_3)(C_2Ph_2)]$ **8**
$[Cp_2TiC_4Ph_4]$ **9**	$[Cp_2Ti(PMe_3)(C_2H_2)]$ **10**
$[Cp_2TiC_4H_4]$ **11**	$[Cp_2Ti(PMe_3)(C_2H_4)]$ **12**
$[Cp_2TiC_4H_8]$ **13**	$[Cp_2Ti(CH_3CN)_2]$ **14**

With **1**, the titanocene unit, $TiCp_2$, has become accessible in solution with unprecedented facility, since the two PMe_3 ligands may be replaced by a large number of substrates under very mild conditions; all products are obtained in excellent yields. With carbon monoxide, it forms, within a few minutes, first the mono- and then the dicarbonyl complex, **4**[7] and **5**,[2] respectively. With the chelating ligand dmpe, **6**[5] is formed. Diphenyl sulfide reacts immediately with **1** forming **7**.[8] With diphenylacetylene, first the complex **8**[9] and subsequently the metallacycle **9**[10] are formed. Acetylene reacts with **1** affording the first C_2H_2 complex **10**, the first metallacyclopentadiene derivative of a group 4 transition metal **11**, and polyacetylene $+HC=CH+_x$. Ethylene is dimerized catalytically under pressure (60 bar) in the presence of **1** at room temperature; NMR spectroscopic studies at −50 °C indicate that, in addition, the ethylene complex **12** and the saturated metallacycle **13**[11] occur as intermediates. Acetonitrile displaces the two PMe_3 ligands of **1**, whereby the disubstitution product **14** and other, as yet unidentified, products arise. Preliminary studies indicate that **1** also reacts with isonitriles, diazoalkanes, sulfur diimides, carbon dioxide, carbon disulfide, nitrosyl chloride, hydrogen and other substrates.

Experimental Procedure

A solution of Cp_2TiCl_2 (10.0 g, 40.2 mmol) in 200 mL of tetrahydrofuran (THF) was treated under argon with 4.3 g (180 mmol) of magnesium turnings and with 19 mL (200 mmol) of trimethylphosphane and stirred. The red suspension soon turned blue, and shortly thereafter became red-brown. After 20 h, the solvent was removed at 10^{-2} bar and the residue extracted with pentane. After concentration of the orange-brown solution and cooling to −78 °C, black needles formed, which decomposed at ca. 105 °C. Yield: 13.3 g (100%).

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1, 95936-00-8; **4**, 56770-61-7; **5**, 12129-51-0; **6**, 94631-20-6; 7, 1292-47-3; **8**, 79670-58-9; **9**, 1317-21-1; **10**, 95936-01-9; **11**, 69968-21-4; **12**, 95936-01-9; **13**, 52124-67-1; **14**, 95936-02-0; Cp_2TiCl_2, 1271-19-8; Cp_2Ti, 1271-29-0; [−HC=CH−]X, 25067-58-7; acetylene, 74-86-2; ethylene, 74-85-1.

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[2] D. J. Sikora, D. W. Macomber, M. D. Rausch, *Adv. Organomet. Chem.*, in press.
[3] Cp_2ZrL_2 (L = $PMePh_2$, PMe_2Ph) were reported as non-isolable compounds: K. I. Gell, J. Schwartz, *J. Chem. Soc. Chem. Commun. 1979*, 244; *J. Am. Chem. Soc. 103* (1983) 2687.
[4] ^{1}H-, ^{13}C-, and ^{31}P-NMR ([D$_8$]toluene, −20 °C): ^{1}H-NMR: $\delta = 4.51$ (t, $J(P,H) = 2.2$ Hz, 10 H, Cp), 0.83 (vt, $J(P,H) = 2.0$ Hz, 18 H, PMe_3); ^{13}C-NMR: $\delta = 91.2$ (Cp), 23.6 (br, m, PMe_3); ^{31}P-NMR: $\delta = 45.2$ (br).—Crystal data: $C_{16}H_{28}P_2Ti$, $M_w = 330.45$ g mol^{-1}, Fdd2, $Z = 24$, $a = 44.018(15)$, $b = 28.755(6)$, $c = 8.603(3)$ Å; $\rho_{calcd} = 1.209$ g cm^{-3}. Intensity measurements at room temperature; all 2053 independent reflections observed to $\theta_{max} = 23°$ used. H atoms not considered; $R = 0.075$, $R_w(F) = 0.074$. Further details of the crystal structure determination may be obtained from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2, by quoting the depository number CSD 51211, the names of the authors, and the full journal citation.
[5] G. S. Girolami, G. Wilkinson, M. Thornton-Pett, M. B. Hursthouse, *J. Chem. Soc. Dalton Trans. 1984*, 2347.
[6] B. H. Edwards, R. D. Rogers, D. J. Sikora, J. L. Atwood, M. D. Rausch, *J. Am. Chem. Soc. 105* (1983) 416.
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[8] G. Facchinetti, C. Floriani, *J. Chem. Soc. Dalton Trans. 1974*, 2433.
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[10] J. L. Atwood, W. E. Hunter, H. Alt, M. D. Rausch, *J. Am. Chem. Soc. 98* (1976) 2454.
[11] a) J. X. McDermott, G. M. Whitesides, *J. Am. Chem. Soc. 96* (1974) 947; b) J. X. McDermott, M. E. Wilson, G. M. Whitesides, *ibid. 98* (1976) 6529.

Synthesis of $[(\eta^5\text{-}C_5H_5)_2Mo(\eta^2\text{-}CH_2O)]$: A Formaldehyde Complex of Molybdenum**

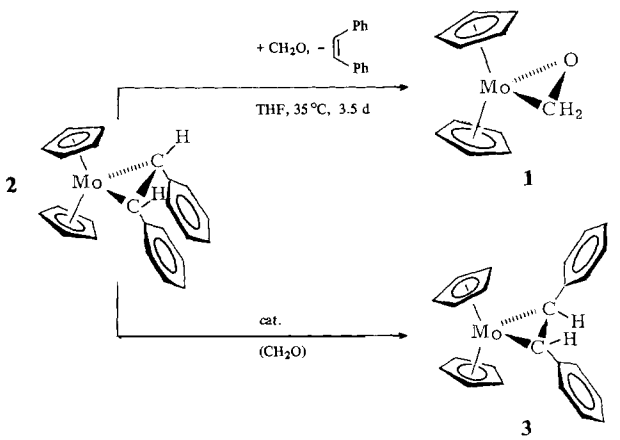
By *Gerhard E. Herberich** and *Jun Okuda*

Dedicated to Professor F. Gordon A. Stone on the occasion of his 60th birthday

Organometallic complexes containing formaldehyde ligands are of considerable interest as model compounds for intermediates in the homogeneous reduction of CO.[1] The sterically compact and electronically flexible metallocene fragments $M(C_5H_5)_2$ of early transition metals are suitable for the investigation of formaldehyde coordination in complexes containing different metals but having comparable ligand environments.

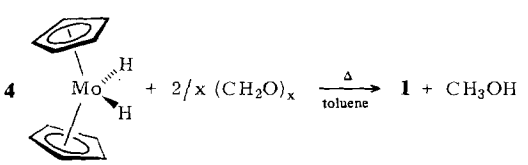
Whereas vanadocene reacts with paraformaldehyde to give a mononuclear formaldehyde complex via addition of a CH_2O unit,[1b] zirconocene hydrides afford bi- and trinuclear derivatives containing bridging CH_2O ligands upon treatment with CO.[1c] We report here the molybdenocene formaldehyde complex **1**.[2]

The molybdenocene complex **2**,[3] which is labile toward substitution, reacts with formaldehyde or with paraformaldehyde in tetrahydrofuran (THF) to give the formaldehyde complex **1**; the substitution-inert (*E*)-stilbene complex **3** is simultaneously formed by catalytic isomerization of the (*Z*)-stilbene complex **2**.[4]



The reaction of molybdenocene hydride **4** with paraformaldehyde to give **1** is more convenient, affords higher yields, and exhibits practically no side reactions.[5,6] In contrast to the aforementioned carbonylation of the zirconium hydrides, the carbonylation of **4** does *not* lead to a formaldehyde complex.[7]

The spectroscopic data for **1** support a "metallaoxirane" structure with η^2-coordinated formaldehyde. The NMR signals of the H and C atoms of the CH_2O ligands are shifted to higher field relative to those of free CH_2O ($\Delta\delta(^1H)$: 6.57 ppm; $\Delta\delta(^{13}C)$: 149.2 ppm). This can be explained by strong back-bonding from the metal to the π^*-acceptor orbital of the "oxaethene". This bonding model is also in accord with the dramatic frequency shift of the ν_{CO} absorption of the formaldehyde. In the IR spectrum of **1**, in addition to the characteristic band pattern of the $Mo(C_5H_5)_2$ fragment, an intense band at 1155 cm^{-1} is observed which corresponds to the C–O bond.[8] Since the same band appears for $[V(C_5H_5)_2(CH_2O)]$ at 1160 cm^{-1},[1b] the back-bonding in both compounds is apparently of similar strength.



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CAS Registry numbers:
1, 95935-99-2; **2**, 94157-52-5; **3**, 96038-41-4; **4**, 1291-40-3; CH_2O, 50-00-0.

[1] a) W. E. Buhro, A. T. Patton, C. E. Strouse, J. A. Gladysz, F. B. McCormick, M. C. Etter, *J. Am. Chem. Soc. 105* (1983) 1056, and references cited therein. b) S. Gambarotta, C. Floriani, A. Chiesi-Villa, C. Guastini, *ibid. 104* (1982) 2019; c) *ibid. 105* (1983) 1690; K. Kropp, V. Skibbe, G. Erker, C. Krüger, *ibid. 105* (1983) 3353.

[2] *C. Floriani* et al. (Pisa, Italy) have synthesized **1** by a different route and characterized it by X-ray structure determination; C. Floriani, private communication.

[3] G. E. Herberich, J. Okuda, *Chem. Ber. 117* (1984) 3112.

[4] J. Okuda, Dissertation, Technische Hochschule Aachen 1984; the chromatographic workup afforded **1** in 28% yield.

[5] *Experimental procedure:* A solution of **4** (450 mg, 1.97 mmol) in toluene (10 mL) was treated with paraformaldehyde (600 mg, 20 mmol) and the suspension refluxed for 2 h. After removal of the solvent, the residue was chromatographed on an Al_2O_3 column (7% H_2O; $l = 20$ cm, $\varnothing = 2$ cm). Traces of unreacted **4** were eluted with CH_2Cl_2 and **1**, as an orange band, with CH_2Cl_2/THF (3:1 v/v). The crude product was recrystallized from hexane/CH_2Cl_2 (4:1 v/v) at −20°C. Air-sensitive, orange-yellow platelets. Yield 420 mg (83% from **4**). M.p. = 178–179°C (decomp.); sparingly soluble in ether and aliphatic hydrocarbons, soluble in toluene, CH_2Cl_2, and THF. Correct elemental analysis (C, H).—EI-MS (70 eV): *m/z* 258 (14%; M^+), 228 (100%; $MoC_{10}H_{10}^+$).—^{1}H-NMR (60 MHz, CD_2Cl_2): $\delta(CH_2) = 3.03$ (s), $\delta(C_5H_5) = 4.70$ (s).—^{13}C-NMR (67.88 MHz, $CDCl_3$): $\delta(CH_2) = 44.9$ (t, $J(CH) = 167$ Hz), $\delta(C_5H_5) = 86.8$ (d, $J(CH) = 179$ Hz).—IR (KBr, [cm^{-1}]): 1155 vs [ν(CO)]; further bands: 2902 m, 2820 s [$\nu(CH_2)$]; 3090 s, 1414 s, 1028 s, 1000 s, 873 s, 826 s.

[6] For the mechanistic background, see A. Nakamura, *J. Organomet. Chem. 164* (1979) 183.

[7] M. A. Adams, K. Folting, J. C. Huffman, K. G. Caulton, *J. Organomet. Chem. 164* (1979) C29.

[8] ν(CO) of free CH_2O: 1746 cm^{-1}. Reference material: [1].

Synthesis, Dynamic Behavior, and Structure of $[Sn\{C(PMe_2)_3\}_2]$—a Homoleptic Tetraphosphanetin(II) Complex with Pseudo Trigonal Bipyramidal Structure**

By *Hans Heinz Karsch,** *Armin Appelt*, and *Gerhard Müller*

Complexes of main-group elements whose coordination sphere is formed exclusively or predominantly by phosphane ligands are rare, a situation contrasted by the corresponding transition-metal complexes. Recently, however, we were able to obtain phosphane lithium complexes containing *anionic* phosphane ligands, e.g., phosphinomethanides **I** or phosphinomethylaluminates **II**.[1,2] Further examples of such main-group metal complexes were not known.

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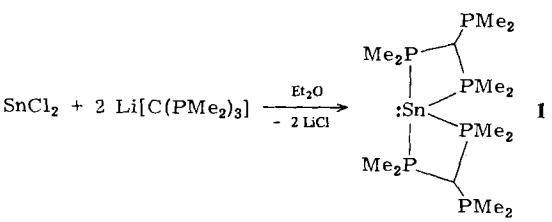
[**] Phosphane complexes of main-group elements, Part 4. This work was supported by the Deutsche Forschungsgemeinschaft. Part 3: [1b].

$[(Me_2P)_nCH_{(3-n)}]^-$ I $[Me_{(4-n)}Al(CH_2PMe_2)_n]^-$ II

In order to determine the extent to which other main-group metals are complexed by anionic phosphane ligands, we have attempted to prepare an Sn^{II} complex of **I**. Sn^{II} was chosen to be a particularly suitable complex center for the following reasons:

- The phosphinomethanide-Sn^{II} system is comparable to the analogous silylmethanide-Sn^{II} system,[3] where coordination occurs via the carbanion.
- Simple, molecular coordination compounds of Sn^{II} are rare.[4]
- Homoleptic, phosphane-Sn^{II} complexes have not yet been isolated;[5] to our knowledge, structural data for molecular P–Sn^{II} compounds are not available.

The reaction of $SnCl_2$ with LiI in diethyl ether leads, only for n = 3, to an isolable Sn^{II} complex, **1**,[6] which is stable at room temperature (84% yield).



The NMR spectra of **1** are in accord with a pseudo trigonal bipyramidal (ψ-tbp) structure if rapid pseudorotation is assumed to occur at −80 °C, which exchanges the atoms in the axial and equatorial positions of the tbp skeleton. Moreover, at room temperature, a further dynamic process becomes apparent: all phosphorus atoms equilibrate ($\Delta G^{\neq}_{20\,°C} = 12.7$ kcal/mol). In this process, however, the $^{119}Sn^{31}P$ coupling persists. Its value at 30 °C corresponds to the weighted average of the low-temperature values. The $\delta^{31}P$ value at 30 °C also corresponds to such an average of the low-temperature values, whereas $\delta^{119}Sn$ is not affected. Therefore, on the basis of the NMR spectroscopic results, a fundamental change in the coordination geometry with changing temperature can be effectively ruled out. The dynamic behavior could be explained by involvement of the carbanion and/or the free phosphino groups in the coordination sphere of tin.

Further information concerning the equilibration process can be obtained by replacement of the phosphino groups in **1** by the $SiMe_3$ group.

$$SnCl_2 + 2\,Li[C(PMe_2)_2SiMe_3] \xrightarrow[-2\,LiCl]{Et_2O} [Sn\{C(PMe_2)_2SiMe_3\}_2]$$

2[7] **3**

The NMR spectra of **3**,[8] which contains two anions of **2** as ligands, at 30 °C correspond to the low-temperature spectra of **1**. Apparently, **3** is not a fluxional system in solution—with the exception of the pseudorotation also assumed in this case. Thus, it is evident that the dynamic behavior of **1** is induced by the non-coordinating phosphino groups, with only a short life-time for the transition state.

An X-ray structure determination[9] shows the presence of a ψ-tbp geometry at Sn^{II} in the crystal (Fig. 1). The Sn^{2+} ion acts as a spiro center of two four-membered rings. Thus, it is coordinated by both P atoms of each bidentate tris(phosphino)methanide ion. One equatorial coordination site of Sn (distorted tbp geometry) is vacant, indicating that the free electron pair of Sn^{II} is probably oriented in this direction. Both the bonding angles at Sn and the axial Sn–P2/P5 bonds, which are markedly longer than the equatorial Sn–P1/P4 bonds, rule out a tetragonal pyramidal Sn coordination. Similar bonding geometries for tetracoordinated Sn^{II} are also induced by ligands with O-donor atoms.[4]

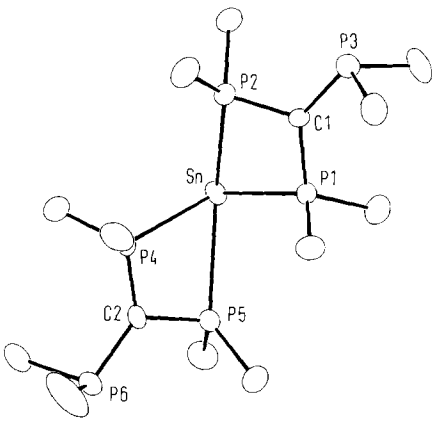


Fig. 1. Molecular structure of **1** (ORTEP, vibration ellipsoids at the 50% probability level, without H atoms). Important bond distances [Å] and bond angles [°]: Sn–P1 2.602(2), Sn–P2 2.790(2), Sn–P4 2.598(2), Sn–P5 2.839(2), C1–P1 1.733(6), C1–P2 1.754(6), C1–P3 1.792(6), C2–P4 1.735(6), C2–P5 1.765(6), C2–P6 1.791(6), Sn–C1 3.265(4), Sn–C2 3.313(4); P1–Sn–P2 62.9(1), P4–Sn–P5 62.8(1), P2–Sn–P4 95.1(1), P1–Sn–P4 105.9(1), P2–Sn–P5 142.5(1); sum of valence angles at C1/C2 359.7/360.0.

Formally, five non-bonding electron pairs (at Sn, C1, C2, P3, P6) have to be taken into consideration in **1**. Interaction between these electron pairs is apparently minimal in the arrangement found.

Thus, **1**—along with LiI[2]—is another structurally characterized main-group metal complex of the tris(dimethylphosphino)methanide ion. In contrast to LiI, the coordination of the ligands in **1** occurs exclusively via the P atoms. In this case, the exactly planar-coordinated carbanionoid centers C1 and C2 surprisingly are not used for coordination. An interaction with the Sn center is observed neither in an intramolecular nor in an intermolecular fashion.

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CAS Registry numbers:
1, 96129-03-2; $SnCl_2$, 7772-99-8; $Li[C(PMe_2)_3]$, 70377-69-4.

[1] a) H. H. Karsch, A. Appelt, G. Müller, *J. Chem. Soc. Chem. Commun. 1984*, 1415; b) *Organometallics*, in press.
[2] a) H. H. Karsch, G. Müller, *J. Chem. Soc. Chem. Commun. 1984*, 569; b) H. H. Karsch, L. Weber, D. Wewers, R. Boese, G. Müller, *Z. Naturforsch. B 39* (1984) 1518.
[3] P. J. Davidson, D. H. Harris, M. F. Lappert, *J. Chem. Soc. Dalton Trans. 1976*, 2268.
[4] a) M. Veith, O. Recktenwald, *Top. Curr. Chem. 104* (1982) 1; b) V. I. Shiryaev, Y. F. Mironov, *Russ. Chem. Rev. 52* (1983) 184.
[5] a) Starting from $Sn(SbF_6)_2$ and tertiary bis- and trisphosphanes, $[(phosphane)_xSn]^{2+}$ complexes (x = 3, 4?) having in part unknown structures (NMR) are formed in nitromethane: P. A. W. Dean, D. D. Phillips, L. Polensak, *Can. J. Chem. 59* (1981) 50; P. A. W. Dean, *ibid. 61* (1983) 1795; b) there are four examples of adducts of the type R_3PSnX_2 (X = Cl, Br; R = *t*Bu, NMe_2): W.-W. du Mont, B. Neudert, *Z. Anorg. Allg. Chem. 441* (1978) 86; c) dimeric tin(II)bisphosphide $[(tBu_2P)_2Sn]_2$ with threefold Sn–P coordination: W.-W. du Mont, H.-J. Kroth, *Angew. Chem. 89* (1977) 832; *Angew. Chem. Int. Ed. Engl. 16* (1977) 792.
[6] Yellow, air-sensitive crystals (pentane), decomp. >69 °C; EI-MS (20 °C): *m/z* 510 (^{120}Sn: M^+).—$^{31}P\{^1H\}$-NMR ($C_6D_5CD_3$, −80 °C): A_4X_2 ($A_2A'_2XX'$); $\delta P(A) = -17.2$ ("t", $J = 13.7$ Hz); $\delta P(X) = 41.5$ ("quin", $J = 13.7$ Hz).—(+30 °C): $\delta P = -25.4$(s).—^{119}Sn-NMR ($C_6D_5CD_3$):

$-80°C$: $\delta Sn = -258.0$ (quin, t, $J = 776$, 102 Hz). — $+30°C$: -258.9 (sept, $J = 551$ Hz).

[7] H. H. Karsch, A. Appelt, unpublished.

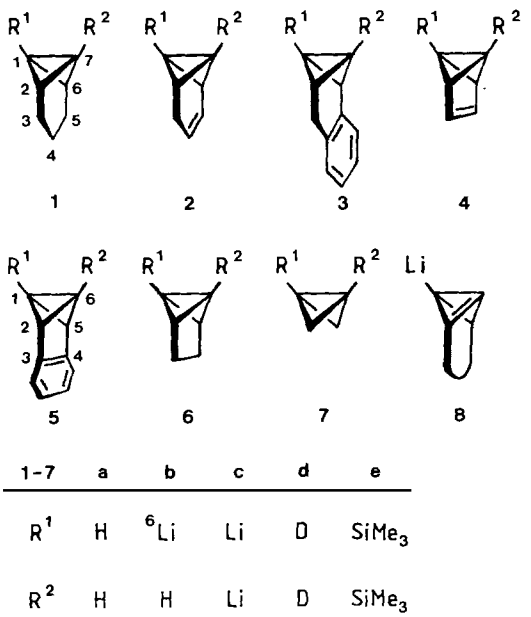
[8] Yellow, air-sensitive crystals (pentane), m.p. = 93–94°C. — NMR ($C_6D_5CD_3$, 30°C): $\delta^{31}P = -22.7$ (s); $\delta^{119}Sn = -175.4$ (quin, $J = 737$ Hz). — ($-30°C$): no significant change.

[9] $C_{14}H_{36}P_6Sn$, $M = 508.98$, $P2_1$; $a = 6.540(2)$, $b = 16.338(6)$, $c = 11.720(4)$ Å, $\beta = 98.15(3)°$, $V = 1239.64$ Å^3, $\rho_{(calcd.)} = 1.363$ g/cm^3 for $Z = 2$ at $T = -35°C$. 4327 independent reflections of which 162 are unobserved ($I < 2.0\sigma(I)$), $+h$, $+k$, $\pm l$, and Friedel reflections, $(\sin\vartheta/\lambda)_{max.} = 0.593$ Å^{-1}, $F(000) = 520$, $Mo_{K\alpha}$-radiation, $\lambda = 0.71069$ Å, ω-scans, Syntex $P2_1$). Empirical absorption correction ($\mu(Mo_{K\alpha}) = 14.11$ cm^{-1}), based on ψ-scans of six reflections; Patterson methods; $R = 0.038$, $R_w = 0.043$, $w = k/\sigma^2(F_0)$, $k = 1.72$ in the last cycle (non-H-atoms anisotropic, H-atoms constant, 189 parameters, 1 block, SHELX 76); $\Delta\rho_{(fin.)} = +1.69/-2.09$ e/Å^3. Further details of the crystal structure investigation are available on request from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2, on quoting the depository number CSD 51 179, the names of the authors, and the journal citation.

On the Aggregation of Lithiated Bicyclobutane Derivatives in Solution**

By *Arnulf-Dieter Schlüter,* Helmut Huber,* and *Günter Szeimies*

The degree of aggregation of organolithium compounds in solution can easily be established by determination of the ^{13}C-^6Li-NMR coupling pattern.[1] *Fraenkel* et al.[2a] and *Seebach* et al.,[2b] in particular, obtained a wealth of information about the structure of monolithiated compounds from low-temperature ^{13}C-NMR spectra. We report here on the aggregation behavior of the mono- and dilithiated bicyclobutane derivatives **1b**—**4b** and **5c**, respectively, in tetrahydrofuran (THF).[3] **5c**, like the still controversial 1,2-dilithioethane,[4] is a saturated, vicinally dilithiated hydrocarbon.



The bicyclobutanes **1a**—**4a** were lithiated at C-1 with one molar equivalent of *n*Bu^{6}Li[2b] in ether at 20°C. After removal of the solvent,[5] a ca. 3 M solution of the "anion" in THF/[D$_6$]benzene was prepared with the oily or powdery residue. The appearance of a coupling fine structure was observed in the low-temperature ^{13}C-NMR spectrum beginning at $-45°C$; baseline-separated multiplets were observed throughout the spectrum at $-60°C$. In all cases a quintet with the intensity distribution 1 : 2 : 3 : 2 : 1 and a ^{13}C-^6Li coupling constant of ca. 10 Hz was obtained for the signal of the ^6Li-bearing C-atom (**1b**: 10.1; **2b**: 10.3;[6] **3b**: 9.4, **4b**: 9.6; error: ±0.6 Hz). As shown in Figure 1a by the C-1 signal of **4b** obtained by accumulation of only 300 pulses a good signal-to-noise ratio can be achieved with natural carbon isotope distribution.

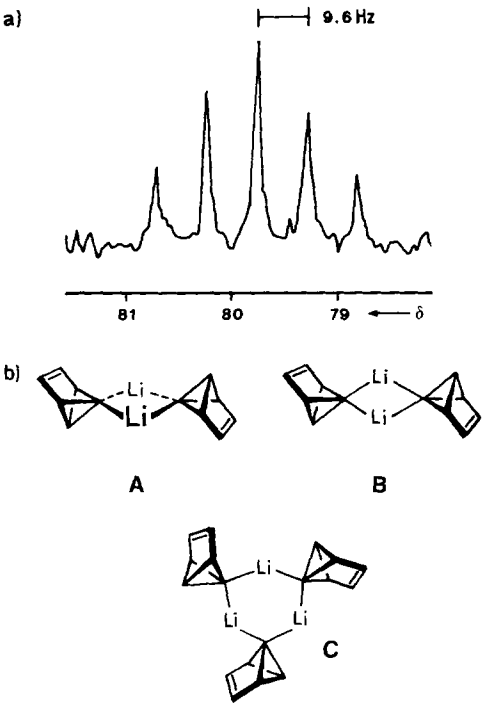


Fig. 1. a) The C-1 signal of [^{6}Li]1-lithiobenzvalene **4b** in the ^{13}C-NMR spectrum at $-76°C$ after 300 pulses; ca. 3 M in THF. b) Some of the aggregations consistent with the coupling pattern. Structure **B** is favored.

7b is present as dimer, both in the solid state[7] and in solution.[2b] On the basis of the NMR data it is also reasonable to assume dimeric structures like A or B in Figure 1b for **1b**—**4b**. But trimers of type C (Fig. 1b) or oligomers with large rings cannot be ruled out. It is remarkable that all bridgehead lithiated bicyclobutane models examined so far prefer the same degree of aggregation.

We next attempted to lithiate bicyclobutanes at both bridgehead positions[8] and to obtain information about the state of aggregation of the products. The elimination of lithium hydride from 1,ω-dilithioalkanes ($\omega = 1 - n$),[9] an unsolved problem in the synthesis of 1,2-dilithioethane,[10] should not occur in the case of the doubly metalated bicyclobutane since highly strained olefins of type **8** would be formed by loss of LiH. Indeed, the hydrocarbons **1a**—**6a** could be metalated at both bridgeheads to give the "dianions" **1c**—**6c**, in each case with 2.0 molar equivalents of *n*BuLi in ether at 20°C.[11] The work-up of the suspensions thus formed with deuterium oxide and chloro(trimethyl)silane, respectively, led to **1d**—**6d** or to **1e**—**6e**. The data listed in Table 1 show that high degrees of lithiation were obtained in a short time with those bicyclobutanes which carry sp^2-hybridized carbon atoms in the *endo-,endo*-annelated bridges and/or have small angles between the three-membered ring faces of the bicyclobutane moiety.

The ^1H- and particularly the ^{13}C-NMR spectra of the "dianions"[13] show unusually broad, unstructured bands.

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Table 1. Degree of double deuteration [12] and silylation of the bicyclobutanes **1a**–**6a** as a measure of the lithiability of the two bridgeheads with 2.0 mole equivalents of *n*BuLi in ether at 20°C.

Educt	Degree of dideuteration [%] [a]	Degree of silylation [%] [b]	*t*
1a	15	15	3 d
2a	95	30	3 d
3a	100	55	1 d
4a	– [c]	21 [d]	2 h
5a	100	70	1 h
6a	95	53	3 d

[a] ^{1}H-NMR spectroscopically. [b] Determined on the isolated product. [c] The proportion of **4d** could not be determined because of signal overlapping. [d] In competition with the second metalation, **4b** rearranges to phenyllithium.

Only in the case of **5c** was it possible to assign all the signals.[14] The cause of the drastic line-broadening is, in our opinion, the intermolecular cross-linking. Greater contributions to the widths at half height ($W_{1/2}$) by dynamic effects or by spin-spin coupling are unlikely. Thus, the $W_{1/2}$ values[14] change neither with variation of temperature (−50°C to +70°C) or concentration (0.4 to 2.2 M) nor with the use of the ^{6}Li isotope. A deaggregation of the cross-linked structures by addition of up to ten molar equivalents of various donors to solutions of **5c** in THF or ether was not accomplished.[15] **5c** can be stored for several days at room temperature in solution without change.

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[1] L. D. McKeever, R. Waack, M. A. Doran, E. B. Baker, *J. Am. Chem. Soc. 90* (1968) 3244; S. Bywater, P. Lachance, D. J. Worsfold, *J. Phys. Chem. 79* (1975) 2148; F. Wehrli, *J. Magn. Reson. 30* (1978) 193.

[2] a) G. Fraenkel, P. Pramanik, *J. Chem. Soc. Chem. Commun. 1983*, 1527, and references cited therein; b) D. Seebach, R. Hässig, J. Gabriel, *Helv. Chim. Acta 66* (1983) 308, and references cited therein.

[3] For the association behavior of organolithium compounds see, e.g.: T. L. Brown, *Pure Appl. Chem. 23* (1970) 447; J. P. Oliver, *Adv. Organomet. Chem. 15* (1977) 235; J. L. Wardell in G. Wilkinson, F. G. A. Stone, E. W. Abel: *Comprehensive Organometallic Chemistry, Vol. 1*, Pergamon Press, Oxford 1982, p. 43.

[4] 1,2-Dilithioethane is assumed as intermediate: V. Rautenstrauch, *Angew. Chem. 87* (1975) 254; *Angew. Chem. Int. Ed. Engl. 14* (1975) 259. It seems to us that the synthesis of 1,2-dilithioethane from lithium and ethylene (yield 27–30%) or from lithium and 1,2-dihaloethane (yield 6–9%) is not confirmed: H. Kuus, *Uch. Zap. Tartu. Gos. Univ. 193* (1966) 130 (*Chem. Abstr. 69* (1968) 67443q); *Tartu Riikliku Ulik. Toim. 219* (1968) 245 (*Chem. Abstr. 71* (1969) 49155j).

[5] DANGER: Undissolved **4b** has a tendency to decompose explosively!

[6] We obtained no evidence of a diastereomeric mixture.

[7] R. P. Zerger, G. D. Stucky, *J. Chem. Soc. Chem. Commun. 1973*, 44.

[8] **3c** has already been detected: I. Murata, T. Nakazawa, M. Kato, T. Tatsuoka, Y. Sugihara, *Tetrahedron Lett. 1975*, 1647.

[9] See, e.g.: J. W. Seetz, G. Schat, O. S. Akkerman, F. Bickelhaupt, *J. Am. Chem. Soc. 104* (1982) 6848; P. von R. Schleyer, A. J. Kos, E. Kaufmann, *ibid. 105* (1983) 7617.

[10] B. Bogdanović, B. Wermeckes, *Angew. Chem. 93* (1981) 691; *Angew. Chem. Int. Ed. Engl. 20* (1981) 684.

[11] According to *Streitwieser*'s "Ion-Triplet Model", directly adjacent dianionic charges are well stabilized by two monovalent cations: A. Streitwieser, Jr., *Acc. Chem. Res. 17* (1984) 353.

[12] We found that deuterolysis does not always suffice for the quantitative detection of bicyclobutane dianions. When **5a** is treated with more than two mole equivalents of *n*BuLi at −30°C in ether, according to the ^{1}H-NMR spectrum, **5b** is formed quantitatively with no **5c** present. Nevertheless, after addition of this mixture to tenfold excess deuterium oxide, up to 60% **5d** is obtained.

[13] Prepared with exactly (!) 2.0 mole equivalents of *n*BuLi.

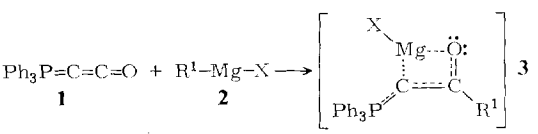
[14] ^{1}H-NMR ([D$_8$]THF; $W_{1/2}$ values (±15%) in Hz (in brackets); standard: TMS int.): $\delta = 0.59$ (28; 2H, 2-H, 5-H), 5.94 (22; 4H, aromat. H); ^{13}C-NMR (ether/[D$_6$]benzene): δ (±1 ppm) = 43 (130; C-2; C-5), 84 (> 190; C-1; C-6), 116, 122 (30; aromat. C); 158 (50; C-3; C-4).

[15] Bis(dimethylamino)ethane, [12]crown-4, hexamethylphosphoric acid triamide (−60°C), *n*BuLi/potassium *tert*-butoxide, and dimethoxyethane.

Chain-Lengthening Difunctionalization of Grignard Compounds by Reaction with Ketenylidenetriphenylphosphorane

By *Hans Jürgen Bestmann,* Martin Schmidt,* and *Rainer Schobert*

The readily accessible ketenylidenetriphenylphosphorane **1**[1] reacts with Grignard reagents **2** to give addition compounds of still unknown structure. Such adducts, which are best formulated as in **3**, are hydrolyzed by water to acyl ylides **4**. This reaction sequence thus enables a chain-lengthening of **2** by two C atoms with concomitant introduction of a carbonyl function and an ylide function with CC coupling. Together with the secondary reactions (carbonyl olefination and saponification) a possibility is thus opened up for the acylation of Grignard compounds, i.e. for the conversion of Grignard compounds into various kinds of ketones.[2] Table 1 shows that this new methodology can be exploited for the synthesis of a wide spectrum of ylides **4**.[3]



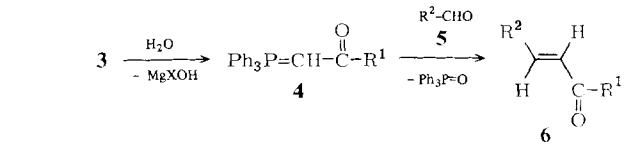


Table 1. Yields and melting points of the acyl ylides **4** obtained by reaction of **1** with **2** and subsequent hydrolysis.

4	R^1	Yield [%]	M.p. [°C]
a	C_2H_5	94	222 (221–222 [4])
b	*n*-C_4H_9	85	oil
c	$CH(CH_3)-(CH_2)_2-CH_3$	77	oil
d	$(CH_2)_{10}$–O-tetrahydro-1-pyranyl	65	oil
e	$(CH_2)_9$–O-tetrahydro-1-pyranyl	61	oil
f	$(CH_2)_5$-1,3-dioxolan-2-yl	60	oil
g	$C(CH_3)=CH_2$	86	148
h	C_6H_5	65	178 (178 [5])

Compounds **4**, which are usually recovered as oils and can be readily purified by chromatography, show all the typical, strongly shifted carbonyl bands for acyl ylides be-

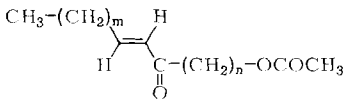
Table 2. Yields and boiling points of the ketones **6** obtained by reaction of **4** with **5**. R^1, see Table 1.

6	R^2	Yield [%][a]	B.p. [°C/torr]
b	CH_3	54	68– 70/13 (65.5–66/10 [8])
c	C_6H_5	52	99–101/0.13
d	C_2H_5	42	136–140/0.01
e	*n*-C_4H_9	38	122–126/0.05 [b]
g	*n*-C_7H_{15}	36	69– 71/0.01
h	(*E*)-$CH=CH-(CH_2)_2-CH_3$	48	124–126/0.3

[a] Referred to **4**, not optimized. [b] Kugelrohr distillation, bath temperature.

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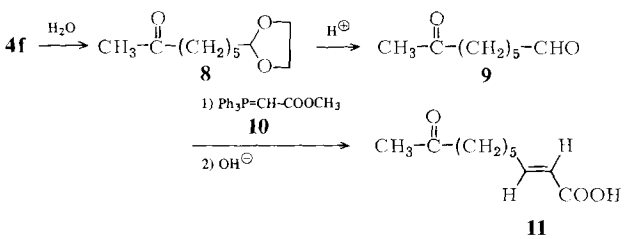
tween 1510 and 1530 cm^{-1} in their IR spectra.[6,7] For further characterization, a Wittig reaction was carried out with aldehydes **5** to give (*E*)-α,β-unsaturated ketones **6**.[6] Table 2 lists some examples.[7]



7d: m = 1, n = 10; **7e**: m = 3, n = 9

Reaction of compounds **6d** and **6e** with acetyl chloride in glacial acetic acid[9] furnished the corresponding acetates **7** in ca. 80% yield. They are carbonyl homologues of lepidoptera pheromones,[10] which are of special interest for structure-activity investigations (**7d**, **7e**: b.p. (Kugelrohr) 105–108°C/0.01 torr and 120–123°C/0.01 torr, respectively).

Hydrolysis[5] of **4f** afforded the acetal **8** (62% yield, b.p. (Kugelrohr) 120–123°C/13 torr), which after treatment with acid to give the free 7-oxooctanal **9**[11] was allowed to react with the ylide **10**. Subsequent saponification led to formation of the queen substance **11** (57% yield based on **8**, m.p. 52°C), which is thus relatively easily accessible.[12]



11

Experimental

General procedure: **4**: A Grignard solution was prepared from magnesium turnings (0.97 g, 40 mmol) and 40 mmol alkyl halide (preferably bromide) in anhydrous tetrahydrofuran (THF) (final volume 150 mL). The boiling solution was treated dropwise over a period of 8–10 h with a solution of **1** (9.06 g, 30 mmol) in THF (150 mL) under N_2; the final mixture was then boiled under reflux for a further 2 h (in the case of **4g**: reaction temperature 40°C, addition over a period of 4 h, then stirring for 2 h at 40°C).—After cooling, the reaction mixture was poured into 60 mL of saturated ammonium chloride solution, the aqueous phase separated off, and the solvent removed from the organic phase. The residue was partitioned between 150 mL each of dichloromethane and water; the aqueous phase was extracted with dichloromethane, and the combined organic extracts were washed with a little water. After drying over magnesium sulfate, the solvent was removed by distillation and the residue was either recrystallized from ethyl acetate by addition of ether or chromatographed on silica gel 60 [column height 20 cm, diameter 4 cm; hydrocarbon impurities were first eluted with hexane/ether (3 : 1) and then **4** was eluted with ether/dichloromethane (1 : 1)].

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[1] H. J. Bestmann, D. Sandmeier, *Chem. Ber. 113* (1980) 274; Review: H. J. Bestmann, *Angew. Chem. 89* (1977) 361; *Angew. Chem. Int. Ed. Engl. 16* (1977) 349.

[2] For further methods for the conversion of **2** into ketones cf. A. S. Kende, D. Scholz, J. Schneider, *Synth. Commun. 8* (1978) 59; K. Utimoto, Y. Wakabayashi, Y. Shishiyama, M. Inoue, H. Nozaki, *Tetrahedron Lett. 22* (1981) 4279.

[3] For further methods for the synthesis of acyl ylides and their reactions cf. H. J. Bestmann, *Angew. Chem. 77* (1965) 651; *Angew. Chem. Int. Ed. Engl. 4* (1965) 645; H. J. Bestmann, R. Zimmermann, *Fortschr. Chem. Forsch. 20* (1971) 1.

[4] A. Fujiwara, H. Takahashi, M. Ohta, *Bull. Chem. Soc. Jpn. 35* (1962) 2042.

[5] H. J. Bestmann, B. Arnason, *Chem. Ber. 95* (1962) 1513.

[6] For the stereochemistry of the Wittig reaction cf. H. J. Bestmann, *Pure Appl. Chem. 52* (1980) 771.

[7] All the new compounds gave correct elemental analyses ^{1}H-NMR, ^{31}P-NMR, and mass spectra.

[8] R. Luft, *Ann. Chim. 4* (1959) 745.

[9] M. Schwarz, R. W. Waters, *Synthesis 1972*, 567.

[10] Review: H. J. Bestmann, O. Vostrowsky, *Chem. Phys. Lipids 24* (1979) 335.

[11] M. Barbier, M. F. Hügel, *Bull. Soc. Chim. Fr. 1961* 1, 951.

[12] For further syntheses cf. H. J. Bestmann, R. Kunstmann, H. Schulz, *Justus Liebigs Ann. Chem. 699* (1966) 33; T. Fujisawa, T. Sato, T. Itoh, *Chem. Lett. 1982*, 219.

Synthesis and Structure of *trans*-[MCl(=C=CHR)(P*i*Pr$_3$)$_2$] (M = Rh, Ir): The First Square-Planar Vinylidenemetal Complexes**

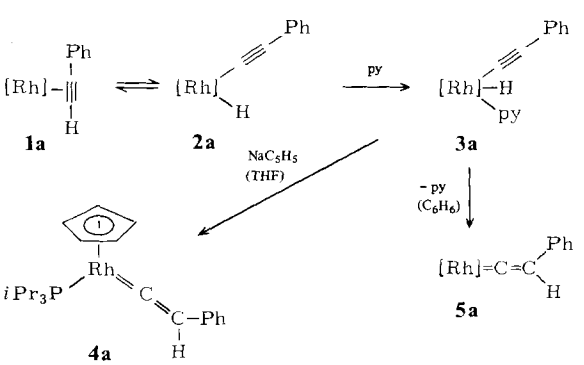
By *Francisco Javier García Alonso, Arthur Höhn, Justin Wolf, Heiko Otto,* and *Helmut Werner**

Dedicated to Professor F. G. A. Stone on the occasion of his 60th birthday

Vinylidenes :C=CRR′, like carbenes :CRR′ or other highly reactive organic molecules, can be stabilized in the coordination sphere of a transition metal. However, mononuclear square-planar vinylidenemetal complexes are, as yet, unknown. Although it has been repeatedly postulated that they are formed as intermediates in reactions of d^8 compounds, e.g., of rhodium(I) with alkynes,[1] their existence has not been proved.

Recently, we have shown that an equilibrium between the alkyne complex **1a** and the alkynyl(hydrido) compound **2a** exists in solution, and that on addition of pyridine this equilibrium is completely shifted to the right.[2] Complex **3a**, which gives **4a** on reaction with NaC_5H_5 in tetrahydrofuran (THF),[2] is rather labile in solution and reacts in benzene at room temperature by elimination of pyridine to produce **5a**. This compound is also obtained almost quantitatively directly from **1a**, presumably via **2a** as intermediate.[3a] Similarly, the synthesis of **5b** and **5c**[3b] has been achieved by the use of **1b** and **1c** as starting materials.[4]

Reaction of **1b** with pyridine gives the octahedral compound **3b**, the properties of which[5] closely correspond to those of **3a**. When R = H or Me, no five-coordinate intermediate of type **2** can be detected by NMR spectroscopy.



[Rh] = RhCl(P*i*Pr$_3$)$_2$

trans-[RhCl(RC≡CH)(PR′$_3$)$_2$] ⟶ *trans*-[RhCl(=C=CHR)(PR′$_3$)$_2$]

1a–c **5a–c**

a: R = Ph; **b**: R = Me; **c**: R = H; R′ = *i*Pr

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Apparently, in this case, the equilibrium between the alkyne and the alkynyl(hydrido) complex, which has been confirmed for **1a** ⇌ **2a**,[2] is strongly shifted to the side of the alkyne complex **1b**, **c**.

The composition of compounds **5a**–**c**, which are dark red solids (stable in air for a short period), has been confirmed by elemental analysis and mass spectra and by IR and NMR data.[3] The position of the ^{13}C-NMR signal of C_α of the vinylidene ligand seems to be most characteristic; it is observed in the same region (δ ca. 300 ppm) as the ^{13}C-NMR signal of a metal-bound carbene C atom.[6]

Figure 1 shows the result of the X-ray structure analysis of **5b**.[7] The metal is coordinated in a square-planar arrangement with the phosphanes in *trans* positions. The Rh–C1–C2 linkage is almost linear; together with C3 it forms a plane that is perpendicular (angle 88.39°) to the best plane containing the atoms Rh, P1, P2, Cl, C1, and C2. This structural feature is in agreement with the formation of a $d_\pi p_\pi$ bond between Rh and C1 and points to the formal analogy between allenes and vinylidenemetal complexes (i.e., "metallaallenes").[8] The Rh–C1 distance is similar to that in **4a**[2] and comparable with the Rh–C bond length in square-planar carbonylrhodium(I) compounds (e.g., $[Rh(CO)_2Cl]_2$: Rh–C = 181 pm (average value)[9]). The proposal that vinylidenes are excellent π-acceptor ligands[1] is thus amply confirmed.

We have also been successful in preparing the iridium complexes **8a**–**c** in 80–90% yield.[10] The alkynemetal compounds **6a**–**c**[11] react much more slowly than the rhodium compounds **1a**–**c**, and for **6a**, **b** the reaction is complete only after 36 h at 100°C (in toluene). In the reaction of **6a**, it has been possible to isolate a five-coordinate intermediate **7a**,[12] which is strikingly different from isomers **6a** and **8a**, particularly in its spectroscopic properties. *Thus, it has been proved for the first time that the conversion $M(\eta^2\text{-}RC_2H) \rightarrow M(=C=CHR)$ proceeds in two steps via the intermediate $MH(C_2R)$, which is formed by intramolecular oxidative addition of the alkyne to the metal.* The rearrangement of the cluster $RuCo_2(CO)_9(\mu_3\text{-}\eta^2\text{-}HCC\mathit{t}Bu)$ to give the isomer $RuCo_2(CO)_9(\mu_3\text{-}\eta^2\text{-}CCH\mathit{t}Bu)$ probably follows a similar route.[13]

8a–**c** are to the best of our knowledge the first vinylidene*iridium* complexes. Some properties of the violet (**8a**) or red (**8b**, **c**) crystalline solids deserve particular mention.

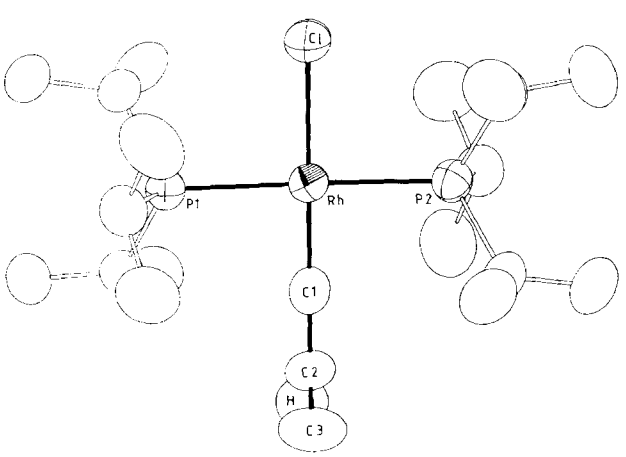
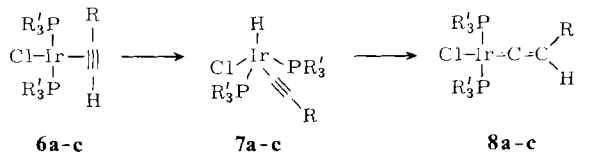


Fig. 1. Crystal structure of **5b** [7]. Selected bond lengths [pm] and angles [°]: Rh–P1 234.4(2), Rh–P2 234.2(2), Rh–Cl 236.6(2), Rh–C1 177.5(6), C1–C2 132(1), C2–C3 150(1), C2–H 107; P1–Rh–P2 173.9(1), Cl–Rh–C1 175.8(2), P1–Rh–Cl 91.9(1), P1–Rh–C1 88.2(2), P2–Rh–Cl 91.2(1), P2–Rh–C1 89.1(2), Rh–C1–C2 177.9(6), C1–C2–C3 126.2(7), C1–C2–H 124, C3–C2–H 110.



6a-c **7a-c** **8a-c**

a: R = Ph; **b**: R = Me; **c**: R = H; R' = *i*Pr

These are first the thermal stability and the inertness towards air, and secondly the unusual high-field shift of the signal of the C*H*R and CH_2 vinylidene protons in the ^{1}H-NMR spectra.[10]

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CAS Registry numbers:
1a, 85452-93-3; **1b**, 95935-77-6; **1c**, 96038-38-9; **3a**, 85452-95-5; **3b**, 95935-78-7; **5a**, 95935-79-8; **5b**, 95935-80-1; **5c**, 95935-81-2; **6a**, 93240-02-9; **6b**, 95935-82-3; **6c**, 93239-99-7; **7a**, 93240-03-0; **7b**, 95935-83-4; **7c**, 95978-16-8; **8a**, 95935-84-5; **8b**, 95935-85-6; **8c**, 95935-86-7.

[1] M. I. Bruce, A. G. Swincer, *Adv. Organomet. Chem. 22* (1983) 60.
[2] J. Wolf, H. Werner, O. Serhadli, M. L. Ziegler, *Angew. Chem. 95* (1983) 428; *Angew. Chem. Int. Ed. Engl. 22* (1983) 414.
[3] a) **5a** is prepared by stirring a solution of 280 mg (0.50 mmol) of **1a** in 20 mL of hexane at 50°C for 2 h. After evaporation of the solvent and recrystallization from THF/pentane (1:3) at 25 to −78°C, dark red crystals are obtained, m.p. = 143°C (decomp.); yield 80%; correct C, H, Rh analysis. **5b** and **5c** were prepared similarly from **1b** and **1c**; yield 85% (**5b**), 86% (**5c**).—b) **5a**: M_r = 560 (MS); IR (nujol): ν(C=C) = 1620 cm^{-1}; ^{1}H-NMR (C_6D_6): δ = 1.26 (dvt, J_{HH} = 7.0, N = 13.5 Hz, PCHCH_3), 2.70 (m, PCH), 7.16 (m, C_6H_5), =CHPh masked by the PCHCH_3 signal: ^{13}C-NMR ($CDCl_3$): δ = 20.3 (s, PCHCH_3), 23.8 (vt, N = 19.2 Hz, PCH), 111.7 (dt, J_{RhC} = 13.9, J_{PC} = 7.0 Hz, C_β), 295.2 (dt, J_{RhC} = 58.7, J_{PC} = 16.3 Hz, C_α).—**5b**: m.p. = 126°C (decomp.); M_r = 498 (MS); IR (KBr): ν(C=C) = 1670 cm^{-1}; ^{1}H-NMR (C_6D_6): δ = 1.30 (dvt, J_{HH} = 7.0, N = 14.0 Hz, PCHCH_3), 2.07 (dt, J_{HH} = 7.4, J_{PH} = 2.2 Hz, =CHCH_3), 2.72 (m, PCH), =CHMe masked by the PCHCH_3 signal; ^{13}C-NMR (C_6D_6): δ = 1.6 (s, =CHCH_3), 20.2 (s, PCHCH_3), 23.3 (vt, N = 18.9 Hz, PCH), 98.5 (dt, J_{RhC} = 15.5, J_{PC} = 6.1 Hz, C_β), 292.1 (dt, J_{RhC} = 55.5, J_{PC} = 16.3 Hz, C_α).—**5c**: m.p. = 145°C (decomp.); M_r = 484 (MS); IR (KBr): ν(C=C) = 1620 cm^{-1}; ^{1}H-NMR (C_6D_6): δ = −0.05 (dt, J_{RhH} = 0.8, J_{PH} = 3.3 Hz, =CH_2), 1.40 (dvt, J_{HH} = 7.0, N = 14.0 Hz, PCHCH_3), 2.90 (m, PCH); ^{13}C-NMR (C_6D_6): δ = 20.2 (s, PCHCH_3), 23.4 (vt, N = 20.1 Hz, PCH), 89.2 (dt, J_{RhC} = 16.3, J_{PC} = 5.3 Hz, C_β), 290.6 (dt, J_{RhC} = 56.5, J_{PC} = 15.6 Hz, C_α).
[4] **1b** und **1c** are prepared analogously to **1a** [2] and the compounds *trans*-$[RhCl(C_2R_2)(PiPr_3)_2]$ (R = Me, Ph); see H. Werner, J. Wolf, U. Schubert, K. Ackermann, *J. Organomet. Chem. 243* (1983) C63.
[5] **3b** is prepared similarly to **3a** in pentane as solvent. Colorless air-sensitive crystals, m.p. = 87°C (decomp.); yield 45%; correct C,H,N,Rh analysis; IR (KBr): ν(RhH) = 2180, ν(C≡C) = 2120 cm^{-1}; ^{1}H-NMR ($CDCl_3$, −30°C): δ = −17.95 (dt, J_{RhH} = J_{PH} = 14.0 Hz, RhH), 1.06 and 1.15 (dvt, J_{HH} = 7.0, N = 14.0 Hz, PCHCH_3, two signals due to diastereotopy), 1.88 (s, C_2CH_3), 2.76 (m, PCH), 7.24 (m, NC_5H_5); ^{31}P-NMR (C_6D_6): δ = 35.62 (d, J_{RhP} = 98.3 Hz).
[6] G. M. Bodner, S. B. Kahl, K. Bork, B. N. Storhoff, J. E. Wuller, L. J. Todd, *Inorg. Chem. 12* (1973) 1071.
[7] Monoclinic, space group $P2_1/a$, Z = 4; a = 1508.1(4), b = 1099.4(5), c = 1618.4(5) pm, β = 104.15(2)°, V = 2602 · 10^6 pm^3; $\rho_{calcd.}$ = 1.27 g/cm^3, $\rho_{exp.}$ = 1.29 g/cm^3; 5° ≤ 2θ ≤ 45° ($Mo_{K\alpha}$, λ = 71.069 pm, ω-scan); 3393 independent reflections, Lorentz and polarization corrections, Patterson method (Syntex XTL), positions of the hydrogen atoms from difference Fourier syntheses; R_1 = 0.040, R_2 = 0.051 for 3151 structure factors ($F_0 \geq 3.92\sigma(F_0)$). Further details of the crystal structure analysis are available on request from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2, on quoting the depository number CSD 51207, the names of the authors, and the journal citation.
[8] H. Werner, J. Wolf, G. Müller, C. Krüger, *Angew. Chem. 96* (1984) 421; *Angew. Chem. Int. Ed. Engl. 23* (1984) 431.
[9] L. F. Dahl, C. Martell, D. L. Wampler, *J. Am. Chem. Soc. 83* (1961) 1761.
[10] **8a**: m.p. = 162°C (decomp.); M_r = 650 (MS); IR (KBr): ν(C=C) = 1630 cm^{-1}; ^{1}H-NMR (C_6D_6): δ = −2.80 (t, J_{PH} = 2.7 Hz, =CHPh), 1.27 (dvt, J_{HH} = 6.9, N = 13.6 Hz, PCHCH_3), 2.89 (m, PCH), 7.22 (m, C_6H_5); ^{13}C-NMR (C_6D_6): δ = 20.20 (s, PCHCH_3), 23.27 (vt, N = 13.2 Hz, PCH), 110.67 ("s", J_{PC} < 5 Hz, C_β), 261.92 (t, J_{PC} = 12.4 Hz, C_α).—**8b**:

m.p. = 119 °C (decomp.); M_r = 588 (MS); IR (KBr): ν(C=C) = 1670 cm^{-1}; ^{1}H-NMR (C_6D_6): δ = −3.97 (tq, J_{PH} = 2.8, J_{HH} = 7.1 Hz, =C*H*Me), 1.30 (dvt, J_{HH} = 7.0, N = 13.4 Hz, PCHCH_3), 2.33 (dt, J_{PH} = 2.2, J_{HH} = 7.1 Hz, =CHCH_3), 2.92 (m, PC*H*); ^{13}C-NMR (C_6D_6): δ = −9.64 (s, =CHCH_3), 20.02 (s, PCHCH_3), 22.69 (vt, N = 11.8 Hz, PCH), 96.93 ("s", J_{PC} < 5 Hz, C_β), 260.04 (t, J_{PC} ≈ 13.6 Hz, C_α).—**8c**: m.p. = 165 °C (decomp.); M_r = 574 (MS); IR (KBr): ν(C=C) = 1640 cm^{-1}; ^{1}H-NMR (C_6D_6): δ = −4.23 (t, J_{PH} = 2.9 Hz, =CH_2), 1.29 (dvt, J_{HH} = 7.2, N = 13.9 Hz, PCHCH_3), 3.00 (m, PC*H*); ^{13}C-NMR (C_6D_6): δ = 19.91 (s, PCHCH_3), 22.63 (vt, N = 13.3 Hz, PCH), 87.34 ("s", J_{PC} < 5 Hz, C_β), 257.63 (t, J_{PC} = 12.4 Hz, C_α); ^{31}P-NMR (C_6D_6): δ = 30.96 (s).

[11] For preparation of **6a**, **c** see H. Werner, A. Höhn, *J. Organomet. Chem. 272* (1984) 105; **6b** is prepared similarly; bright yellow crystals, m.p. = 104 °C (decomp.); IR (KBr): ν(C≡C) = 1930 cm^{-1}.

[12] **7a** is prepared by dissolving **6a** in pentane at −10 °C and purified by recrystallization from pentane (25 to −78 °C). Red crystals, air-stable for a short time; m.p. = 130 °C; yield 95%; M_r = 650 (MS); IR (KBr): ν(C≡C) = 2090, ν(IrH) = 1926 cm^{-1}; ^{1}H-NMR (C_6D_6): δ = −43.25 (t, J_{PH} = 12.0 Hz, IrH), 1.27 and 1.29 (dvt, J_{HH} = 7.0, N = 13.8 Hz, PCHCH_3, two signals due to diastereotopy), 3.10 (m, PC*H*), 7.23 (m, C_6H_5).

[13] W. Bernhardt, H. Vahrenkamp, *Angew. Chem. 96* (1984) 139; *Angew. Chem. Int. Ed. Engl. 23* (1984) 141.

Sequencing of Short Peptides Using FAB Mass Spectrometry—Increased Information via Derivatization

By *Dieter Renner* and *Gerhard Spiteller**

In 1981, *Barber* et al.[1] found that polar compounds such as peptides, which, due to their nonvolatility, cannot be studied using electron-impact mass spectrometry, are ionized upon fast atom bombardment (FAB). The resulting FAB mass spectra essentially show the masses of positive and negative ions formed by protonation and deprotonation, respectively, of the molecule. Since fragments are also observed in the spectra, there have been numerous attempts to correlate these with the structure. Such correlations can be carried out for model peptides with known structures, in part because only those fragments need to be sought which have a relationship to the structure and because other ions present can be conveniently ignored. Therefore, in the absence of additional information, a structure elucidation via interpretation of the FAB spectrum of an underivatized peptide was only possible in special cases.[2–4]

In the course of our efforts to use FAB mass spectrometry for the structure elucidation of short peptides, we had to separate, using HPLC, mixtures of peptides that contained no chromophoric groups. In order to improve detection of the peptides, we derivatized them with dansyl chloride (DnsCl).[5]

In contrast to the FAB spectra[6] of the underivatized peptides, in which the charge of the fragments is localized on the C-terminal as well as the N-terminal end of the molecule (Fig. 1), the spectra of the dansyl derivatives exhibit intense and structure-specific cleavage patterns, all of which relate to the derivatized end of the molecule and resulted from cleavage of the peptide bond (Fig. 2). The fragmentation pattern is recognizable from the formulas.

Apparently, the introduction of an electron-rich, stable aromatic system results in both a preferential ionization and an increased tendency to form fragments. Thus, the derivatization of peptides is advantageous not only for the detection in purification steps, but also for the subsequent mass spectrometric analysis. For underivatized peptides,

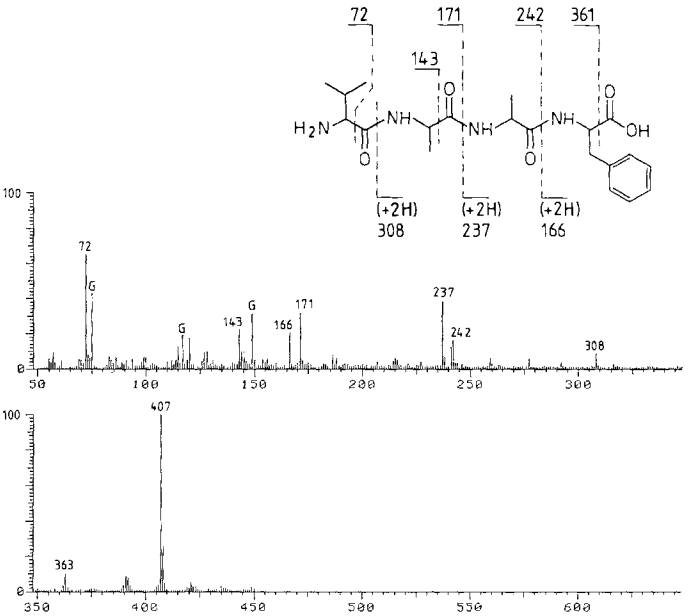


Fig. 1. FAB mass spectrum of positive ions of Val-Ala-Ala-Phe; m/z 407 = $[MH]^+$: the signals labeled "G" are due to the matrix material (glycerin).

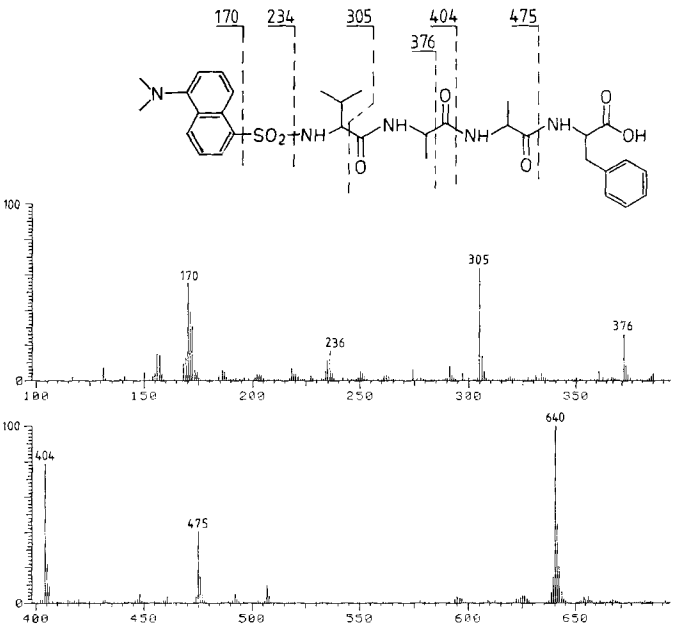


Fig. 2. FAB spectrum of positive ions of Dns-Val-Ala-Ala-Phe; m/z 640 = $[MH]^+$.

structure-specific cleavage products are hardly recognizable, and, therefore, sequence determination is difficult. For derivatized peptides, on the other hand, the amino acid sequence can be unequivocally determined.

We also reacted peptides with a bromine-containing aromatic sulfonyl chloride since the two isotopes ^{79}Br and ^{81}Br allow unequivocal labeling of the fragments. Labeling with 2-bromo-5-(dimethylamino)benzenesulfonyl chloride (Bdbs-Cl)[5] is favorable for peptides containing up to ten amino acids. For longer peptides, the isotope pattern of bromine exhibits strong overlapping due to the high content of ^{13}C. In these cases, dansyl derivatives are preferred. As already found by *Sethi* et al.,[7] the bromine-containing compounds are partly debrominated during the recording of the spectra; the bromine atom is replaced by a hydrogen

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atom. Another series of fragments is thereby formed, whose masses are 78 and 80 amu smaller than those of bromine-containing peptide fragments (Fig. 3).

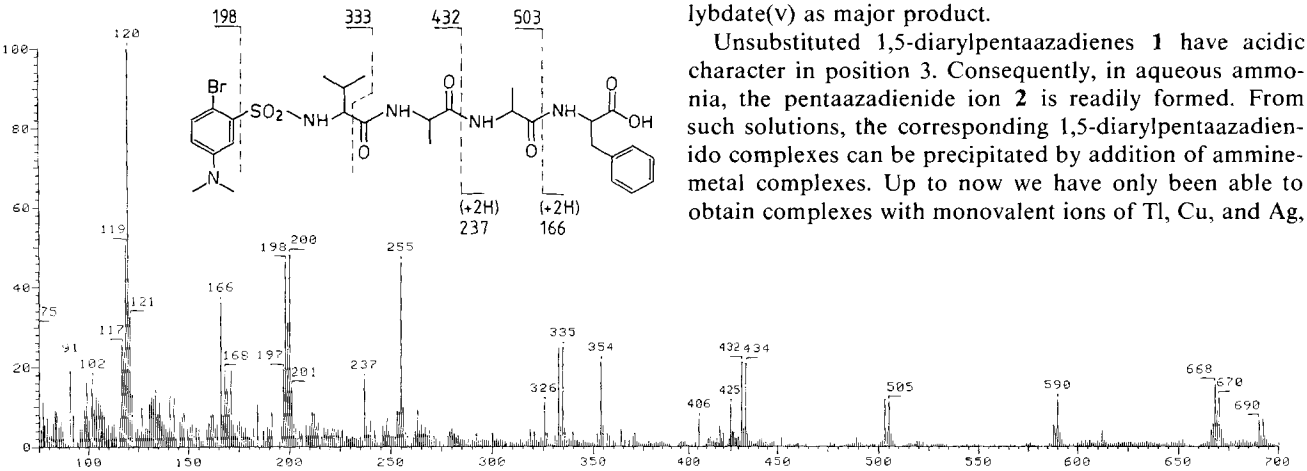


Fig. 3. FAB spectrum of positive ions of Bdbs-Val-Ala-Ala-Phe; m/z 668 = $[M\mathrm{H}]^+$, m/z 690 = $[M\mathrm{Na}]^+$. Bromine-free fragments: m/z 120, 255, 354, 425, 590.

The interpretation is more difficult for peptides whose amino acids contain side-chain functional groups. In each case studied, however, we obtained more informative spectra from the derivatized than from the free peptides.

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CAS Registry numbers:
Val-Ala-Ala-Phe, 21957-32-4; Dns-Val-Ala-Ala-Phe, 96095-87-3; Bdbs-Val-Ala-Ala-Phe, 96095-86-2.

[1] M. Barber, R. S. Bordoli, R. D. Sedgwick, A. N. Tyler, *J. Chem. Soc. Chem. Commun. 1981*, 325.
[2] D. H. Williams, C. V. Bradley, S. Santikarn, G. Bojesen, *Biochem. J. 201* (1982) 105.
[3] M. E. Rose, M. C. Prescott, A. H. Wilby, I. J. Galbin, *Biomed. Mass Spectrom. 11* (1984) 10.
[4] K. B. Tomer, F. W. Crow, M. L. Gross, K. D. Kopple, *Anal. Chem. 56* (1984) 880.
[5] Experimental procedure for the derivatization with Dns-Cl or Bdbs-Cl: The peptide (1 μmol) is dissolved in 0.2 M $NaHCO_3$ (60 μL). After addition of a 50 mM solution of Dns-Cl or Bdbs-Cl in acetone (mole ratio peptide : reagent = 1 : 3), the mixture is incubated for 1.5 h at 40°C. Subsequently, the acetone is distilled off and the products acidified with 10% H_3PO_4. The derivatized peptide is isolated by RP-HPLC. Fractions are collected at frequent intervals, combined, and freeze dried. The residue is dissolved in a small amount of methanol for the FAB mass spectrometric analysis.
[6] Finnigan MAT 8500 mass spectrometer with modified ion source for FAB-MS; xenon canon (ION TECH LTD., Teddington, U.K.); matrix material: glycerin; the glycerin background was subtracted from the FAB spectra.
[7] S. K. Sethi, C. C. Nelson, J. A. McCloskey, *Anal. Chem. 56* (1984) 1977.

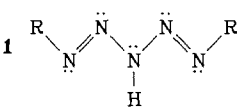
Complexes of 1,5-Di(*p*-tolyl)-1,4-pentaazadien-3-ide, Crystal Structures of [Cu(tolylNNNNNtolyl)]$_3$ and [Ni(tolylNNNNNtolyl)$_2$]$_2$**

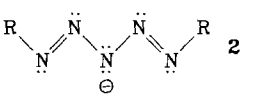
By *Johannes Beck* and *Joachim Strähle**

Suitably substituted 1,4-pentaazadienes are stable at room temperature.[1,2] We have studied the reactions of 1,5-diaryl-3-methylpentaazadienes with compounds of molybdenum in various oxidation states. Cleavage of the N_5 chain always takes place in such reactions. In the reaction with $MoCl_5$ we obtained arenediazonium hexachloromolybdate(v) as major product.

Unsubstituted 1,5-diarylpentaazadienes **1** have acidic character in position 3. Consequently, in aqueous ammonia, the pentaazadienide ion **2** is readily formed. From such solutions, the corresponding 1,5-diarylpentaazadienido complexes can be precipitated by addition of amminemetal complexes. Up to now we have only been able to obtain complexes with monovalent ions of Tl, Cu, and Ag, divalent ions of Mn, Ni, Zn, Cd, Pd, and Cu, and trivalent cobalt. The structures of **3**, **4**, and **5** have been determined.[3]

The dimeric bis(1,5-ditolyl-1,4-pentaazadien-3-ido)nickel(II), **3**, is formed in the form of a brown, crystalline powder from ammoniacal solution.[4] It is paramagnetic; at room temperature, $\mu = 3.1$ B.M., corresponding to two unpaired electrons per metal ion. The complex decomposes at 120°C. From a tetrahydrofuran (THF)/*n*-hexane mixture, monoclinic single crystals of the composition **3** · THF crystallize out. Crystallization of a triclinic and a tetragonal modification was also observed. The structure analysis[5] (Fig. 1) shows that in **3** four N_5 zig-zag chains, whose longitudinal axes run parallel, each coordinate two Ni^{2+}





[Ni(*p*-tolyl-NNNNN-*p*-tolyl)$_2$]$_2$ **3**

[Cu(*p*-tolyl-NNNNN-*p*-tolyl)]$_3$ **4**

[Tl(*p*-tolyl-NNNNN-*p*-tolyl)]$_2$ **5**

Cu(*p*-tolyl-NNNNN-*p*-tolyl)$_2$ **6**

ions in a distorted octahedral fashion. The atoms N1, N3 and N_5 of each N_5-chain participate in the coordination. The base of the octahedron is formed by two chelate-like-bonded N_3-fragments. The mean N–Ni–N angle of 59.3° in the chelate ring is relatively small, while the neighboring angles of 117–125° in the base of the octahedron are greater than the ideal value. The Ni–N distances within the base are 213 pm. The distances to the apices of the octahedron are somewhat shorter (207 pm). The Ni–N distances indicate single bonding, as is also found in amminenickel complexes[6,7] and in dimeric bis(1,3-diphenyltriazenenickel(II)).[8]

Reaction of an ammoniacal solution of 1,5-ditolylpentaazadiene with tetraamminecopper(II) ions initially leads to formation of a brown precipitate of **6**. This Cu(II) compound is readily soluble in almost all organic solvents. Independently of the solvent employed, evolution of nitrogen and reduction to **4** takes place on heating. The color of the solution turns deep-red. From THF/*n*-hexane,

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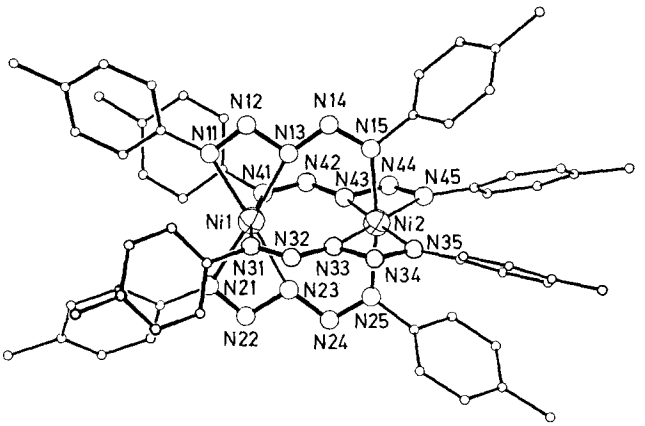


Fig. 1. Structure of **3** in the crystal. Important bond lengths [pm] and angles [°]: Ni–N 205.2(3) to 214.0(3), N1–N2 127.2(4) to 128.2(4), N2–N3 133.8(4) to 135.8(4), N3–N4 134.2(4) to 138.7(4), N4–N5 126.9(4) to 129.3(4), Ni1–Ni2 331.0(1); N–N–N 104.4(3) to 113.5(3). The first of the two figures alongside the N atoms refers to the chain, the second, the only figure given in the text, refers to the number of the N atom in the chain.

monoclinic $4 \cdot THF \cdot 0.5\,C_6H_{14}$[9] crystallizes in the form of red pseudohexagonal platelets. The complex is air-stable, and, unlike **3**·THF, it decomposes explosively on heating to 160°C. Associated with its weak paramagnetism, the magnetic moment increases between 113 and 303 K from $\mu = 0.33$ to 0.52 B.M. per Cu^+ ion.

In **4**[10] (Fig. 2), three N_5 zig-zag chains coordinate three linearly arranged Cu^+ ions with N1, N3, and N5, such that each metal atom is in a trigonal-planar environment. The Cu–N distances to the outer N1 and N5 atoms, with a mean value of 203.6 pm, are somewhat longer than the distances to the more strongly basic atoms N3 (mean distance Cu2–N3: 194.5 pm). They largely correspond to the sums of the covalent radii (202 pm[11]), and to the Cu–N distances in tetrameric (1,3-dimethyltriazene)copper(I)[12] and dimeric (1,3-diphenyltriazene)copper(I).[13] The Cu–Cu distances of 234.8 and 235.8 pm in the linear Cu_3^{3+} chain of **4** are the shortest values found so far in Cu^I complexes. Comparable Cu–Cu distances of about 242 to 246 pm are found, for example, in alkyl-[14] and arylcopper(I) compounds[15] or in the iodocuprate $Cu_3I_4^-$.[16] It is still not fully clear whether such short Cu–Cu distances can be explained in terms of bonding interactions. In the case of the Cu_3^{3+} unit, a dsp^3 hybridization of the Cu atoms is conceivable, such that two Cu–Cu bonds can be formed, with each of the outer Cu atoms still having an unpaired electron. The observed magnetic properties are consistent with this model if an antiferromagnetic coupling is assumed. The terminal atoms Cu1 and Cu3 are each bent out from the planes of the three coordinating N atoms by about 18 pm, thus indicating repulsion between the Cu atoms.

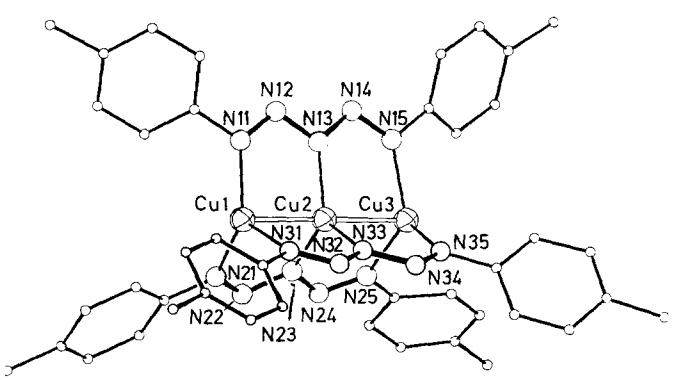


Fig. 2. Structure of **4** in the crystal. Important bond lengths [pm] and angles [°]: Cu1–N1 200.6(5) to 205.2(6), Cu2–N3 194.1(5) to 195.2(6), Cu3–N5 202.7(5) to 205.0(5), Cu1–Cu2 234.8(2), Cu2–Cu3 235.8(2), N1–N2 126.7(6) to 127.2(7), N2–N3 132.4(7) to 135.4(7), N3–N4 132.0(6) to 134.2(7), N4–N5 127.1(6) to 129.6(6), Cu1–Cu2–Cu3 180.00(1), N1–Cu1–N1 114.0(2) to 123.1(2), N3–Cu2–N3 116.6(2) to 121.7(2), N5–Cu3–N5 114.7(2) to 122.4(2), N–N–N 109.7(6) to 113.9(6). The first of the two figures alongside the N atoms refers to the respective chain, the second, the only figure given in the text, refers to the number of the N atom in the chain.

In the dimeric Tl^I complex **5**,[3] two Tl^+ ions are coordinated trigonal-pyramidally by two N_5-chains, resulting, as in **3**, in an alternating chelate-like and monodentate bonding of the metal ions.

The interatomic distances in the planar N_5 chains of all the complexes so far investigated are consistent with partial delocalization of the π-electrons. The shorter N1–N2 and N4–N5 distances of about 128 pm are slightly longer than a NN double bond, while the longer N2–N3 and N3–N4 bonds are markedly shorter than the value normally found for a NN covalent single bond.[11]

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CAS Registry numbers:
3, 96129-15-6; **4**, 96129-17-8; $[Ni(NH_3)_6]^{2+}$, 15365-74-9; $[Cu(NH_3)_4]^{2+}$, 16828-95-8.

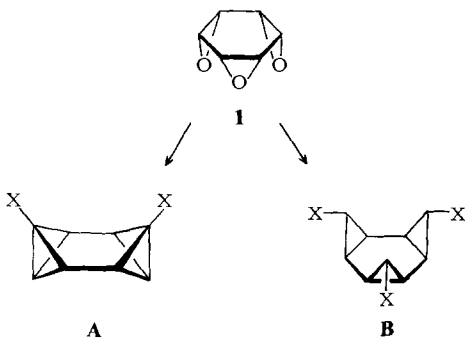
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[4] Procedure: To a saturated solution of 1,5-di-*p*-tolyl-1,4-pentaazadiene (0.2 g, 0.79 mmol) in concentrated aqueous ammonia was added a slight excess of $[Ni(NH_3)_6]^{2+}$ (likewise in concentrated ammonia). Over a period of several hours, a light brown precipitate of **2** separated out. This was filtered off and washed with water to remove the excess ammonia. The precipitate was then dried over P_2O_5 in vacuo. Yield quantitative.
[5] **3**·THF: $P2_1/n$, $a = 1180.0(2)$, $b = 2898.7(6)$, $c = 1801.1(5)$ pm, $\beta = 91.71(1)°$, $Z = 4$, $R = 0.075$ for 6788 independent reflections with $I > 3\sigma(I)$ (Enraf-Nonius CAD4, $Cu_{K\alpha}$); see also [10].
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[9] Procedure: To a saturated solution of 1,5-di-*p*-tolyl-1,4-pentaazadiene in concentrated aqueous ammonia was added an excess of $[Cu(NH_3)_4]^{2+}$ (likewise in concentrated ammonia). A brown, crystalline precipitate of **6** separated out immediately. Addition of $[Cu(NH_3)_4]^{2+}$ was continued until the supernatant liquor was intense green and no further precipitate separated. The precipitate was filtered off and washed with water to remove the excess ammonia. The precipitate was then dried over P_2O_5 in vacuo. Reduction to **4** was accomplished by heating in THF: the brown Cu(II)-compound was dissolved in a little THF under N_2 and the resulting solution heated to boiling. Vigorous evolution of gas was observed and the color of the solution changed from brown to intense red. Treatment of the solution with *n*-hexane led to precipitation of deep-red crystals of $4 \cdot THF \cdot 0.5\,C_6H_{14}$.
[10] **4**: $P2_1/c$, $a = 1477.3(1)$, $b = 1478.7(4)$, $c = 2284.5(2)$ pm, $\beta = 91.06(1)°$, $R = 0.064$ for 2569 independent reflections with $I > 3\sigma(I)$ (Enraf-Nonius CAD4, $Cu_{K\alpha}$). Further details of the crystal structure investigations are available on request from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2, on quoting the depository number CSD 51225, the names of the authors, and the full citation of the journal.
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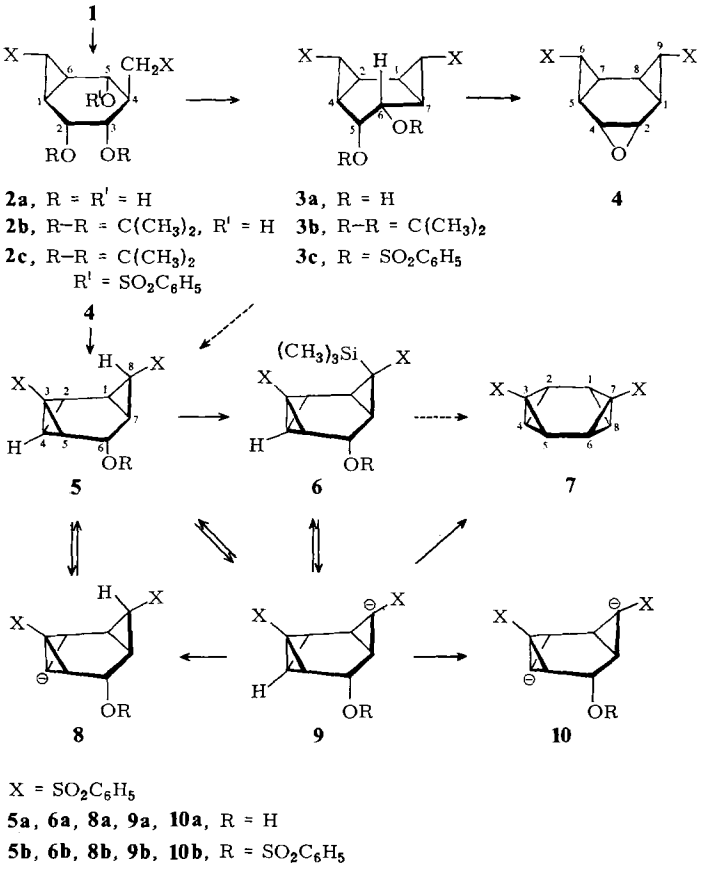
(*Z*)-3,7-Bis(phenylsulfonyl)pentacyclo-[5.1.0.0^{2,4}.0^{3,5}.0^{6,8}]octane, an Octabisvalene Derivative**

By *Christoph Rücker** and *Horst Prinzbach*

Dedicated to Professor Günther Wilke on the occasion of his 60th birthday

"Octabisvalene" **A** (X = H),[1] which is still unknown, is the third saturated and highly strained (E_{st} = 130–140 kcal/mol) valence isomer of cyclooctatetraene (the others being cubane and cuneane).[2] Starting from *cis*-benzenetrioxide **1**, we have now achieved the synthesis of the first octabisvalene derivative **7** (X = $SO_2C_6H_5$).[3]





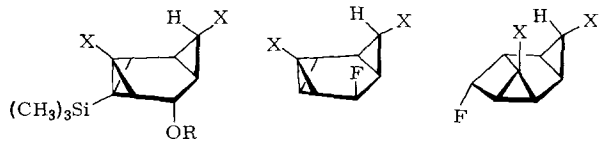
Scheme 1.

The route shown in Scheme 1 is based on the finding (cf. the preparation of the carbocyclic *cis*-tris-σ-homobenzene skeleton **B** from **1**)[4] that the bicyclic, crystalline triol **2a** can be obtained in nearly quantitative yield by reaction of **1** with five equivalents of phenylsulfonylmethyllithium[5] [tetrahydrofuran (THF), −20→20°C, 2 d, m.p. = 232°C, $J_{2,3}$ = 2.6, $J_{3,4}$ = 12, $J_{4,5}$ = 10.5 Hz]. The phenylsulfonyl groups were expected, inter alia, to favor the α-deprotonation in **3b**, **4**, and **5** (as observed in the formation of **2a**) over competing metalations. **2a** was transformed into the acetal **2b** (100%), which was then esterified to **2c** (87%). **2c** was cyclized to **3b** with two equivalents of lithium diisopropylamide (LDA) (THF, −20°C, 30 min, 90%, m.p. = 231°C, $J_{4,5} \cong 0$ Hz). The diol **3a** (100%), the bissulfonate **3c** (>90%), and (via three steps)[6] the epoxide **4** (53%, m.p. = 245°C, $J_{1,2} \cong 0$, $J_{1,9}$ = 4 Hz) can be obtained from **3b** by standard procedures.

In the *endo*-6-carbanion of **4**, the stereoelectronic situation for cyclization to **5a** (substitution at C-4) was considered, a priori, favorable:[7] indeed, this step is highly selective using four equivalents of *n*-butyllithium (THF, −78°C, 30 min, 89%, <5% addition of *n*-BuLi, m.p. = 191°C, $J_{2,4}$ = 3.5, $J_{4,5}$ = 3.5, $J_{2,5}$ = 3.8, $J_{5,6}$ = 3.5, $^1J_{C\text{-}4,H}$ = 210 Hz). Thus, there is no evidence for four-membered-ring formation (substitution at C-2 of **4**), inversion of the anion, or σ→π isomerization (which is plausible in the case of the *exo* anion).[8] Not unexpectedly, the high acidity of 4-H[9] in **5a**, **b** and of 4-H and 8-H in **7** (and also of the *o*-phenyl protons) causes complications in the ring closure to **7**. H/D-Exchange experiments with **5b** show that the deprotonation to **8b** is faster than to **9b**. The carbanion **8b** can be trapped as silyl derivative **11b** by metalation in the presence of $(CH_3)_3SiCl$[10] (2 equivalents of lithium tetramethylpiperidide, THF, −78°C, 2 h); **11b** (40% along with **5b**) is of interest as a C-4 protected precursor of **7**. **6a** ($J_{2,5}$ = 4 Hz, *endo* configuration of the silyl group confirmed by NOE) is formed from **5a** and two equivalents of *n*-BuLi after addition of $(CH_3)_3SiOSO_2CF_3$; **11a** ($J_{2,5}$ = 3.7 Hz) is formed along with several R(X)-*ortho*-silylated products from **5a** and two equivalents *n*-BuLi after addition of $(CH_3)_3SiCl$. **6a** and **11a** are isolated by chromatography (20% and 42%, respectively). Upon treatment of **5b** with sufficiently strong bases (1–2 equivalents of *n*-BuLi, LDA) under various conditions, decomposition occurs almost instantaneously. Presumably, the dicarbanion **10b** is highly labile. The monocarbanion **9b** was therefore generated by treatment of **6b** with "dry" (ca. 0.2 equivalents of H_2O) tetrabutylammonium fluoride:[11] the octabisvalene derivative **7** is formed in 20% yield [separated chromatographically (HPLC on silica gel, 33% ethyl acetate in hexane), colorless crystals, m.p. = 198°C, MS (CI, NH_3): *m/z* 402 ($M^{\oplus} + NH_4^{\oplus}$)] along with **5b** (35%) and the fluorides **12** (35%) and **13** (10%); the latter are formed from **5b** in a control experiment. Accordingly, improved yields of **7** are to be expected by more rigorous exclusion of proton sources. In the attempts thus far to obtain **7** directly from **3c** (via **5b**) (1–2 equivalents of *n*-BuLi, THF, −78 to −30°C), much polymeric material was formed along with **5b** and a small amount of **7** (β-HOR elimination?).

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11a, R = H;
11b, R = $SO_2C_6H_5$
X = $SO_2C_6H_5$

12 **13**

The ^{1}H-NMR spectrum of **7** [$CDCl_3$, 250 MHz: $\delta = 7.8-7.3$ (10H), 3.17 (AA'A''A'''), 2.75 (BB')] was satisfactorily simulated with the following coupling constants: $J_{1,2} = 4.77$, $J_{1,4} = 0.13$, $J_{1,5} = -0.20$, $J_{1,6} = 5.68$, $J_{1,8} = 3.44$, $J_{4,8} = 0.27$ Hz. Of the ^{13}C-NMR signals ($CDCl_3$) of the octabisvalene skeleton, $\delta = 43.0$ (C-1, -2, -5, -6), 35.1 (C-3, -7), and 21.3 (C-4, -8), the last one exhibits a C,H-coupling of 214 Hz, which is typical for bicyclobutane bridgeheads.[12] Upon heating in solution ($CDCl_3$), **7** begins to decompose at ca. 200°C.

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Photochemically Initiated, Electron-Transfer-Catalyzed Diels-Alder Reactions of Electron-Rich Dienophiles**

By *Jiri Mlcoch* and *Eberhard Steckhan**

Similarly to the endoperoxide formation between 1,3-dienes and triplet oxygen[1] or the preparation of dioxetanes,[2] Diels-Alder (DA) reactions can be catalyzed via an electron-transfer chain mechanism using radical cations of triarylamines.[3] In this way, DA products are available which otherwise are formed only with difficulty or not at all. The scope of application, however, is relatively narrow.[4] We now report DA reactions in which a chain reaction is photochemically initiated by electron transfer (Scheme 1).

$$\text{Sens}^{\oplus} \xrightarrow{h\nu} [\text{Sens}^{\oplus}]^*$$

$$[\text{Sens}^{\oplus}]^* + \text{En} \overset{\text{ET}}{\rightleftharpoons} [\text{Sens}]^{\odot} + [\text{En}]^{\odot\oplus}$$

$$[\text{En}]^{\odot\oplus} + \text{diene} \longrightarrow [\text{DA product}]^{\odot\oplus}$$

$$[\text{DA product}]^{\odot\oplus} + \text{En} \overset{\text{ET}}{\rightleftharpoons} \text{DA product} + [\text{En}]^{\odot\oplus}$$

Scheme 1. Sens = sensitizer; En = dienophile; ET = electron transfer.

2,4,6-triphenylpyrylium tetrafluoroborate, which has already proved useful for the catalysis of cycloreversions,[5] functions as sensitizer. Electron transfer to the sensitizer can be detected by fluorescence quenching.

2,4,6-triphenylpyrylium tetrafluoroborate has the advantage that only concentrations of 0.1 to 1.5 mol-% are needed and that it can be excited with light having wavelengths >345 nm ($\lambda_{max} = 354$, 404 nm).[5] It has the following advantages over 1,4-dicyanobenzene-[6] and 9,10-dicyanoanthracene-[7]sensitized [4+2]-photocycloadditions: appreciably lower concentrations of sensitizer are required; the irradiation time is drastically diminished; simple light sources, such as halogen or xenon lamps, can be used (some reactions even take place in sunlight); and the scope of application shows promise of being broader since the reaction of 1-acetoxy-1,3-cyclohexadiene, which had not yet been feasible,[6] was also performed successfully.

The DA reaction is most effectively sensitized when the olefins are dissolved in dichloromethane and irradiated with a 250-W xenon lamp ($\lambda \geq 345$ nm), and when a 0.01 M solution of the sensitizer in dichloromethane is added in such a way that a weak fluorescence is constantly maintained. If the olefins are added to the irradiated solution of sensitizer, the fluorescence is temporarily quenched. It usually returns, however, after the olefin is consumed. In acetonitrile, the reaction takes place poorly or not at all.

In the case of styrene **6a**, 1-acetoxy-1,3-cyclohexadiene **1c**, and 1-acetoxy-1,4-cyclohexadiene **3**, a stoichiometric oxidation by the excited sensitizer is observed in addition to the electron-transfer-catalyzed reaction. Thus, styrene forms phenylnaphthalene derivatives via oxidative dimerization and the acetoxycyclohexadienes **1c** and **3** are dehydrogenated to phenyl acetate. If only **3** is used, no DA dimers are obtained and phenyl acetate is the only product. The DA product **2d** from the reaction of **1c** with **3** can be explained by rearrangement of **3** to 2-acetoxy-1,3-cyclohexadiene **4** during the reaction. This could take place at the radical cation stage via sigmatropic 1,3-hydrogen shift.

Dienes that do not have a rigid *syn*-arrangement of the double bond system, such as 1-acetoxy-1,3-butadiene and 2,3-dimethyl-1,3-butadiene have not reacted thus far.

The reaction discussed here is of practical interest, since, due to the electron transfer from an electron-rich alkene to the excited sensitizer, the olefin radical cation, being a good electron-poor dienophile, is formed according to the redox "umpolung" principle.[8] The reverse process, the redox umpolung of an electron-rich diene into its electron-poor radical cation, could be a means of initiating DA reactions with inverse electron demand that are otherwise

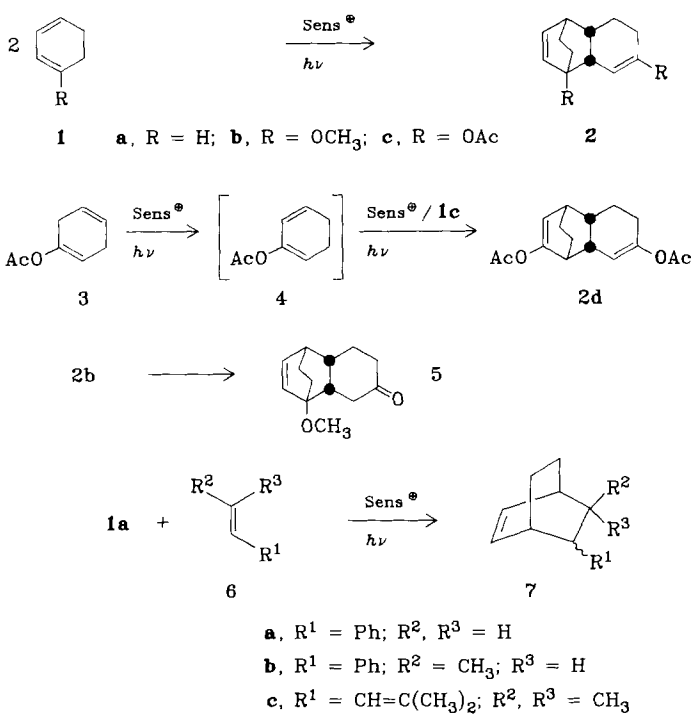
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Table 1. Results of the electron-transfer-catalyzed Diels-Alder reactions sensitized by triphenylpyrylium tetrafluoroborate.

Starting material [mmol]	Sensitizer [mmol]	Irradiation time [min]	Products [a]	Yield GC [b] [%] (*endo* : *exo*)	Yield isolated [c] [%] [mmol]
1a (5)	0.075	80	**2a**	82 (6 : 1)	80 (4)
1a (1)	0.022	20	**2a**	82 (6 : 1)	
1b (10) [d]	0.0075	45	**5**	70 (1.2 : 1)	63 (7)
1b (1) [d]	0.005	30	**5**	67 (1.2 : 1)	
1c (2)	0.003	10	**2c** [e]	25 (6 : 1)	22 (0.44)
3 (2)	0.005	15	[f]		
and **1c** (2.25) / **3** (5)	0.020	80	**2c** / **2d** [e]	46 (6 : 1) / 38 [g] (3 : 2)	75 [j] (5.4)
and **1c** (1.3) / **3** (3.7)	0.18 [i]	60	**2c** / **2d** [e]	36 (6 : 1) / 26 [g] (3 : 2)	
and **1a** (2) / **6c** (10)	0.1	1080	**2a** / **7c**	12 (6 : 1) / 39 [g] (5 : 3)	34 (0.8)
and **1a** (1) / **6a** (5)	0.06	90	**2a** / **7a** [h]	11 (6 : 1) / 38 [g] (10 : 1)	34 (0.34)
and **1a** (1) / **6a** (1)	0.05	50	**2a** / **7a** [h]	19 (6 : 1) / 13 [g] (10 : 1)	
and **1a** (1) / **6b** (10)	0.03	15	**2a** / **7b**	46 (5 : 1) / 32 [g] (≥ 98 : 2)	29 (0.29)
and **1a** (2) / **6b** (10)	0.035	30	**2a** / **7b**	48 (5 : 1) / 19 [g] (≥ 98 : 2)	19 (0.38)

[a] The structures and compositions of all products were confirmed by MS, 90-MHz and 400-MHz ^{1}H- and ^{13}C-NMR spectra as well as by elemental analysis. The configurations of the products were determined by analysis of their ^{1}H- and ^{13}C-NMR spectra. As expected [10], the olefinic carbon atoms and the vinylic hydrogen atoms of the bicyclo[2.2.2]octene system of the *endo* products exhibit pronounced high-field shifts. The configuration of **7b** could be assigned very well from the ^{13}C-NMR spectrum using a system of increments for substituted bicyclooctenes [11] based on bicyclo[2.2.2]octene. [b] Yield determined by gas chromatography. [c] Yield of products isolated by liquid chromatography. [d] 0.5 mmol $NaHCO_3$ was added. [e] Phenyl acetate was also a product. [f] 25% phenyl acetate as the only identified product. [g] The yields of the crossed DA products refer, in each case, to the component present in smaller amount. [h] Oxidation products of styrene are formed as side products, e.g., 1-phenyl-1,2-dihydronaphthalene, 4-phenyl-1,2,3,4-tetrahydro-1-naphthol, 4-phenyltetralone, as well as larger amounts of polymeric styrenes. [i] The total amount of the sensitizer, 2,4,6-tris(4-bromophenyl)pyrylium tetrafluoroborate, was present from the start. [j] **2c** and **2d** were isolated together and part of the product separated for analytical purposes using HPLC on silica gel Lichrosorb Si 60 (7 μm) with CCl_4/diethyl ether (10 : 1) as eluent.



not possible. In the DA reaction that is photochemically initiated by 2,4,6-triphenylpyrylium tetrafluoroborate, the suprafacial stereospecificity of the usual DA reaction is retained. This is demonstrated by the reaction of **1a** with *trans*-1-phenyl-1-propene **6b**, which leads almost exclusively to the *trans,endo* product **7b**.

The oxidizing power of the sensitizer can be varied by substitution in the *para* position of the phenyl ring. Thus, for example, 2,4,6-tris(4-bromophenyl)pyrylium tetrafluoroborate[9] was successfully used for the sensitization of the DA reaction of the mixture of **1c** and **3** (see Table 1).

General experimental procedure

The olefins, dissolved in 40 mL of dichloromethane, are placed in a glass vessel equipped with a cooling mantel (water cooling ca. 15 °C). The irradiation is carried out with a 250-W xenon lamp (Osram XBO 250 OFR; lamp housing LAX 1450, Müller Elektronik, Moosinning), filtering the light to $\lambda \geq 345$ nm (Oriel Long Pass Filter Model 5146). Under irradiation, a 0.01 M solution of 2,4,6-triphenylpyrylium tetrafluoroborate in dichloromethane is added sufficiently slowly so as to maintain a steady weak fluorescence. After termination of the reaction (consumption of one olefin component as monitored by gas chromatography; duration, see Table), the mixture is treated with a saturated solution of Na_2CO_3 and the dichloromethane distilled off. The aqueous phase is perforated with ether and the product isolated by column chromatography (silica gel, 63–200 μm, column dimensions, 60 × 2.0 and 80 × 2.5 cm; eluent, dichloromethane for **2a**, **2c**, and **2d**, pentane for **7a**, **7b**, and **7c**, and tetrachloromethane/diethyl ether (1 : 1) for **5**. The purification of **5** and of **7c**, as well as the separation of *exo*- and *endo*-**2d**, was carried out by HPLC on Lichrosorb Si 60 (7 μm) (column length 50 cm; diameter 1.6 cm) with the eluents tetrachloromethane/diethyl ether (1 : 1) for **5**, cyclohexane for **7c**, and tetrachloromethane/diethyl ether (10 : 1) for **2d**.

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CAS Registry numbers:
1a, 592-57-4; **1b**, 2161-90-2; **1c**, 74502-18-4; *exo*-**2a**, 703-36-6; *endo*-**2a**, 703-35-5; *exo*-**2c**, 96194-84-2; *endo*-**2c**, 96244-46-1; *exo*-**2d**, 96194-85-3; *endo*-**2d**, 96244-47-2; **3**, 96194-83-1; *exo*-**5**, 96244-45-0; *endo*-**5**, 86336-25-6; **6a**, 100-42-5; **6b**, 873-66-5; **6c**, 764-13-6; *endo*-**7a**, 96244-48-3; *exo*-**7a**, 96244-49-4; *endo*-**7b**, 96194-86-4; *exo*-**7b**, 96244-50-7; *endo*-**7c**, 76960-42-4; *exo*-**7c**, 76986-20-4; 2,4,6-triphenylpyrylium tetrafluoroborate, 448-61-3.

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$[\{1,3,5\text{-}(CH_3)_3H_3C_6\}_6Tl_4][GaBr_4]_4$ — Synthesis and Structure of a Mixed Mono- and Bis(arene)thallium Complex**

By *Hubert Schmidbaur,* Wolfgang Bublak, Jürgen Riede,* and *Gerhard Müller*

Complexes of neutral arenes with p block metals are still limited to very few elements of the third[1] and fourth main groups.[2] Apart from recently discovered exceptions[1a,b,e] all the reported examples are complexes in which a single arene is bound centrally to the metal. It is apparent that the tendency for this type of compound to be formed is determined by the conformity of the orbital symmetry of the HOMO of the hydrocarbon and of the LUMO of the metal—in compliance with current concepts regarding such interactions.[3] After the first entry to the complexes of divalent metals of the fourth main group (Ge^{II}, Sn^{II}, Pb^{II})[2] and analogous derivatives of monovalent metals of the third main group (Ga^{I}, In^{I})[1] we have now been able to complete this series on two scores concomitantly with the preparation of an unusual thallium(I) compound.

The existence of Tl^{I}-arene complexes had already been postulated some years ago, but final proof thereof was still lacking.[4] The complex salts $Tl[AlCl_4]$, $Tl[AlBr_4]$, $Tl[GaCl_4]$, and $Tl[GaBr_4]$ are readily soluble in hot benzene. On cooling, colorless crystals are formed, the benzene content of which, however, steadily decreases at room temperature in a stream of nitrogen, so that no defined phases can be obtained. In vacuo, the complex salts remain free of benzene. Attempted crystallization with hexamethylbenzene also met without success. With mesitylene (Mes, 1,3,5-trimethylbenzene), however, the situation is much more favorable; thus, e.g., with $Tl[GaBr_4]$ the crystalline phase of the title compound is formed, for which thermogravimetric measurements (20 to 150°C) surprisingly gave a molar ratio of mesitylene : complex salt of 1.5.

An X-ray structure analysis of the mesitylene adduct[5] revealed, as the most important finding, that a skeletal framework of tetrameric $Tl_4[GaBr_4]_4$ with crystallographic centrosymmetry is present. One or two mesitylene molecules are alternately coordinated to the $Tl^{\oplus}$ cations (Fig. 1). Accordingly, the large aggregate contains both mono- as well as bis(arene)metal moieties, which are bridged in a complicated way by $GaBr_4$ tetrahedra.

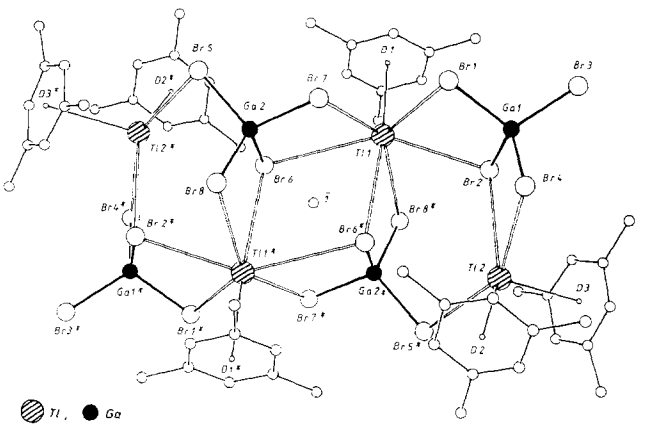


Fig. 1. Perspective diagram of the centrosymmetric tetrameric unit in the crystal (H atoms omitted) [5]. Important bond lengths [Å] and angles [°]: for Tl1: Tl1-D1 2.94, Tl1-Br1 3.520(2), Tl1-Br2 3.349(2), Tl1-Br8* 3.476(2), Tl1-Br6 3.675(2), Tl1-Br7 3.377(2), Tl1-Br6* 3.507(2), D1-Tl1-Br6* 164.8; for Tl2: Tl2-D2 3.01, Tl2-D3 3.03, Tl2-Br2 3.567(2), Tl2-Br4 3.346(2), Tl2-Br5* 3.485(2), Tl2-Br6* 4.025(2), D2-Tl2-D3 119.7.

In the $(Mes)Tl^{\oplus}$ structural unit the metal atom Tl 1 is located almost directly above the center of the ring at a distance of 2.94 Å (η^6-coordination). The coordination sphere of Tl is extended by six bromine atoms in the form of a strongly distorted pentagonal pyramid; three $GaBr_4$ anions are chelating, one apical-equatorial, the other two symmetrical and bis-equatorial. Such an arrangement has recently also been found in $[\{(CH_3)_6C_6\}_4Ga_4][GaCl_4]_4$.[1c]

The $(Mes)_2Tl^{\oplus}$ structural units are characterized by two mesitylene molecules oriented at an angle of 60.5° to each other, whereby the metal atoms Tl2 are once again located almost symmetrically (3.00 and 3.02 Å, respectively) above the ring centers (η^6-coordination). In the immediate neighborhood there are three irregularly arranged Br atoms, while a fourth Br atom (Br6*) is located somewhat further away. Once again two chelate contacts are formed. The coordination geometry thus shows similarities to that of $[(Mes)_2In(InBr_4)]$. In the latter case, however, the plane through the three bromine atoms bisects the angle between the two arene molecules.[1e] No pronounced stereochemical activity of the lone electron pair is recognizable in the coordination spheres of Tl1 and Tl2.

Thus, all heavy elements of the third group in the ns^2 valency state form both mono- as well as bis-π-complexes with neutral arenes. In principle, their geometries are obviously alike, and the differences in the measured atomic distances are regular from complex to complex.[1] Fundamentally, however, they differ from the arene complexes of the $d^{10}s^0$-configurated coinage-metal cations, in which the

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[+] X-ray structure analysis.

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metals, in accord with the change in orbital symmetry, are without exception attached to the arene acentrically.[6] Complexes of Tl^I with anionic arenes of the type $(C_5H_5)Tl$ are already well established classical organometallic reagents. Their structures are automatically governed also by an ionic bonding component.[7]

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[5] Crystal structure data: triclinic, space group $P\bar{1}$, $a=11.239(3)$, $b=12.245(2)$, $c=15.423(3)$ Å, $\alpha=102.05(1)$, $\beta=92.77(2)$, $\gamma=100.58(2)°$, $V=2032.2$ Å^3, $\rho_{exp}=2.53$ g/cm^3 for $Z=2$. 6364 independent reflections, empirical absorption corrections based on ψ-scans of eight reflections (ω-scan, $\Delta\omega=0.9°$, $+h$, $\pm k$, $\pm l$, $(\sin\vartheta/\lambda)_{max}=0.573$, $Mo_{K\alpha}$, $\lambda=0.71069$ Å, $F(000)=1404$, $\mu(Mo_{K\alpha})=166.1$ cm^{-1}, $T=-35°C$, Syntex $P2_1$). Solution of structure by Patterson method, $R=0.059$, $R_w=0.056$ for 352 refined parameters and 4638 structure factors with $F_o>4\sigma(F_o)$ ($w=k/\sigma^2(F_o)$, $k=1.98$ in the last cycle, non-H atoms anisotropic, H constant, SHELX 76). $\Delta\rho_{(max)}$(final) $=+1.61/-1.85$ e/Å^3. Further details of the crystal structure analysis are available on request from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2 (FRG), on quoting the depository number CSD 51180, the names of the authors, and the full citation of the journal.

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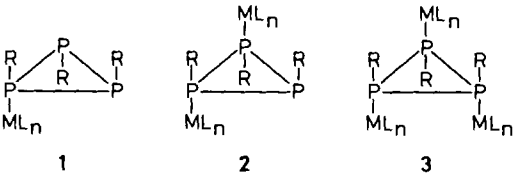
A Novel Type of Cyclotriphosphane Complex: Synthesis and Structure of $[Ni_2(\mu\text{-}P_3iPr_3)_2(CO)_4]$**

By *Marianne Baudler,* Franz Salzer, Josef Hahn*, and *Eberhard Därr*

Dedicated to Professor Günther Wilke on the occasion of his 60th birthday

Complexes of the series **1**,[1] **2**,[1] and **3**[2] containing triorganocyclotriphosphane ligands $(PR)_3$ have already been described. We have now synthesized the first binuclear complex of the type $[L_nM(\mu\text{-}P_3R_3)_2ML_n]$, in which the P_3 rings are linked as four-electron ligands to the ML_n moieties to give a six-membered P_4M_2 metallacycle.

Reaction of triisopropylcyclotriphosphane **4**[3] with $Ni(CO)_4$ (*n*-pentane, 10°C→room temperature) affords



1 **2** **3**

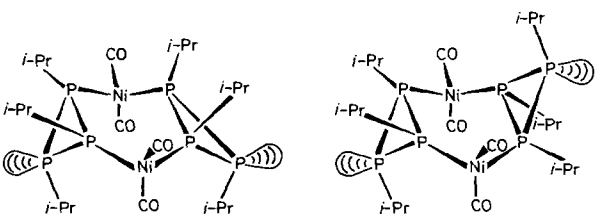
bis(μ-triisopropylcyclotriphosphane)bis(dicarbonylnickel) **5** in almost quantitative yield. The formation of **5** proceeds via the mononuclear complex $[Ni(P_3iPr_3)(CO)_3]$,

$$2\,(PiPr)_3 + 2\,Ni(CO)_4 \xrightarrow{-4\,CO} [Ni_2(\mu\text{-}P_3iPr_3)_2(CO)_4]$$

4 **5**

which is detectable at the beginning of the reaction by ^{31}P-NMR spectroscopy; on continued reaction, further, as yet not fully characterized, intermediate products appear.

5 is formed as a mixture of the isomers **5a** and **5b**, which differ from each other in the relative arrangement of the phosphorus three-membered rings. **5a** precipitates as a light-beige solid (decomposition at ca. 100°C, isomeric purity >99%), whereas **5b**, which is present in the filtrate (isomeric mixture ca. 1:1), can be enriched to ca. 90% by stepwise crystallization of **5a** at −30°C to −100°C. In solution (tetrahydrofuran (THF), benzene, *n*-pentane), **5a** rearranges into **5b** above 0°C until equilibrium (ca. 1:1) is established.



5a **5b**

The composition of compound **5**, which is only slightly sensitive to air and moisture, is confirmed by elemental analysis and cryoscopic molecular weight determination. In the mass spectrum (20 eV, 50°C), no signal is observed for the molecular ion; characteristic fragments are $M^{\oplus}-2CO$, $M^{\oplus}-3CO$, and $M^{\oplus}-Ni(CO)_4$. The IR spectrum of **5a** (*n*-pentane) shows two CO bands at 2018 (s) and 1971 (m) cm^{-1}.

The constitution of **5a,b** follows from the NMR data.[4] For both isomers, an AA'A''A'''MM' system is observed in the $^{31}P\{^1H\}$-NMR spectrum in the high field region characteristic for coordinated cyclotriphosphanes.[1] For all P atoms of **4**, the coordination chemical shift[5] is positive (downfield shift), but for the P_A nuclei (**5a**: $\Delta=55.5$; **5b**: $\Delta=55.1$) it is significantly greater than for the P_M nuclei (**5a**: $\Delta=11.3$; **5b**: $\Delta=16.2$). Accordingly, the cyclotriphosphane **4** in **5a,b** is bound as a bidentate bridging ligand.[6] The configurations of **5a,b** follow from the $^{13}C\{^1H,^{31}P\}$-NMR spectra: in the case of **5a**, two singlets (intensity ratio 1:1) are observed for the CO ligands, whereas in the case of **5b**, only one signal is observed which does not show any splitting, even at −120°C. In both isomers, the P_4Ni_2 ring should be boat-shaped and in the case of **5b** should achieve the NMR-spectroscopically observed C_{2h} symmetry in solution by rapid pseudorotation.

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The formation of **5a,b** is clearly energetically favored over that of the corresponding mononuclear complex containing a P_2Ni three-membered ring.

Experimental

5a: Freshly distilled $Ni(CO)_4$ (3.24 g, 19.0 mmol) was added dropwise to a stirred solution of **4** [3] (4.2 g, 18.9 mmol) in *n*-pentane (50 mL) at 10°C under inert gas. As soon as evolution of CO had ceased, the mixture was warmed to room temperature within 30 minutes and stirred for a further 17–20 h until a total of 38.1 mmol CO had been liberated. The light-beige solid was filtered off at 10°C on a cooled frit and washed twice with 10 mL cold methanol. Yield: 3.8 g (59%) of almost colorless, isomerically pure **5a**. A further crop of **5a** could be recovered from the mother liquor.

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CAS Registry numbers:
4, 84783-89-1; **5a**, 96129-18-9; **5b**, 96192-78-8; $Ni(CO)_4$, 13463-39-3.

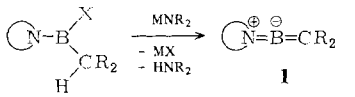
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[2] G. Huttner, H. D. Müller, A. Frank, H. Lorenz, *Angew. Chem. 87* (1975) 597; *Angew. Chem. Int. Ed. Engl. 14* (1975) 572.
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[4] Selected NMR parameters: $^{31}P\{^1H\}$-NMR (THF, 0°C, 24.3 MHz): **5a**: $\delta = -76.8$ (λ^4P), -117.3 (λ^3P), $^1J(\lambda^4P,\lambda^3P) = -165.0$ Hz, $^1J(\lambda^4P,\lambda^4P) = -200$ to -253 Hz (in this region, the value can be varied without affecting a meaningful assignment or change in the appearance of the signal groups; an accurate calculation is not possible because of the absence of weak intensity outer signals), $^2J(\lambda^4P,\lambda^4P) = +22.0$ Hz, $^3J(\lambda^4P,\lambda^4P) = -39.9$ Hz, $^3J(\lambda^4P,\lambda^3P) = +0.6$ Hz, $^4J(\lambda^3P,\lambda^3P) = +1.3$ Hz; **5b**: $\delta = -77.2$ (λ^4P), -112.4 (λ^3P), $^1J(\lambda^4P,\lambda^3P) = -163.8$ Hz, $^1J(\lambda^4P,\lambda^4P) = -200$ to -258 Hz (see above), $^2J(\lambda^4P,\lambda^4P) = +21.4$ Hz, $^3J(\lambda^4P,\lambda^4P) = -37.2$ Hz, $^3J(\lambda^4P,\lambda^3P) = +1.9$ Hz, $^4J(\lambda^3P,\lambda^3P) = +0.5$ Hz.—$^{13}C\{^1H,^{31}P\}$-NMR ([D$_6$]-benzene, 24°C, 75.47 MHz): **5a**: $\delta = 198.81$, 200.33 (CO), 28.41 (λ^4PC), 21.54, 22.08 (λ^4PCC), 25.41 (λ^3PC), 21.73 (λ^3PCC); **5b**: $\delta = 199.67$ (CO), 29.10 (λ^4PC), 21.23, 21.91 (λ^4PCC), 25.14 (λ^3PC), 22.08 (λ^3PCC).
[5] Coordination chemical shift $\Delta = \delta_{complex} - \delta_{free\ ligand}$; S. O. Grim, D. A. Wheatland, W. McFarlane, *J. Am. Chem. Soc. 89* (1967) 5573.
[6] Related to compound **5** is the tetraphosphatrisilanortricyclene complex $[P_4(SiMe_2)_3Cr(Co)_4]_2$ [7a], in which, according to X-ray structure investigations [7b], however, only *one* configurational isomer (C_s symmetry, corresponding to **5b**) occurs; moreover, the P_3 moiety in this complex is rigidly bound in a tricyclic molecular skeleton and strongly favored in its donor ability by the three *cis* oriented Me_2Si groups [8].
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9-Fluorenylidene-2,2,6,6-tetramethylpiperidinoborane: an Allene Isoester with Two-Coordinated Boron and B=C Double Bond**

By *Bernhard Glaser* and *Heinrich Nöth**

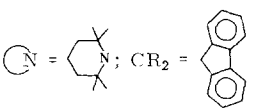
MO studies on the cation $[H_2N{=}B{-}CH_3]^{\oplus}$ suggest that its deprotonation to the amino(methylene)borane $H_2N{=}B{=}CH_2$ containing a BC double bond[1] should be possible.[2] For this allene isoester, a linear NBC skeletal structure is energetically favored over other conformers. The amino(methylene)borane will rapidly oligomerize; hence, bulky substituents are necessary for its kinetic stabilization. Especially suitable for this purpose is, for example, the 2,2,6,6-tetramethylpiperidino (tmp) group, with which stable cations of the type $(R_2N)_2B^{\oplus}$[3] or amino(imino)boranes $R_2N{=}B{\equiv}N{-}R'$[4] can be generated.

We obtained the amino(methylene)borane **1** in 60–70% yield by dehalogenation of 9-fluorenyltetramethylpiperidinoboron halides. **1** crystallizes from toluene or benzene as a 1:1 solvate; from hexane, it is obtained free of solvent.



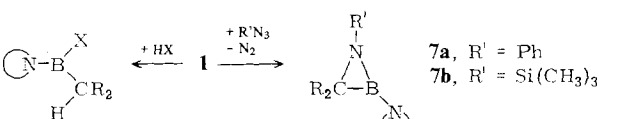
2a, X = F
2b, X = Cl

M = Li, Na; NR_2 = $N[Si(CH_3)_3]_2$, $N[Si(CH_3)_3]C(CH_3)_3$

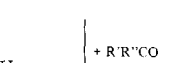


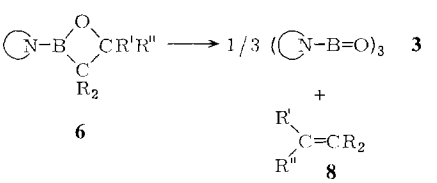
The following results are in accord with the proposed structure for **1**: a) mass spectrometric and cryoscopic molecular weight; b) $\delta(^{11}B) = 59.2$;[5] c) $\delta(^{14}N) = -220$; this value corresponds to the shielding of the N-nucleus in the linear cations $[R_2N{=}B{=}NR_2]^{\oplus}$ ($\delta(^{14}N) = -240$));[6] d) $^4J(^{19}F^{13}C)$ coupling to the methyl groups of the tmp substituents missing (on generating **1** from **2a**); e) $\delta(^{13}C) = 83.2$ for the C-atom of the R_2C group bound to the boron atom and only observed at -30°C (this shift is found also for similarly substituted C-atoms in allenes[7]); f) no $^1J(^{13}C^1H)$ coupling in the ^{13}C-NMR spectrum of **1** for the signal of the C-atom bound to boron; g) the ^1H-NMR spectrum shows no signal in the range $\delta = 2-7$, thus clearly confirming the absence of a proton on C-9 of the fluorene system); h) two IR bands at 1717 and 1740 cm^{-1} in the intensity ratio 4:1 which we assign to $\nu_{as}(N^{11}BC)$ and $\nu_{as}(N^{10}BC)$.[8]

In addition, the high reactivity of **1** also substantiates its unsaturated character: hydrogen chloride, methanol, and dimethylamine add to **1** at -30°C to give the aminoboranes **2b**,[9] **4**,[10] and **5**,[11] respectively. Reaction of benzophenone with **1** produces the cycloadduct **6a**, a 1-oxa-2-boretane, the structure of which was confirmed by an X-ray structure analysis.[12] It decomposes quantitatively to

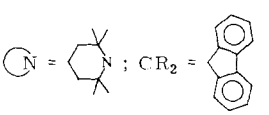


2b, X = Cl
4, X = OCH_3
5, X = $N(CH_3)_2$





6/8: **a**, R', R'' = Ph; **b**, R' = Ph, R'' = H



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the diphenylmethylenefluorene **8a**[13] via a Wittig-like reaction. The cycloadduct **6b** of benzaldehyde[14] and **1** affords the olefin **8b** at 110°C. Finally, it is interesting that azides react with **1** at room temperature with evolution of N_2 to give the azaboriridines **7**.[15]

Experimental

1: A solution of **2a** (10.84 g, 32 mmol) in toluene (100 mL) was treated with lithium *tert*-butyl(trimethylsilyl)amide (5.25 g, 34.7 mmol) at room temperature under nitrogen. After 15 hours' stirring, the insoluble material was removed by centrifugation. On cooling the red solution to −25°C, platelet-shaped crystals precipitated. To increase the yield the solution was then cooled to −78°C and the solid isolated. The crystals, which are very sensitive to hydrolysis, effloresce on drying in a vacuum. Yield: 6.75 g (66%); m.p. 174–176°C; ^{13}C-NMR ($CDCl_3$, 243 K): δ = 16.7, 32.9, 38.0, 56.6 (tmp); 83.2 (B–C), 119.8, 120.9, 121.1, 124.8, 133.0, 144.1 (fluorenyl moiety).

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1, 96097-03-9; **2a**, 96097-04-0; **2b**, 96097-05-1; **4**, 96097-06-2; **5**, 96097-07-3; **6a**, 96097-08-4; **6b**, 96097-09-5; **7a**, 96097-10-8; **7b**, 96097-11-9; **8a**, 4709-68-6; **8b**, 1836-87-9; $((CH_3)_2\overline{CCH_2CH_2CH_2C(CH_3)_2}NB{=}O)_3$, 96097-12-0; $(CH_3)_2\overline{CCH_2CH_2CH_2C(CH_3)_2}NB{=}O$, 96097-13-1; PhN_3, 622-37-7; $(CH_3)_3SiN_3$, 4648-54-8; Benzophenone, 119-61-9; Benzaldehyde, 100-52-7; boron, 7440-42-8.

[1] Systems with a high degree of double bonding include methyleneborates (M. W. Rathke, R. Kow, *J. Am. Chem. Soc. 94* (1972) 6854; A. Pelter, B. Singaram, L. Williams, J. W. Wilson, *Tetrahedron Lett. 24* (1983) 623; A. Pelter, B. Singaram, J. W. Wilson, *ibid. 24* (1983) 635), borinate anions and their transition-metal complexes (G. E. Herberich, H. J. Becker, C. Engelke, *J. Organomet. Chem. 153* (1978) 265; G. E. Herberich, G. Greiss, H. F. Heil, J. Müller, *Chem. Commun. 1971*, 1328; G. E. Herberich, A. K. Naithani, *J. Organomet. Chem. 241* (1983) 1), as well as borabenzene- and boranaphthalene-pyridine (R. Boese, N. Finke, J. Henkelmann, G. Maier, P. Paetzold, H. P. Reisenauer, G. Schmid, *Chem. Ber. 118* (1985) 1644), and a boranediylborirane (cf. [5]).
[2] H. Nöth, R. Staudigl, H.-U. Wagner, *Inorg. Chem. 21* (1982) 706.
[3] H. Nöth, B. Rasthofer, S. Weber, *Z. Naturforsch. B39* (1984) 1058.
[4] H. Nöth, S. Weber, *Z. Naturforsch. B38* (1983) 1460.
[5] The ^{11}B nucleus in **1** is deshielded as compared to that in **2a** and **2b** ($\delta(^{11}B)$ = 33.9 and 42.3, respectively); the chemical shift lies in the range which is given for the three-coordinated boron in the boranediylborirane $[(CH_3)_3Si]_2\overline{C-B(Si)(CH_3)_3C}{=}BC(CH_3)_3$ (H. Klusik, A. Berndt, *Angew. Chem. 95* (1983) 895; *Angew. Chem. Int. Ed. Engl. 22* (1983) 877 ($\delta(^{11}B)$ = 52). Considering more recent theoretical results (P. H. M. Budzelaar, P. von R. Schleyer, W. Krogh-Jesperson, *ibid. 96* (1984) 809 and **23** (1984) 825; G. Frenking, H. F. Schaefer III, *Chem. Phys. Lett. 109* (1984) 521) for this system and $\delta(^{11}B)$ for **1**, together with $\delta(^{11}B)$ = 35–40 for bis(amino)boron(1+) cations the ^{11}B-NMR signal of the boranediylborirane at $\delta(^{11}B)$ = 52 should be assigned to the boron atom with the highest degree of B=C double bonding, and the signal at δ = 18 to the tetracoordinated boron. The signals of $[R_2N{=}B{-}R]^{\oplus}$ lie further downfield [2], cf. B. Wrackmeyer, R. Köster in Houben-Weyl: *Methoden der organischen Chemie, Bd. 13c*, Thieme, Stuttgart 1984, p. 419.
[6] B. Rasthofer, Dissertation, Universität München 1984.
[7] H.-O. Kalinowski, S. Berger, S. Braun: *^{13}C-NMR-Spektroskopie*, Thieme, Stuttgart 1984.
[8] These bands lie at higher frequency than those of the B=C double bond in the boranediylborirane [5] (Raman bands 1675/1716 cm^{-1}) but at lower frequencies than $\nu_{as}(N_2B)$ (1800–1850 cm^{-1}) of the $(R_2N)_2B$ cations: ref. [2], and J. Higashi, A. D. Eastman, R. W. Parry, *Inorg. Chem. 22* (1982) 716. Accordingly, the coupling of the equivalent BN and BC stretching vibrations is not as strong as in the bis(amino)boron cations.
[9] **2b**: m.p. 153–154°C; $\delta(^{11}B)$ = 42.3; $\delta(^{13}C)$ ($CDCl_3$) = 13.2, 32.7, 35.6, 55.9 (tmp), 48.5 (B–*C*), 119.9, 124.2, 126.2, 126.4, 142.1, 146.6 (fluorenyl).
[10] **4**: m.p. 103°C; $\delta(^{11}B)$ = 34.3; $\delta(^{13}C)$ ($CDCl_3$) = 15.0, 33.1, 36.3, 53.3 (tmp), 49.3 (OCH_3), 44.3 (B–*C*), 120.0, 124.3, 125.8, 126.7, 141.7, 146.7 (fluorenyl).
[11] **5**: m.p. 126°C; $\delta(^{11}B)$ = 37.9; $\delta(^{13}C)$ ($CDCl_3$) = 18.3, 28.5, 33.5, 41.8, 52.3 (tmp), 36.2, 42.0 ($N(CH_3)_2$), 46.5 (B–*C*), 119.7, 124.8, 125.1, 126.2, 141.4, 148.3 (fluorenyl).
[12] **6a**: m.p. 156°C (decomp.); $\delta(^{11}B)$ = 36.9; $\delta(^{13}C)$($CDCl_3$) = 16.4, 31.9, 39.9, 53.9 (tmp), 89.0 (O–*C*), 63.5 (B–*C*), 119.3, 125.6, 125.9, 126.2, 126.6, 127.2, 140.6, 145.6, 146.5 (aromat. C).—Monoclinic, space group $P2_1/c$, a = 12.910, b = 11.778, c = 18.678 Å, β = 101.29°, Z = 4, R = 0.0848 and R_w = 0.0776 for 3642 observed reflections, bond lengths in the four-membered ring: BO 1.398(5), CO 1.457(4), CC 1.612(5), BC 1.624(5) Å.
[13] **8a**: m.p. 229°C (Lit. 228°C, M. Rabinowitz, I. Agranat, E. D. Bergmann, *J. Chem. Soc. B1967*, 1281).
[14] **6b**: oil; $\delta(^{11}B)$ = 36.6; $\delta(^{1}H)$ ($CDCl_3$) = 1.06 (6H), 1.10 (6H), 1.42 (m, 6H), 6.00 (1H), 6.60–7.80 (m, 13H).
[15] **7a**: m.p. 151°C; $\delta(^{11}B)$ = 21.3; $\delta(^{13}C)$ ($CDCl_3$) = 16.8, 32.6, 39.2, 54.1 (tmp), 52.3 (B–*C*), 119.7, 119.9, 121.2, 121.3, 125.5, 126.2, 128.9, 139.1, 141.7, 147.7 (aromat. C).—**7b**: m.p. 134°C; $\delta(^{11}B)$ = 24.0; $\delta(^{13}C)$ ($CDCl_3$) = 17.3, 32.3, 39.6, 53.8 (tmp), 1.7 ($Si(CH_3)_3$), 52.9 (B–*C*), 119.7, 121.2, 124.8, 125.9, 138.4, 150.7 (fluorenyl).

Cyanogen as a Bridging Ligand—Preparation and Crystal Structure of Polymeric $[Ag\{(CN)_2\}_2]_n[AsF_6]_n$ with an Undulating Square Cationic Network

By *Herbert W. Roesky,* Hartmut Hofmann, Jürgen Schimkowiak, Peter G. Jones, Karen Meyer-Bäse,* and *George M. Sheldrick*

Dedicated to Professor Rolf Sammet on the occasion of his 65th birthday

Cyanogen has recently become of wide interest.[1] It can be used in the preparation of a variety of heterocycles, with the cyanogen usually remaining intact as an NCCN synthetic unit. In some reactions, however, cleavage of the C–C bond is observed, e.g., when cyanogen functions as a cyanation reagent in the preparation of tetracyanoethene from ethyne.[2] The reaction of cyanogen with sulfur in dimethylformamide in the presence of copper to give 1,2,4-thiadiazole-3,5-dicarbonitrile[3] is also noteworthy. Common to these and other reactions of cyanogen is the active participation of a metal center. The coordination of cyanogen to a metal and the resulting bonding must therefore be of fundamental importance for the course of the catalytic reaction. We were interested therefore in obtaining single crystals of coordination compounds of cyanogen.

Cyanogen is known to react with metal centers both to form "end-on" complexes and to undergo oxidative addition.[4,5] By the reaction of excess cyanogen with the silver salt **1** in liquid SO_2,[6] we have succeeded, as far as we know for the first time, in isolating and determining the crystal structure of a cyanogen complex.

$$[AgAsF_6]_n + 2n\,(CN)_2 \longrightarrow [Ag\{(CN)_2\}_2]_n[AsF_6]_n$$
1 **2** **3**

3 is colorless and water-sensitive and decomposes at 176°C. **2** remains as a linear unit in the reaction and is present in **3** as a bridging ligand between silver atoms. This construction makes possible a polymeric network in which each silver atom is surrounded by four nitrogen atoms in a square planar arrangement (Fig. 1). Only one other example of this coordination geometry—in $Ag_{1.8}Mn_8O_{16}$—is known for silver(I).[7] Weak contacts to the fluorine atoms (276 pm), which, however, can hardly be viewed as covalent interactions, complete a distorted octahedral coordination of the metal. The above-mentioned synthesis of 1,2,4-thiadiazole-3,5-dicarbonitrile[3] becomes more plausible on account of this study, since the planar coordination of the silver by the cyanogen molecules also facilitates coordination to sulfur. It is unknown

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at present how the sulfur is transferred to the cyanogen molecule.

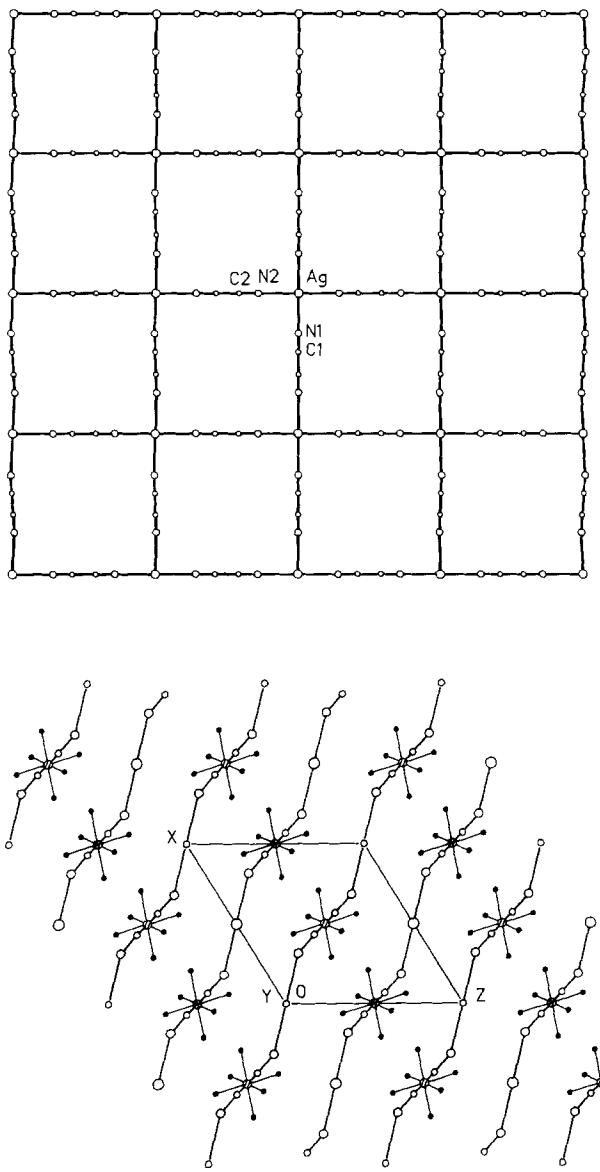


Fig. 1. Above: perspective view of the polymeric layer cation of **3** in the crystal. C2/m, $a = 866.5(4)$, $b = 836.3(3)$, $c = 819.8(4)$ pm, $\beta = 122.06(3)°$, $Z = 2$ (monomers), $T = -40°C$. $Mo_{K\alpha}$, $2\theta_{max} = 55°$. $R = 0.039$, $R_w = 0.043$ for 550 reflections (corrected for absorption) with $F > 4\sigma(F)$. All atoms of the cation lie on special positions; Ag on 0, 0, 0; C1 and N1 on x, 0, z; C2 and N2 on 0, y, 0. The refinement was difficult because of pseudosymmetry (all reflections with odd l are weak) and disorder of the anion. Important bond distances [pm] and bond angles [°]: Ag–N1 239.9(6), Ag–N2 236.4(7), N1–C1 113.8(9), N2–C2 112.8(10), C1–C1′ 138.0(12), C2–C2′ 137.9(14); Ag–N1–C1 152.3(9), N1–C1–C1′ 177.9(14), all other angles 90 or 180°. (C1′ and C2′ are equivalent atoms generated by inversion symmetry). The transformation matrix $0\,-1\,0/-1\,0\,0/-1\,0\,-2$ generates an apparently F-centered orthorhombic cell ($a' = 836.3$, $b' = 866.5$, $c' = 1389.7$ pm), which however, exhibits only monoclinic Laue symmetry. Below: projection of the structure of **3** along the b axis (N2 and C2 lie on this axis and are therefore difficult to recognize). The layers are clearly undulating with an Ag–N1–C1 angle of 152.3°. Only one orientation of the disordered anion is shown. The As atom lies on 0, 0, $\frac{1}{2}$, the F atoms, however, on general positions. Open circles: large, Ag; medium, N; small, C; cross-hatched circles, As; black points, F. Further details of the crystal structure investigation are available on request from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2, on quoting the depository number CSD 51252, the names of the authors, and the journal citation.

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CAS Registry number:
3, 96211-85-7

[1] H. W. Roesky, H. Hofmann, *Chem.-Ztg. 108* (1984) 231.
[2] G. Weddigen (BBC AG), DOS 3127688 (July 14, 1981, Feb. 3, 1983); *Chem. Abstr. 98* (1983) P142984n.
[3] H. W. Roesky, K. Keller, J. W. Bats, *Angew. Chem. 95* (1983) 904; *Angew. Chem. Int. Ed. Engl. 22* (1983) 881; *Angew. Chem. Suppl. 1983*, 1323.
[4] B. Corain, M. Basato, A. Warsone, *Chim. Ind. 61* (1979) 567.
[5] B. Corain, *Coord. Chem. Rev. 47* (1982) 165.
[6] Liquid SO_2 (20 mL) is condensed at −78°C in a pressure vessel containing **1** (1.31 g, 4.4 mmol). The mixture is subsequently heated slowly with stirring to room temperature in order to dissolve **1** homogeneously in SO_2. The mixture is cooled once again to −78°C, and **2** (1.38 g, 26.5 mmol) is condensed into the frozen solution. After thawing, the mixture is stirred for 2 h at room temperature. A light, crystalline precipitate, moderately soluble in SO_2, is formed. After filtration, SO_2 and excess **2** are slowly removed, yielding colorless crystals of **3**, which are very water-sensitive. Yield of **3**: 0.37 g (21%); IR (Nujol): $\nu = 2200$, 2125, 695, and 380 cm^{-1} (cf. CN stretching vibration of gaseous **2** at 2157 cm^{-1}). Strong Raman bands at 2356, 872, 688, 510, and 370 cm^{-1}.
[7] F. M. Chang, M. Jansen, *Angew. Chem. 96* (1984) 902; *Angew. Chem. Int. Ed. Engl. 23* (1984) 906.

Gas-Phase Reactions of Organic Compounds on Raney Nickel**

By *Hans Bock** and *Hans Peter Wolf*

Dedicated to Professor Günther Wilke on the occasion of his 60th birthday

Raney nickel, used advantageously both in industry[2a] and in the laboratory[2b] as an active catalyst for liquid-phase hydrogenations, is prepared from Ni/Al alloys using concentrated caustic soda.[1] Physical investigations[3] have shown that the largely uniform network of pores provides surface areas of up to 100 m^2/g, depending on the method of preparation, and contains regions of ordered Ni crystals. Moreover, the Al component affects not only the texture but also functions as an electron donor to the Ni(3d) band. We report here the reactions of gaseous organic compounds on solid Raney nickel.[1] In comparison with the pyrolysis of such compounds on quartz wool or the catalytic decomposition on nickel turnings, these reactions take place *at much lower temperatures with marked selectivity*.

The following model reactions were studied in a horizontally arranged solid-bed reactor by PE spectroscopic analysis[4] of the gas flow (see Fig. 1): the dehydrogenation of 2-propanol, which competes with its dehydration; the decarbonylation of methyl formate, and the elimination of N_2 from methyl diazoacetate [Reactions (a)–(e)].

$$(H_3C)_2CHOH \xrightarrow{T} H_2 + (H_3C)_2C{=}O \quad (a)$$

$$(H_3C)_2CHOH \xrightarrow{T} H_2O + H_3C{-}HC{=}CH_2 \quad (b)$$

$$HCOOCH_3 \xrightarrow{T_1} CO + H_3COH \xrightarrow{T_2} CO + 2H_2 \quad (c)$$

$$NN{=}CH{-}COOCH_3 \xrightarrow{T} N_2 + CO + H_3C{-}CHO \quad (d)$$

$$NN{=}CH{-}COOCH_3 \xrightarrow{T} N_2 + H_3COOCHC{=}CHCOOCH_3 \quad (e)$$

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[**] Gas-phase reactions, Part 50. This work was supported by the Land Hessen, the Deutsche Forschungsgemeinschaft, and the Fonds der Chemischen Industrie. Part 49: H. Bock, B. Solouki, G. Maier, *Angew. Chem. 97* (1985) 205; *Angew. Chem. Int. Ed. Engl. 24* (1985) 205.

2-Propanol is approximately fifty percent dehydrogenated to acetone upon passage over a 5-cm layer of Raney nickel at room temperature and 10^{-2} mbar [Reaction (a)]; the hydrogen evolved can be identified by its characteristic PES ionization pattern (Fig. 1, middle, insert) after trapping of the condensable gases in an inserted liquid nitrogen cold trap. The elimination of H_2 takes place quantitatively at 350 K (Fig. 1, bottom).

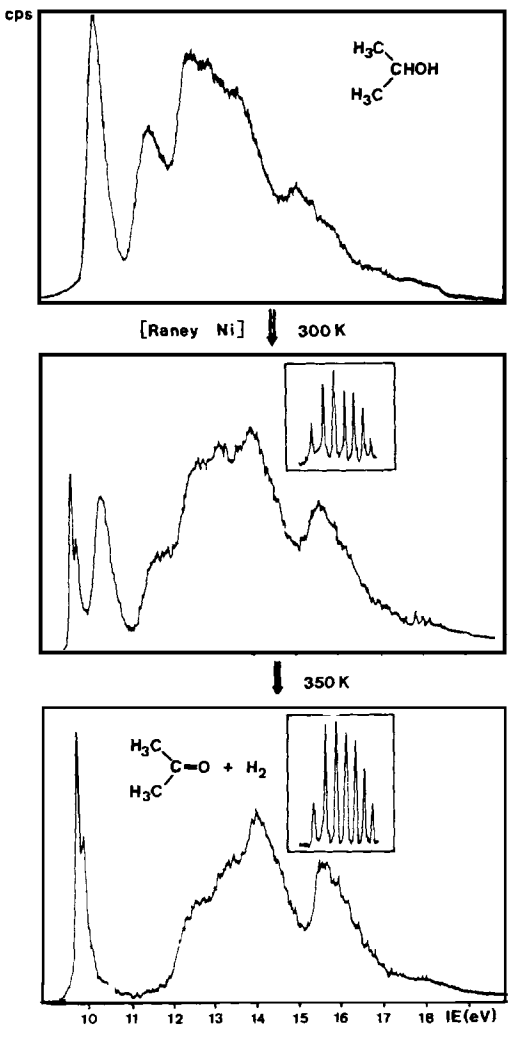


Fig. 1. He(I) PE spectra of 2-propanol (top) and of the product mixture obtained after passage over Raney nickel at 300 K and 350 K (middle and bottom, respectively). The vibrational fine structure of the H_2 band—recorded after condensation of the products at 77 K—is shown in the two inserts.

Raney nickel lowers the required temperature for the thermolysis of 2-propanol by more than 600 K compared with that on quartz wool, which begins with the elimination of water at 870 K to yield propene [Reaction (b)] and in which the dehydrogenation to acetone [Reaction (a)] can only be detected above 970 K. The catalysis by nickel turnings of comparable particle size lowers the temperature only 350 K.[1]

Even larger temperature differences are observed for the decarbonylation of methyl formate [Reaction (c); T_1] under the same reaction conditions:[1] the elimination of CO begins at 1100 K on quartz wool, at 700 K on nickel turnings, and at 370 K on Raney nickel. The methanol formed is completely decomposed to CO and H_2 upon raising the temperature only another 50 K [Reaction (c); T_2]. This enormous catalytic activity, which is also observed for other Ni_x contacts having large surface areas,[5] is due to the known, favorable chemisorption of carbon monoxide[6] and hydrogen[3,6] on the Ni surface.

The largest differences between thermal and catalytic decomposition are found for methyl diazoacetate:[1] on quartz wool, CO is eliminated along with N_2 above 523 K. Acetaldehyde can be identified in the resulting mixture of products PE-spectroscopically by the sharp band at 10.26 eV [Reaction (d)]. In contrast, on Raney nickel, N_2 is evolved already at room temperature, and, after passage of $NN{=}CH{-}COOCH_3$ for several hours at 350 K, a mixture of dimethyl maleate and dimethyl fumarate can be preparatively isolated in an inserted cold trap at 77 K [Reaction (e)]. This surprising result presumably can be explained by dimerization of methoxycarbonylcarbenes formed on the nickel surface—in analogy to the reaction of diazomethane on nickel producing ethene in the classic studies of *Pettit* on the mechanism of the Fischer-Tropsch synthesis.[7]

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$(H_3C)_2CHOH$, 67-63-0; $HCOOCH_3$, 107-31-3; $NN{=}CHCOOCH_3$, 6832-16-2; nickel, 7440-02-0; quartz, 14808-60-7.

[1] H. P. Wolf, Diplomarbeit, Universität Frankfurt 1984, and references therein. Experimental procedure for the Raney nickel used here: Ground and sieved Ni/Al alloy (27 g, particle diameter 1 mm, Degussa, 50 wt.-% Ni) is dissolved under purified N_2 in 30 mL of water. A solution of KOH (5.6 g) in 30 mL of degassed H_2O is added slowly under cooling. After evolution of 4.7 L of H_2 (corresponding to 3.8 g of Al as $KAlO_2$), the reaction is stopped by cooling to 3°C; the suspended Raney Ni is transferred under N_2 into a reaction tube stoppered with quartz wool and dried at 350°C and 1 mbar for 5 h. The Raney nickel is then activated in a stream of H_2 for 2 h and subsequently heated at 10^{-2} mbar until the intense PES ionization peak of H_2O at 12.62 eV has disappeared. Analysis after dissolving in HCl and filtering off 6.2% Al_2O_3: Ni(electrogravimetrically) 57.4%; Al (as Al_2O_3) 36.4%.

[2] See, e.g., a) K. Winnacker, L. Küchler: *Chemische Technologie, Bd. 6 (Organische Technologie II)*, 4th Ed., Hanser, Munich 1982; K. Weissermel, H. J. Arpe: *Industrielle Organische Chemie*, 2nd Ed., Verlag Chemie, Weinheim 1978; b) S. Hünig, G. Märkl, J. Sauer: *Integriertes Organisches Praktikum*, Verlag Chemie, Weinheim 1979.

[3] Review: P. Fouilloux, *Appl. Catal. 8* (1983) 1, and references cited therein.

[4] Review: H. Bock, B. Solouki, *Angew. Chem. 93* (1981) 431; *Angew. Chem. Int. Ed. Engl. 20* (1981) 432, and references cited therein.

[5] Pumice (Merck 2441) [1] or active charcoal (Strem Chem. 4021) are suitable as carriers with high surface areas, O. Breuer, Diplomarbeit, Universität Frankfurt 1984. After impregnation with the Ni^{2+} salt in a sonicating bath, reduction is carried out with hydrogen at temperatures up to 720 K.

[6] For chemisorption studies on nickel [111] surfaces, see, e.g., G. Ertl, *Angew. Chem. 88* (1976) 423; *Angew. Chem. Int. Ed. Engl. 15* (1976) 391 or E. L. Muetterties, *ibid. 90* (1978) 577 and *17* (1978) 545, and references cited therein.

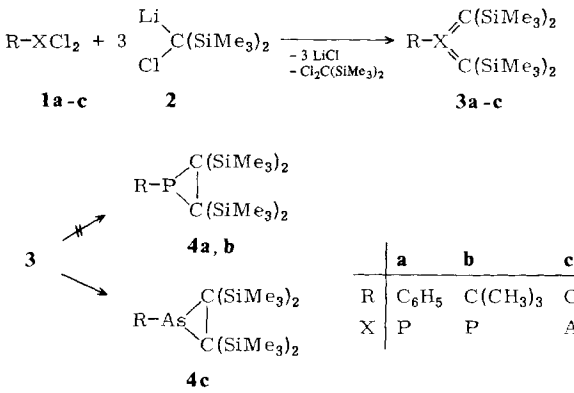
[7] R. C. Brady III, R. Pettit, *J. Am. Chem. Soc. 102* (1980) 6181; *103* (1981) 1287. See also the review of W. A. Herrmann, *Angew. Chem. 94* (1982) 118; *Angew. Chem. Int. Ed. Engl. 21* (1982) 117.

The First Arsirane

By *Rolf Appel,* Thomas Gaitzsch,* and *Falk Knoch*

Dichlorophosphanes **1a,b** react with lithium chloro[bis(trimethylsilyl)]methanide **2** to give stable bis[bis(trimethylsilyl)methylene]phosphoranes **3**.[1,2] Further reaction to give the phosphiranes **4**, which is observed in the case of bismethylenephosphoranes substituted otherwise at the methylene C-atoms,[3,4] does not take place here because of shielding by the bulky trimethylsilyl groups.

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On carrying out this reaction with dichloroarsanes **1c** we have now succeeded for the first time in synthesizing a bismethylenearsorane **3c**. Of the dichloroarsanes $RAsCl_2$ (R = Me, *t*Bu, Ph) tested, only the phenyl compound gave no additional reactions. NMR spectroscopic monitoring of the reaction revealed that initially only the red bismethylenearsorane **3c** is formed below −15°C; unlike the analogous phosphorane it is unstable and rearranges within a short period of time into the stable arsirane **4c**. The composition of the crystalline and colorless substance **4c** precipitating from pentane is secured by elemental analysis and mass spectrum; its structure was confirmed by an X-ray structure analysis (Fig. 1).[5]

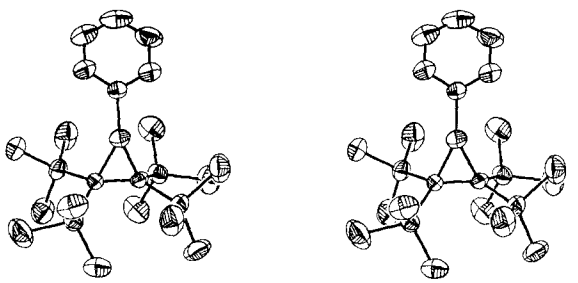


Fig. 1. Stereoview of the crystal structure of **4c**.

The arsirane **4c** is, to our knowledge, the first arsacyclopropane to have been isolated. Only one bicyclic system containing an annelated arsirane ring has so far been reported in the literature.[6]

The characteristic spectroscopic data of **3c** and **4c** are listed along with those of the phosphorus analogues in Table 1.

Table 1. Characteristic ^{13}C-NMR data of **3c** and **4c** compared with those of the corresponding phenyl- and *tert*-butylbismethylenephosphoranes; δ values rel. TMS ext., positive downfield, solvent $CDCl_3$, J [Hz].

	$=C(SiMe_3)_2$	J	$Si-CH_3$	J	$C(SiMe_3)_2$
3a	80.2 (d)	46.8	3.6 (d)	11.0	—
3b	84.0 (d)	37.3	5.5 (d)	15.0	—
3c	105.5 (s)	—	4.1 (s)	—	—
4c	—	—	7.9 (s), 7.3 (s)	—	37.3 (s)

Experimental

59 mL of a commercially available 1.6 M solution of *n*BuLi in hexane (0.09 mol) was added dropwise to a mixture of tetrahydrofuran (200 mL), diethyl ether (20 mL), pentane (20 mL), and dichlorobis(trimethylsilyl)methane (20.6 g, 0.09 mol) cooled to −110°C. The mixture was stirred for 3 h, then treated with a solution of **1c** (6.57 g, 0.03 mol) in THF (10 mL), and allowed to warm to −15°C. The solvents were then removed and the mixture was taken up in 50 mL of pre-cooled pentane and filtered. Finally, solvent and dichlorobis(trimethylsilyl)methane were condensed off as quickly as possible at room temperature in a vacuum. From the solution of the residue in 10 mL pentane, **3c** precipitated as a red solid. At room temperature, **3c** undergoes complete conversion within 12 h into **4c**, which can be recrystallized from pentane. M.p. 91°C (**4c**), yield 67%.

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CAS Registry numbers:
1c, 696-28-6; **3a**, 80359-67-7; **3b**, 96041-40-6; **3c**, 96041-41-7; **4c**, 96041-42-8; $Cl_2C(SiMe_3)_2$, 15951-41-4.

[1] R. Appel, J. Peters, A. Westerhaus, *Angew. Chem. 94* (1982) 76; *Angew. Chem. Int. Ed. Engl. 21* (1982) 80.
[2] R. Appel, K.-H. Dunker, E. Gaitzsch, T. Gaitzsch, *Z. Chem. 24* (1984) 384.
[3] E. Niecke, M. Lauer, D. A. Wildbredt, W. Schoeller, *J. Chem. Soc. Chem. Commun. 1983*, 1171.
[4] R. Appel, G. Lenz, unpublished.
[5] Molecular structure of **4c**: $P\bar{1}$, $a = 954.8(4)$, $b = 1062.5(4)$, $c = 1351.8(5)$ pm, $\alpha = 98.14(3)$, $\beta = 91.27(3)$, $\gamma = 105.40(3)°$, $V = 1306.2(8) \times 10^6$ pm^3, $\rho_{calc} = 1.19$ g/cm^3 $Z = 2$. Direct methods (SHELXTL), 3108 single-crystal diffractometer data, $R = 0.047$ ($R_w = 0.038$). Geometry: mean AsC bond length in the ring 2.023 pm, CC bond length in the ring 1.581 pm; C(aryl)AsC1 angle 111.8°, C(aryl)AsC2 = 109.5°, C1AsC2 = 46.0°. The angle of pitch of the phenyl group on As to the three-membered plane of 113° underscores the pyramidal configuration of the heteroatom. Further details of the crystal structure investigation are available on request from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2, on quoting the CSD number 51 198, the names of the authors, and the full citation of the journal.
[6] B. A. Arbuzov, E. N. Dianova, E. Y. Zabotina, *Zh. Obshch. Khim. 53* (1983) 835; *Chem. Abstr. 99* (1983) 70879m.

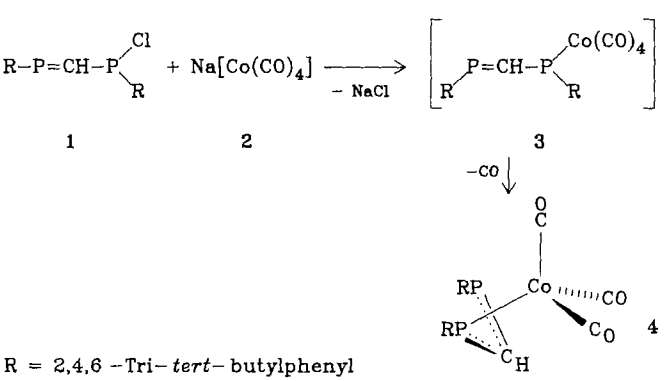
Tricarbonyl(1,3-diphosphaallyl)cobalt, a Phosphorus Analogue of (η^3-Allyl)tricarbonylcobalt**

By *Rolf Appel,* Winfried Schuhn,* and *Falk Knoch*

Dedicated to Professor Günther Wilke on the occasion of his 60th birthday

In transition-metal complexes containing phosphaalkene ligands, η^1-(P) and η^2-(P=C) coordination[1] is observed. We have now obtained the first complex with an η^3-1,3-diphosphaallyl ligand.

The chlorophosphino-substituted methylene phosphane **1**[2] reacts smoothly with sodium tetracarbonylcobalt **2** in



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[**] Lower coordinated phosphorus compounds, Part 38.—Part 37: R. Appel, J. Menzel, F. Knoch, *Chem. Ber.*, in press.

tetrahydrofuran (THF) via **3**, which cannot be detected spectroscopically, to give tricarbonyl(1,3-diphosphaallyl)cobalt **4** (correct elemental analysis); in the process, NaCl is eliminated and CO evolved.

According to the X-ray structure determination (Fig. 1), **4** can be described best as a square pyramid having two P atoms and two CO ligands at the base and a third carbonyl group at the apex, with the allyl C atom below the basal plane pointing towards the Co center. The NMR data[3] (magnetic equivalence of the two aryl-P units) are in accord with this description.

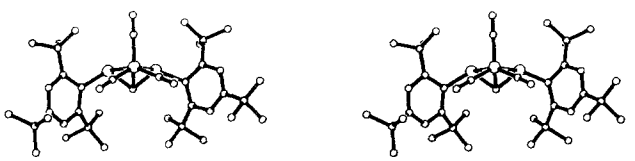


Fig. 1. Stereograph of the crystal structure of **4**.

The following findings support the classification of **4** as a 1,3-diphosphaallyl complex:[4] all three atoms of the PCP triad are bonded to the Co atom; the C1 atoms of the aryl moieties and the PCHP skeleton form a plane; the PC distances within the ligands are the same and lie between a PC single bond and a PC double bond, in contrast to the starting material.

Experimental procedure

A solution of octacarbonyldicobalt (0.85 g, 2.5 mmol) in THF (50 mL) is added to 13 g of 1% sodium amalgam. After stirring overnight at room temperature, the supernatant is decanted and treated with **1** (3.0 g, 5 mmol), then heated at 45 °C for 4 h, during which time the solution undergoes a color change from yellow to rust-brown. The solvent is removed and the residue extracted three times with 20 mL of hexane. The extracts are combined; **3** crystallizes out as orangish brown prisms. Yield: 1.9 g (53%), m.p. = 163 °C (decomp.).

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CAS Registry numbers:
1, 96164-77-1; **2**, 14878-28-5; **4**, 96193-91-8.

[1] a) T. C. Kleebach, R. Lourens, F. Bickelhaupt, *J. Organomet. Chem. 210* (1981) 211; b) S. I. Al-Resayes, S. I. Klein, H. W. Kroto, M. F. Meidine, J. F. Nixon, *J. Chem. Soc. Chem. Commun. 1983*, 930; c) A. H. Cowley, R. A. Jones, L. A. Stewart, A. L. Stuart, *J. Am. Chem. Soc. 105* (1983) 3737; d) R. Appel, C. Casser, M. Immenkeppel, F. Knoch, *Angew. Chem. 96* (1984) 905; *Angew. Chem. Int. Ed. Engl. 23* (1984) 895.

[2] a) V. Barth, Dissertation, Universität Bonn 1983; b) H. H. Karsch, F. H. Koehler, H. U. Reisacher, *Tetrahedron Lett. 25* (1984) 3687.

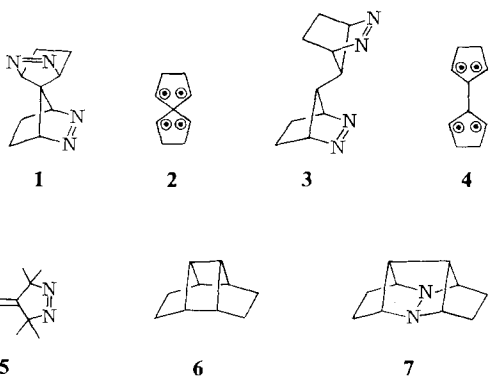
[3] Selected NMR data: ^{31}P-NMR (32.2 MHz, H_3PO_4 ext., C_6D_6): $\delta = 34.4$ (d, $J(PCH) = 7.0$ Hz). ^{1}H-NMR (90 MHz, TMS int., C_6D_6): $\delta = 0.8$ (s, 18 H, CH_3), 1.3 (s, 36 H, CH_3), 5.8 (t, 1 H, CH), 7.0 (br., 4 H, aromat. H). ^{13}C-NMR (20 MHz, C_6D_6): $\delta = 31.1$ (s, *p*-CH_3), 34.5 (t, *o*-CH_3), 34.6 (s, *p*-CCH_3), 39.3 (s, *o*-CCH_3), 90.6 (t, $J(PC) = 86$ Hz, CH), 123.2 (s, aromat. C3), 135.8 ("t", $J(CP + CPP) \approx 52$ Hz, aromat. C1), 150.0 (s, aromat. C-4), 157.1 (m, aromat. C2), 201 (br., CO).

[4] X-ray analysis of **1**: $P2_1/c$; $a = 1732.1(6)$, $b = 1005.8(4)$, $c = 2357.5(9)$ pm, $\beta = 93.38(3)°$. $V = 4100.0 \cdot 10^6$ pm^3, $\rho_{calcd.} = 1.15$ g/cm^3, $Z = 4$. Direct methods (SHELXTL), 4631 reflections, $R = 0.082$ ($R_w = 0.066$ for disorder of the *t*Bu groups). Important bond distances [pm] and bond angles [°] (standard deviations in parentheses): Co–P 238.2(2)/239.5(2), P–C(allyl) 176.9(7)/179.1(7), Co–C(allyl) 203.4(7), Co–C(carbonyl, basal) 179(1)/181(1), Co–C(carbonyl, apical) 184(1); PCP 101.8(4), PCH 129 (H atoms from a difference Fourier synthesis; dihedral angle PCP/PCoP 102. Further details of the crystal structure investigation are available on request from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2, on quoting the depository number CSD 51232, the names of the authors, and the journal citation.

Laser Photolysis of the Bisazoalkane 7-*syn*,7′-*anti*-Bis-2,3-diazabicyclo[2.2.1]hept-2-ene

By *Waldemar Adam,* Klaus Hannemann, Eva-Maria Peters, Karl Peters, Hans Georg von Schnering,* and *R. Marshall Wilson*

Recently the synthesis of the tetraradical **2** by denitrogenation of the bisazoalkane **1** was reported.[1] We have now synthesized the bisazoalkane **3**, from which we wanted to generate the tetraradical **4** by laser photolysis. Although other suitable bisazoalkanes such as the bisazoalkane **5**[2] are known, no formation of tetraradicals could hitherto be observed.[3] Should **4** be formed, then it could react further with intramolecular coupling to give the known[4] hydrocarbon **6**; that is, its formation would be an indication of the intermediary occurrence of the tetrayl **4**. By stepwise cleavage of N_2, the formation of the novel hydrazine **7** would be possible by intramolecular trapping reaction[5] of the diyl with the remaining azo group.



1 **2** **3** **4**

5 **6** **7**

The bisazoalkane **3**[6] was prepared from the known bisurazole,[7] which is formed upon double cycloaddition of 4-phenyl-4*H*-1,2,4-triazole-3,5-dione (PTAD) to 9,10-dihydrofulvalene, by catalytic hydrogenation and subsequent oxidative hydrolysis. The X-ray structure analysis of the bis-azoalkane **3** (Fig. 1, top) showed that the double PTAD cycloaddition led to the *syn,anti*-product.[8]

Both the direct as well as the triplet-sensitized laser photolysis[9] of the bisazoalkane **3** gave, besides unreacted **3**, small amounts (ca. 15%) of the four possible monoazoalkanes **8a**, **d** (major products) and **8b**, **c** (minor products). Cleavage of N_2 from the "upper" azo group led to the isomers **8a**, **b**, while cleavage of N_2 from the "lower" azo group furnished the isomers **8c**, **d**. All the isomers could be completely characterized on the basis of their spectral data and could be recovered in pure form by column and gas chromatography. The X-ray structure analysis of **8c** (Fig. 1, bottom)[8] proved to be a valuable aid for the stereochemical assignment of all isomers. The isomeric com-

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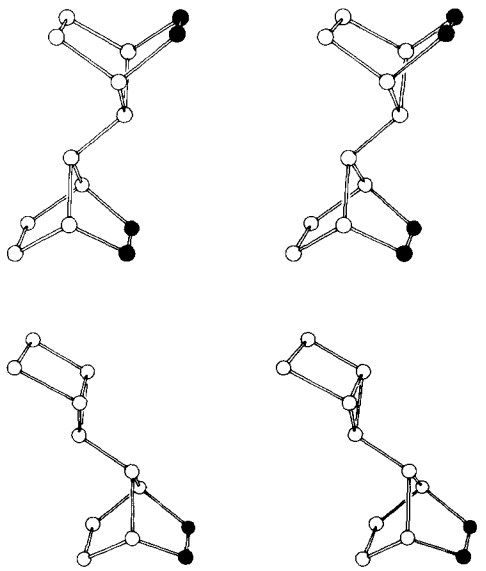
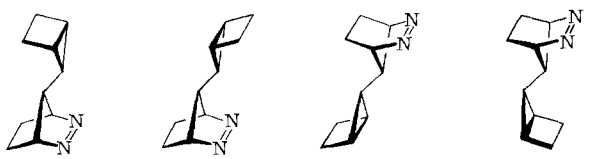


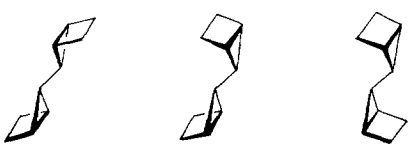
Fig. 1. Stereoviews of the crystal structures of **3** (top) and **8c** (bottom) [8]; ● N, ○ C.

position depended on the irradiation conditions (direct or sensitized); even at optimal intensity (focused laser beam at maximum power) no further products could be detected by capillary gas chromatography.



8a **8b** **8c** **8d**

The complete photolysis (direct as well as sensitized) of the bisazo compound **3** yielded the three possible bi-5,5′-bicyclo[2.1.0]pentanes **9a**—**9c** in roughly statistic amounts.



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For the formation of **4**, two photons have to be successively absorbed (one by each azo chromophore) ($\mathbf{3} \xrightarrow{h\nu} \mathbf{3}^* \xrightarrow{h\nu} \mathbf{3}^{**}$) within the lifetime of an n,π*-excited state (ca. 1 ns), so as to ensure a double N_2-cleavage. Although "two-photon processes" have been observed during pulsed laser irradiation,[11] no cases of a simultaneous double N_2-cleavage leading to a tetraradical has hitherto been reported. Even **2**, which should be favored by stereoelectronic factors such as ring strain and spiroconjugation, is not formed upon photolysis of the bisazo compound. Here too, instead of the required simultaneous double N_2-cleavage, a stepwise process takes place.[10] The generation and detection of polyradicals still remain a challenge.

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[1] a) L. McElwee-White, W. A. Goddard III, D. A. Dougherty, *J. Am. Chem. Soc. 106* (1984) 3461; b) L. McElwee-White, D. A. Dougherty, *ibid. 106* (1984) 3466.
[2] W. Adam, O. De Lucchi, *Angew. Chem. 92* (1980) 815; *Angew. Chem. Int. Ed. Engl. 19* (1980) 762.
[3] R. J. Bushby, S. Mann, *Tetrahedron Lett. 24* (1983) 4743.
[4] L. A. Paquette, R. F. Davis, D. R. James, *Tetrahedron Lett. 1974*, 1615.
[5] a) R. D. Little, G. W. Muller, *J. Am. Chem. Soc. 101* (1979) 7219; b) R. D. Little, K. J. Stone, *ibid. 105* (1983) 6976.
[6] M.p. 190°C (decomp.), recrystallized from ethanol.—^{1}H-NMR ($CDCl_3$; 400 MHz): $\delta = 0.87$ (br. d, $J = 11$ Hz; 1H, 7′-H), 0.90—1.03 (m; 4H, H_n), 1.19 (d, $J = 11$ Hz; 1H, 7-H), 1.47—1.63 (m; 4H, H_x), 4.82 (br. s; 2H, 1′,4′-H), 5.03 (br. s; 2H, 1,4-H).—^{13}C-NMR ($CDCl_3$; 100 MHz): $\delta = 17.96$ (t), 20.89 (t), 46.87 (d), 51.19 (d), 77.95 (d), 79.53 (d).—Correct elemental analysis.
[7] L. A. Paquette, M. J. Wyvratt, H. C. Berk, R. E. Moerck, *J. Am. Chem. Soc. 100* (1978) 5845.
[8] Further details of the crystal structure investigations of **3** and **8c** are available on request from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2, on quoting the depository number CSD 51219, the names of the authors, and the full citation of the journal.
[9] In the direct photolysis (COHERENT supergraphite-argon ion laser; total power ca. 3 W for the 334, 351, and 364 nm UV lines) [3] ≈ 0.01 M in benzene, and in the triplet-sensitized photolysis additionally [benzophenone] ≈ 0.1 M were used.
[10] W. R. Roth, M. Martin, *Justus Liebigs Ann. Chem. 702* (1967) 1; *Tetrahedron Lett. 1967*, 4695.
[11] a) V. S. Letokhov, *Nature (London) 305* (1983) 103; b) T. R. Evans (Ed.): *Applications of Lasers to Chemical Problems (Techniques of Chemistry, Vol. XVII)*, Wiley, New York 1982; c) J. S. Steinfeld (Ed.): *Laser-induced Chemical Processes*, Plenum, New York 1981; d) J. C. Scaiano, P. J. Wagner, *J. Am. Chem. Soc. 106* (1984) 4626.

Synthesis, Structure, and Reactivity of η^3-1-Azaallylmolybdenum Complexes**

By *Michael Green,* Richard J. Mercer, Carolyn E. Morton,* and *A. Guy Orpen*

Dedicated to Professor F. G. A. Stone on the occasion of his 60th birthday

Although the ubiquitous η^3-allyl ligand has been shown to play an important role in many transition metal mediated reactions,[1] little is known about the chemistry of η^3-1-azaallyl complexes[2] where a terminal CH_2 group of the allyl fragment is replaced by an NH group. Such compounds can be formed on reaction of the 2-substituted azirines[3] **1** and **2** with the unsaturated dimolybdenum species $[Mo_2(CO)_4(\eta\text{-}C_5H_5)_2]$. In toluene at room temperature, the initial red-brown color becomes dark green, and column chromatography on alumina afforded orange crys-

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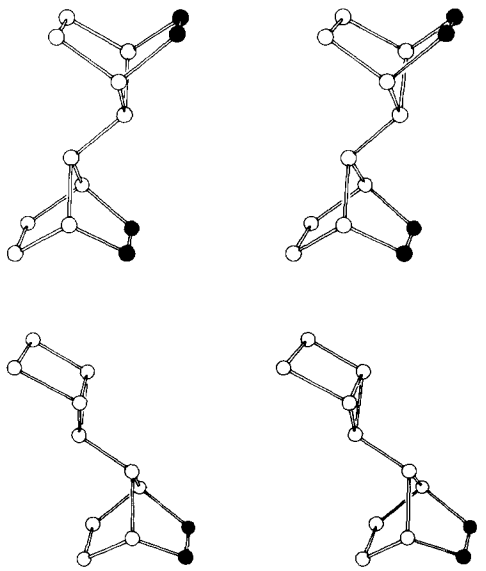
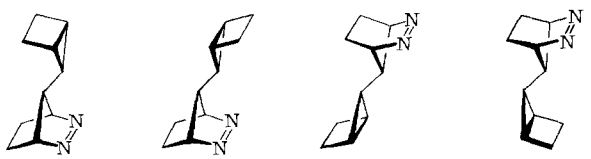


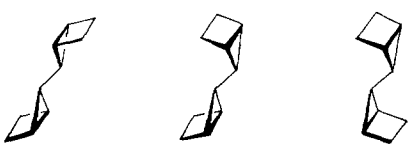
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[5] a) R. D. Little, G. W. Muller, *J. Am. Chem. Soc. 101* (1979) 7219; b) R. D. Little, K. J. Stone, *ibid. 105* (1983) 6976.
[6] M.p. 190°C (decomp.), recrystallized from ethanol.—^{1}H-NMR ($CDCl_3$; 400 MHz): $\delta = 0.87$ (br. d, $J = 11$ Hz; 1H, 7′-H), 0.90—1.03 (m; 4H, H_n), 1.19 (d, $J = 11$ Hz; 1H, 7-H), 1.47—1.63 (m; 4H, H_x), 4.82 (br. s; 2H, 1′,4′-H), 5.03 (br. s; 2H, 1,4-H).—^{13}C-NMR ($CDCl_3$; 100 MHz): $\delta = 17.96$ (t), 20.89 (t), 46.87 (d), 51.19 (d), 77.95 (d), 79.53 (d).—Correct elemental analysis.
[7] L. A. Paquette, M. J. Wyvratt, H. C. Berk, R. E. Moerck, *J. Am. Chem. Soc. 100* (1978) 5845.
[8] Further details of the crystal structure investigations of **3** and **8c** are available on request from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2, on quoting the depository number CSD 51219, the names of the authors, and the full citation of the journal.
[9] In the direct photolysis (COHERENT supergraphite-argon ion laser; total power ca. 3 W for the 334, 351, and 364 nm UV lines) [3] ≈ 0.01 M in benzene, and in the triplet-sensitized photolysis additionally [benzophenone] ≈ 0.1 M were used.
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Synthesis, Structure, and Reactivity of η^3-1-Azaallylmolybdenum Complexes**

By *Michael Green,* Richard J. Mercer, Carolyn E. Morton,* and *A. Guy Orpen*

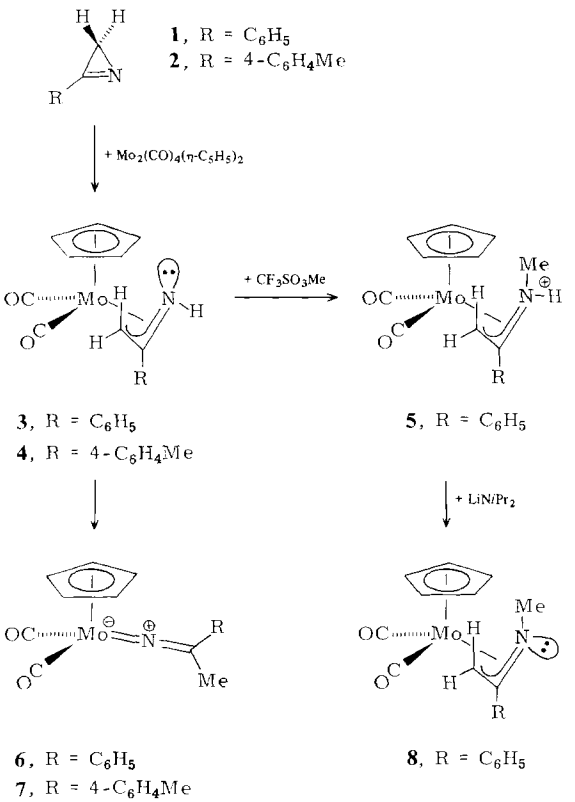
Dedicated to Professor F. G. A. Stone on the occasion of his 60th birthday

Although the ubiquitous η^3-allyl ligand has been shown to play an important role in many transition metal mediated reactions,[1] little is known about the chemistry of η^3-1-azaallyl complexes[2] where a terminal CH_2 group of the allyl fragment is replaced by an NH group. Such compounds can be formed on reaction of the 2-substituted azirines[3] **1** and **2** with the unsaturated dimolybdenum species $[Mo_2(CO)_4(\eta\text{-}C_5H_5)_2]$. In toluene at room temperature, the initial red-brown color becomes dark green, and column chromatography on alumina afforded orange crys-

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tals of **3** and **4**.[4] The elemental analysis and IR, ^{1}H-, and ^{13}C{^{1}H}-NMR spectra[5] suggested that a ring-opening reaction had occurred with formation of azaallyl complexes, where the nitrogen now carries an additional hydrogen atom, which is presumed to originate from the alumina.



The X-ray structure analysis of **4**[6] shows that the $[Mo(CO)_2(\eta\text{-}C_5H_5)]$ fragment has typical dimensions and is bound to an η^3-1-azaallyl moiety. This group adopts an *endo* configuration with respect to the cyclopentadienyl ligand, presumably because this avoids unfavorable contacts involving the *p*-C_6H_4Me group on the central allyl carbon and the C_5H_5 ring. The hydrogen atom carried by the nitrogen lies close to the C_2N plane of the azaallyl ligand. This and the geometry at the nitrogen implies sp^2 hybridization, the lone pair occupying the *anti*- and the hydrogen the *syn*-position, respectively, on the azaallyl fragment. The differences in the Mo–C(8) and Mo–C(9) distances show some tendency towards flattening of the Mo–C(8)–C(9)–N unit, i.e., progression towards the planar geometry familiar for dihetero 'allyls' such as dithioacetates (for which η^2-coordination is common, of course, but η^3-coordination is known[7]).

The structural evidence is unambiguous in indicating that the nitrogen atom possesses a basic functionality. Chemical evidence for the presence of a nitrogen lone pair was provided by the observation that addition (−78 °C, THF) of methyl triflate to **3** followed by proton abstraction with the sterically hindered base lithium diisopropylamide (−78 °C, THF) afforded (70% yield) the orange complex **8**, which was characterized by NMR as the illustrated *anti*-substituted η^3-*N*-methyl-1-azaallyl complex.

It is particularly interesting that the hydrogen atom attached to the nitrogen atom is labile. In methylene chloride or benzene solution the azaallyls **3** and **4** slowly (room temperature, 12 h) rearrange to form the dark green

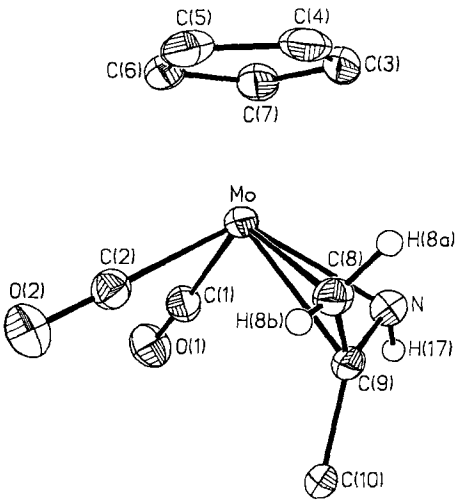


Fig. 1. Molecular structure of **4** [6]. Tolyl group and cyclopentadienyl hydrogens omitted for clarity. Important bond distances [Å] and angles [°]: Mo–C(8) 2.262(3), Mo–C(9) 2.334(3), Mo–N 2.340(3), C(8)–C(9) 1.371(4), C(9)–N 1.380(4), C(8)–H(8a) 0.91(3), C(8)–H(8b) 0.77(3), C(9)–C(10) 1.497(4), N–H(17) 0.99(4), Mo–C(Cp) 2.295(3)–2.404(4); H(17)–N–C(9) 113(2), C(9)–N–Mo 76.2(2), C(8)–C(9)–N 112.6(3).

complexes **6** and **7**. When the reaction was monitored by NMR spectroscopy[5] the N*H* and C*H*$_2$ signals of the azaallyls decreased in intensity to be replaced by a new methyl resonance. In the ^{13}C{^{1}H}-NMR spectrum the η^3-1-azaallyl quaternary carbon at $\delta = 101.02$ is replaced by a quaternary carbon at $\delta = 155.38$, characteristic of an uncoordinated azomethine carbon. It is suggested that **6** and **7** have the illustrated linear azavinylidene-like structure; a type of molecule which has previously[8] been synthesized by reaction of $LiN{=}CtBu_2$ with $[MoCl(CO)_3(\eta\text{-}C_5H_5)]$. In this connection it is interesting to note that the phosphorus analogue $[Mo\{\eta^1\text{-}P{=}C(SiMe_3)_2\}(CO)_2(\eta\text{-}C_5H_5)]$ has recently[9] been prepared by reaction of $K[Mo(CO)_3(\eta\text{-}C_5H_5)]$ with $(Me_3Si)_2C{=}PCl$. There is no precedent for the rearrangement **3**/**4**→**6**/**7**, which involves a formal 1,3-hydrogen shift and resembles an enamine→imine rearrangement.

Thus, this study has demonstrated that η^3-1-azaallylmolybdenum complexes are stable species and can be synthesized from azirines; the nitrogen lone pair can be alkylated, and a novel nitrogen to carbon H-shift provides a route to azavinylidene metal complexes.

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1, 7654-06-0; **2**, 32687-33-5; **3**, 96110-23-5; **4**, 96110-24-6; **5**, 96110-25-7; **6**, 96110-26-8; **7**, 96110-27-9; **8**, 96110-28-0; $Mo\{\eta^1\text{-}P{=}C(SiMe_3)_2\}(CO)_2(\eta\text{-}C_5H_5)$, 91239-79-1; $K[Mo(CO)_3(\eta\text{-}C_5H_5)]$, 62866-01-7; $Mo_2(CO)_4(\eta\text{-}C_5H_5)_2$, 56200-27-2; $(Me_3Si)_2C{=}PCl$, 79454-85-6.

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[2] Heteroallyl species containing two terminal nitrogens or one centrally located nitrogen have been synthesized, but not structurally characterized. H. R. Keable, M. Kilner, *J. Chem. Soc. Dalton Trans. 1972*, 153; T. Inglis, M. Kilner, T. Reynoldson, E. E. Robertson, *ibid. 1975*, 924; T. Inglis, M. Kilner, *ibid. 1975*, 930.

[3] A series of organic heterocyclic molecules have been synthesized by metal-promoted reactions of azirines. H. Alper, F. Urso, D. J. H. Smith, *J. Am. Chem. Soc. 105* (1983) 6737; H. Alper, C. P. Mahatantila, F. W. B. Einstein, A. C. Willis, *ibid. 106* (1984) 2708.

[4] Procedure: All operations were carried out under N_2 and in anhydrous solvents. A solution of $[Mo_2(CO)_4(\eta\text{-}C_5H_5)_2]$ (1.0 g, 2.3 mmol) in toluene

(60 mL) was treated at room temperature with an excess of 2-phenylazirine (0.8 g, 6.9 mmol) and stirred for twelve hours in a sealed tube. The solvent was removed from the resulting dark green solution *in vacuo*, and the solid residue chromatographed on alumina (Brockmann Activity II), eluting the green/yellow zone with diethyl ether. The green residue remaining after removal of solvent was recrystallized from hexane/ether at -20°C to give orange crystals. Yield 150 mg (20%).

[5] **3**: ^{1}H-NMR (CD_2Cl_2, room temperature, $\delta = 7.5-7.2$ (m, 5H, Ph), 5.49 (s, 5H, C_5H_5), 4.34 (br, 1H, NH, $J = 3.94$ Hz), 3.62 (dd, 1H, *syn*-CH, $J = 1.32$, $J = 3.94$ Hz), 2.62 (d, 1H, *anti*-CH, $J = 1.32$ Hz); ^{13}C{^{1}H}-NMR (CD_2Cl_2, room temperature), $\delta = 244.46$ (CO), 136.33 (*ipso*-Ph), 130.11 (Ph), 125.12 (Ph), 95.02 (C_5H_5), 101.02 (CH_2C(R)NH), 30.44 (CH_2(R)NH); IR (ν(CO), CH_2Cl_2), 1949 (s), 1863 (s) cm^{-1}.—**4**: ^{1}H-NMR (CD_2Cl_2), $\delta = 7.4-7.0$ (m, 4H, Ph), 5.50 (s, 5H, C_5H_5), 4.33 (br, 1H, NH, $J = 3.50$ Hz), 3.61 (dd, 1H, *syn*-CH, $J = 1.54$, $J = 3.50$ Hz), 2.59 (d, 1H, *anti*-CH, $J = 1.54$ Hz), 2.34 (s, 3H, C_6H_4Me); IR (ν(CO), CH_2Cl_2) 1949 (s), 1863 (s) cm^{-1}.—**8**: ^{1}H-NMR (CD_2Cl_2), $\delta = 7.32$ (s, 5H, Ph), 5.53 (s, 5H, C_5H_5), 3.08 (d, 3H, N*Me*, $J = 0.55$ Hz), 2.94 (d, 1H, *syn*-CH, $J = 1.65$ Hz), 2.67 (dq, 1H, *anti*-CH, $J = 1.65$, $J = 0.55$ Hz); ^{13}C{^{1}H}-NMR (CD_2Cl_2), $\delta = 248.62$ (CO), 135.21 (*ipso*-Ph), 129.74, 128.96, 128.47 (Ph), 102.95 (CH_2C(R)NMe), 95.81 (C_5H_5), 45.17 (N*Me*), 30.01 (CH_2C(R)NMe); IR (ν(CO), CH_2Cl_2) 1937 (s), 1851 (s) cm^{-1}.—**6**: ^{1}H-NMR (CD_2Cl_2), $\delta = 7.5-7.2$ (m, 5H, Ph), 5.85 (s, 5H, C_5H_5), 2.43 (s, 3H, Me); ^{13}C{^{1}H}-NMR (CD_2Cl_2), $\delta = 246.00$ (CO), 155.38 (N=*C*(Me)Ph), 132.23 (*ipso*-Ph), 128.64 (Ph), 125.56 (Ph), 97.58 (C_5H_5), 18.61 (N=C(*Me*)Ph); IR (ν(CO), CH_2Cl_2) 1951 (s), 1859 (s) cm^{-1}.—**7**: IR (ν(CO), CH_2Cl_2) 1951 (s), 1859 (s) cm^{-1}.

[6] **4**: monoclinic, space group C2/c, $a = 14.890(6)$, $b = 12.975(4)$, $c = 15.229(8)$ Å, $\beta = 98.73(4)°$, $V = 2908(2)$, $Z = 8$, $\rho_{calc} = 1.60$ g cm^{-3}, $F(000) = 1407$, 2294 reflections (293 K), $R = 0.0330$, $R_w = 0.0351$ (Syntex R3, $Mo_{K\alpha}$). The structure was refined by blocked-cascade least squares. Nitrogen (N) and carbon C(8) positions were assigned on the basis of a comparison of the refinements in the illustrated (Fig. 1) arrangement, and that with their positions reversed (difference in R ca. 0.002). All hydrogen atoms were located from difference electron density syntheses. Further details of this structure are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW (England) on quoting the names of the authors and the journal citation.

[7] J. Hyde, K. Venkatasubramanian, J. Zubieta, *Inorg. Chem. 17* (1978) 414; M. Tatsumisago, G. Matsubayashi, T. Taueka, S. Nishigaki, K. Nakatsu, *Chem. Lett. 1979*, 889.

[8] M. Kilner, *Adv. Organomet. Chem. 10* (1972) 115.

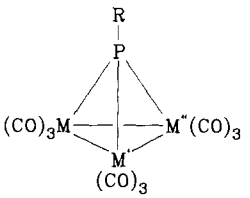
[9] A. H. Cowley, N. C. Norman, S. Quashie, *J. Am. Chem. Soc. 106* (1984) 5007.

Cluster Expansion with Cp(CO)Rh Fragments**

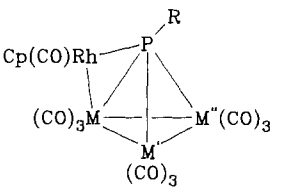
By *Darjusch Mani* and *Heinrich Vahrenkamp**

For cluster expansion experiments to date, mainly anionic mononuclear complexes or anionic clusters, the number of which is obviously limited, have been used. For this purpose, only complexes affording $Fe(CO)_3$ units have clearly emerged as a source for neutral fragments.[1] We hoped that the RhCp unit (Cp = cyclopentadienyl), which is isovalent and isoelectronic with the $Fe(CO)_3$ unit, would be similarly useful. In order to effect cluster skeletal expansion and, at the same time, to introduce the catalytically active element rhodium, we have therefore reacted the FeCo or RuCo clusters **1** with $Cp(CO)_2Rh$.

In all five cases, the desired pentanuclear clusters **3**, all of which are new, were formed when the starting materials were allowed to react in a mole ratio of 1:2 at 80—100°C for ca. 20 h in benzene or toluene. The total turnovers were about 75% and the yields of **3a** and **b** were 70—90% (relative to the extent of the reaction), those of **3c**—**e** 6—30%; the unused starting clusters were recovered. The constitutions of the clusters **3** are assumed to be like those of known PM_5 clusters;[2] this is in accord with the spectra.[3]

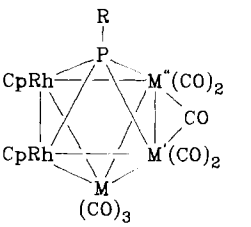


1a–e



2b,c,d

	R	M	M'	M"
a	Me	Fe	Co	Co
b	Ph	Ru	Co	Co
c	Me	Ru	RuH	Co
d	Me	Ru	FeH	Co
e	*t*Bu	Ru	FeH	Co



3a–e

The reactions appear to be general: the $PFeCo_4$ cluster analogous to **3a** was formed from **1a** and $Cp(CO)_2Co$, and the cluster analogous to **1a** but containing S instead of MeP afforded a product mixture, which, according to the spectra, also contains the $SFeCo_2Rh_2$ cluster analogous to **3a**.

At low reaction temperatures (60—80°C) and after short reaction times (3—8 h), the tetranuclear clusters **2b**, **c**, and **d** were obtainable as intermediates from **1b**, **c**, and **d** in just about 90% yield; they reacted further to give **3b**, **c**, and **d**. The cluster type **2** was identified by X-ray structure determination of **2b**,[4] as well as by the usual methods.[3] The tetranuclear clusters **2** are thermally sensitive, in contrast to the pentanuclear clusters **3**. In refluxing benzene, they are mainly transformed back into **1** over the course of several hours; part of the rhodium that is thereby lost is found again in the form of **3**. Attempts to cleave CO thermally, photochemically, or oxidatively from **2**, in order to obtain, via aggregation, clusters with tetrahedral M_4 skeletons, were unsuccessful.

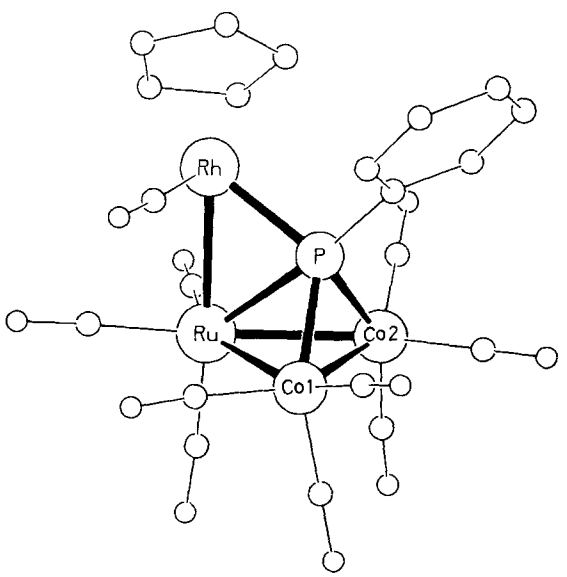


Fig. 1. Crystal structure of **2b**. Important bond lengths: Ru—Rh 279.3(1), Ru—Co1 272.0(1), Ru—Co2 268.7(1), Co1—Co2 255.8(1), Rh—P 227.3(2), Ru—P 261.9(1), Co1—P 218.1(2), Co2—P 218.5(2) pm.

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Figure 1 clearly shows that the clusters **2** exhibit an unusual molecular skeleton. All components of **1** are still present; **1** as a whole acts as a two-electron ligand with respect to the Cp(CO)Rh unit. This naturally changes the electron distribution in the cluster, but the 18-electron rule remains fulfilled for all four metal atoms. The demands on the Ru–P side of **1b** are evident in the markedly longer Ru–P bond and the sideways displacement of the phenyl group on phosphorus. Clusters having organometallic fragments attached, such as **2b**, were, to be best of our knowledge, unknown. The unusual electronic nature of this configuration corresponds to the ability of the rhodium-containing fragment to be removed thermally.

The geometry of **2b** is also in accord with another description of the bonding: due to the approximate linearity of the Ru–P–C sequence (174°), the central $PhPRu(CO)_3$ molecular moiety can be viewed as a phosphanediyl complex, which, in its free form, would have a Ru–P triple bond. Analogously to an alkyne, this group can bridge the $Co_2(CO)_6$ unit and/or function as a side-on ligand with respect to the Cp(CO)Rh unit. The electron count would thus correspond to that in the μ_3-η^2-alkyne-bridged trinuclear clusters.[5] However, the triple bond surrounded by three metal atoms, which is observed here for **2b**, has no precedent.

The clusters **2d**, **3d**, and **3e** contain four different metal atoms. Therefore, studies of the chirality, in light of catalytic optical induction, are of interest, as are attempts to incorporate further heterometal atoms, which could make use of the hydride function in the clusters **c**, **d**, and **e** or of the **2** → **3** transformation.

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[2] M. J. Mays, P. R. Raithby, P. L. Taylor, K. Henrick, *J. Chem. Soc. Dalton Trans. 1984*, 959.
[3] All new clusters were characterized by elemental analysis and EI mass spectra. The IR and NMR spectra of **2b**, **c**, **d**, and of **3a**–**e** are very similar. Representative IR spectra (C_6H_{12}, ν(CO) [cm^{-1}]): **2b**: 2083 m, 2040 vs, 2032 s, 2022 m, 2000 vw, 1988 w, 1976 vw; **3b**: 2030 w, 2002 vs, 1997 m, 1988 s, 1971 m, 1827 w (br). — ^{1}H-NMR data ($CDCl_3$, TMS int., δ(Cp): **2b**: 5.32; **3b**: 5.31. The NMR spectra of **2c** and **2d** indicate the presence of mixtures of isomers.
[4] P$\bar{1}$, a = 973.1(4), b = 1456.7(5), c = 907.1(2) pm, α = 102.26(2), β = 94.55(3), γ = 87.75(3)°, Z = 2, 3206 reflections, R = 0.027. Further details of the crystal structure investigation are available on request from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2, by quoting the depository number CSD 51157, the names of the authors, and the journal citation.
[5] E. Sappa, A. Tiripicchio, P. Braunstein, *Chem. Rev. 83* (1983) 203.

Photosignal II as an Indicator for Damage to Forests – EPR Spectroscopic Investigation of Spruce Needles**

By *Hartmut B. Stegmann,* Hans J. Ruff,* and *Klaus Scheffler*

EPR spectroscopy is a very sensitive and selective method for the detection of paramagnetic species. For this reason, we have attempted to determine whether the pollutants SO_2 and NO_x, which are much under discussion, exert an effect on the photosynthetic apparatus and whether these effects can be detected by EPR spectroscopy. Although the relationship between photosynthesis and tree death has already been pointed out,[1] EPR studies, which are capable of very sensitively detecting disturbances in the electron transport chains, have not been carried out.

Externally undamaged whole needles from 20 spruces *(Picea abies L.)* of various ages and from a variety of locations in the vicinity of Tübingen (Schönbuch, Rammert, Alb) were studied. The EPR spectra of spruce needles, which were investigated in the dark without any pretreatment, show essentially two types of signals. About 50% of all samples studied exhibit a strong and relatively well-resolved six-line spectrum, which can be unequivocally assigned to Mn^{2+}. The other needles show only negligible Mn^{2+} signals. The factors responsible for this variation between different trees are still unclear. The further studies were carried out on needles containing very little Mn^{2+}. Independent of the manganese content, absorption at g = 2.005 is found for all samples; this absorption exhibits a significant structure over a range of ± 15 G (cf. Fig. 1).

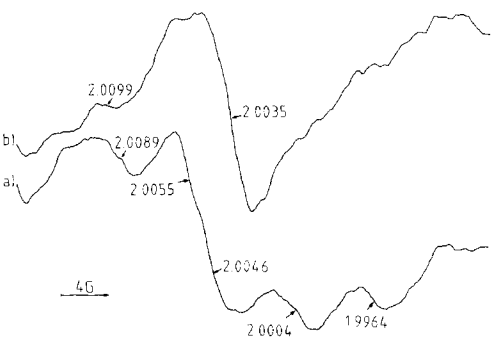


Fig. 1. EPR spectrum of various spruce needles in the g = 2.005 region. The samples were collected in October and November 1984. The signals were obtained with a Varian E-line spectrometer connected to a Bruker data system ER 140 by accumulation of 50 scans using an FF lock (5-mW microwave energy; modulation 1 G). Spectrum a): tree 17 (S 0); spectrum b): tree 15 (S 3).

Needles from trees that, according to the conventional, subjective criteria, are assigned to the damage level S 0,[2] show signals at g = 2.0089, g = 2.0100, g = 2.0055, g = 2.0046, g = 2.0004, and g = 1.9964 (cf. Fig. 1 and Fig. 2, spectrum a) in each case). In contrast, needles from trees assigned to the damage level S 3 show a completely different EPR signal (cf. Fig. 1, spectrum b)).

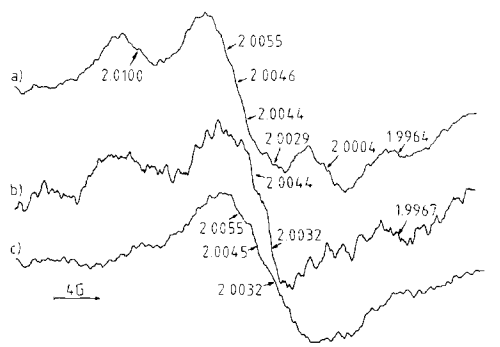


Fig. 2. EPR spectra of various spruce needles in the g = 2.005 region (same experimental conditions as in Fig. 1). Spectrum a): tree ST (S 0); spectrum b): tree 16 (S 3); spectrum c): tree ST after treatment with NO_x. In order to allow short reaction times and thus avoid aging processes, the concentration of NO_x in this very preliminary experiment was very high relative to that in the natural environment.

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Spectrum b) of Figure 1 consists essentially of only one component at $g = 2.0035$, which is totally absent in a). Differences in location seem to be of secondary importance for the EPR signals of the needles of undamaged trees since the spectra a) in Figures 1 and 2 are practically identical. For needles from damaged trees, however, differences are found which could make possible a differentiation according to objective criteria and thus allow the early recognition of damage. For instance, the signal at $g = 2.0044$ is clearly recognizable in spectrum b) of Figure 2, even though the main absorption is the component at $g = 2.0032$.

When spruce needles are exposed for ca. 2 h to light in an atmosphere containing 10^{-4} mol/L NO_x, the EPR spectrum changes appreciably (cf. Spectrum c) in Figure 2). The signal at $g = 2.0100$ has practically fully vanished and the $g = 2.0055$ component has lost intensity, whereas the absorption at $g < 2.0032$ has increased in importance. Spectrum c) is therefore more like spectrum b) than spectrum a), which was recorded immediately prior to treatment with NO_x. Similar spectra are obtained upon simultaneous treatment with NO_x and SO_2.

These findings do not mean that only NO_x and SO_2 can damage the electron transport chain. Other pollutants, such as ozone and photooxidants, can possibly have similar effects. Studies of spruce needles from areas having clean air should afford further conclusions. Treatment with aqueous acids, such as sulfuric acid (pH = 1), does not lead to a change in the EPR signal, even after several hours; therefore, the needle damage occurs preferentially via the gas phase.

The EPR signals that we have recorded for undamaged spruce needles correspond largely to the signals found for isolated chloroplasts and referred to as "Signal II slow".[3] While the chloroplast signals depend strongly on the preparation procedure, only small differences are observed for different samples in the investigations of whole healthy spruce needles. Seasonal variations of these signals are not known. With regard to the assignment of Signal II (S II) in the photosynthetic processes of plants, it is at present assumed that the signal is directly associated with the water splitting reaction of Photosystem 2.[3] Much less is known about the chemical structure of the radicals responsible for S II. Whereas some authors assume the involvement of several species,[4] others prefer homogeneous redox systems of the plastosemiquinone type,[5] with the structure of S II being due to unresolved hyperfine structure. We are not in agreement with this latter point of view, since the difference spectra (light-dark) exhibit an increase in the signals at $g = 2.0055$ and $g = 2.0046$ upon irradiation. Our results indicate that NO_x and SO_2 affect to varying degrees the various paramagnetic species that are responsible for S II. For massive damage, which need not be attributed exclusively to NO_x and SO_2, practically only "one" signal with $g = 2.0035$ is still observed. Similar absorptions have been reported in connection with Photosystem 2.[6]

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CAS Registry numbers:
NO_x, 11104-93-1; SO_2, 7446-09-5; Mn, 7439-96-5.

[1] See, e.g., H. K. Lichtenthaler, C. Buschmann in C. Sybesma: *Advances in Photosynthesis Research*, Martinus Nijhoff/Dr. W. Junk Publishers, The Hague 1984; *Allg. Forstz. 39* (1984) 12, and references cited therein.

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[3] A. J. Hoff, *Phys. Rep. 54* (1979) 75, and references cited therein.

[4] N. N. Nishi, A. J. Hoff, J. Schmidt, J. H. Van der Waals, *Chem. Phys. Lett. 58* (1978) 164.

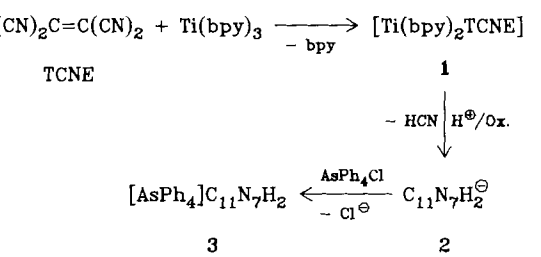
[5] P. J. O'Malley, G. T. Babcock, *Biochim. Biophys. Acta 765* (1984) 370; P. J. O'Malley, G. T. Babcock, R. Prince, *ibid. 766* (1984) 283.

[6] F. K. Fong: *Light Reaction Path of Photosynthesis*, Springer, Berlin 1982.

Synthesis of a Novel Stable Carbanion: 1,1,2-Tricyano-2-(3,4-dicyano-5-imino-2,5-dihydro-1*H*-pyrrol-2-ylidene)ethanide by Reduction of Tetracyanoethylene with Tris(2,2'-bipyridine)titanium**

By *Giulia Dessy, Vincenzo Fares, Alberto Flamini,** and *Anna Maria Giuliani*

Reduction of tetracyanoethylene (TCNE) and subsequent acidification normally furnishes tetracyanoethane.[1] In the presence of $Ti(bpy)_3$,[2] however, an anionic dihydropyrrole derivative **2**[3] was obtained which could be isolated as the salt **3** (Scheme 1). The structure of the anion (Fig. 1) was elucidated by a single-crystal X-ray structure analysis. Despite high standard deviations the tautomeric pyrrolide could be ruled out. This finding is additionally supported by IR and ^{13}C-NMR spectra.[4]



Scheme 1.

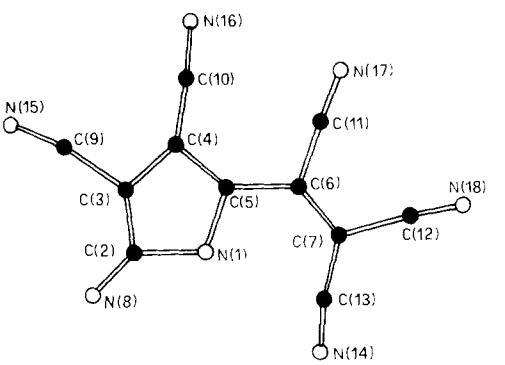


Fig. 1. Structure of the anion **2** in the crystal of **3** (hydrogen atoms have been omitted) $P2_1/c$; $a = 9.435(4)$, $b = 13.655(7)$, $c = 24.487(13)$ Å, $\beta = 106.97(4)$, $R = 0.066$ (1382 reflections). Further details of the crystal structure investigation are available on request from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2, on quoting the depository number CSD 51272, the names of the authors, and the full citation of the journal. Selected bond lengths [Å] and angles [°]: C3–C4 1.42(6), C4–C5 1.39(4), C5–N1 1.45(4), N1–C2 1.51(6), C2–C3 1.31(7), C2–N8 1.17(7), C5–C6 1.46(4), C6–C7 1.35(3), C2–C3–C4 128(4), C3–C4–C5 98(3), C4–C5–N1 109(3), C5–N1–C2 112(2), N1–C2–C3 93(4).

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In order to clarify the mechanism of the reduction of TCNE in the presence of $Ti(bpy)_3$ we have studied in detail each of the individual steps (Fig. 2) shown in Scheme 1. In the first step the intermediate **1** is formed by replacement of one bipyridine ligand by TCNE, which, in the process, is reduced to tetracyanoethanediide ($TCNE^{2\ominus}$). In other words, $Ti(bpy)_3$ causes a two-electron reduction of TCNE, as is also proven by the zero magnetic moment and the IR spectrum of **1**[5] (prominent $TCNE^{2\ominus}$ bands at 2160, 2095, and 1260 cm^{-1}).[6]

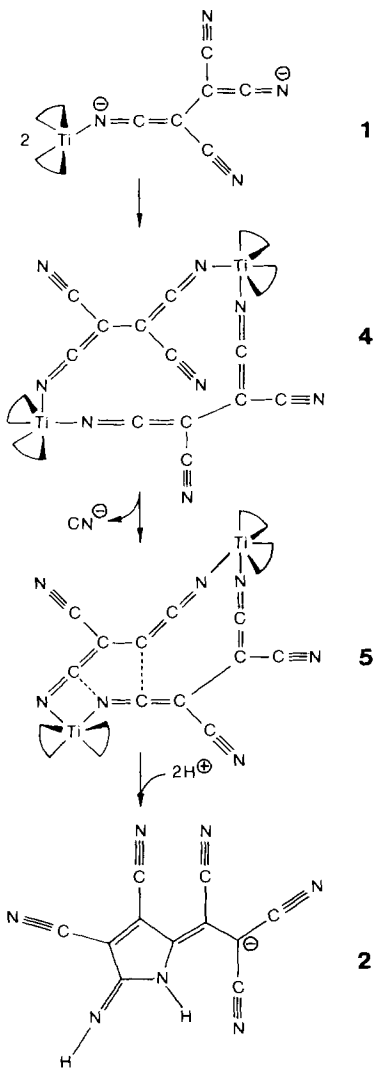


Fig. 2. Reaction scheme explaining the formation of the anion **2**. The charges are only partly indicated.

This coordinatively unsaturated species **1**, which is formed at low temperatures, can be stabilized by polymerization or dimerization. Several dimers with different conformations can be formed; one of them could be, e.g., **4**, containing two $TCNE^{2\ominus}$ bridges (*cis* and *trans* referred to titanium). If **4** is concomitantly oxidized and protonated in a second step, HCN is liberated;[7] finally, the anion **2** and the polymeric cationic titanium(IV) complex $[Ti(bpy)_2O]_n^{2n\oplus}$ are formed via the more stable complex **5**.

The anion **2** is thus formed by condensation of two TCNE molecules:

$$2\,TCNE + 4e^{\ominus} \longrightarrow 2\,TCNE^{2\ominus} \xrightarrow{+3H^{\oplus}} \underset{\mathbf{2}}{C_{11}N_7H_2^{\ominus}} + HCN$$

The formation of **2** is favored by titanium because it can bind $TCNE^{2\ominus}$ via a nitrogen atom. Such a reaction appears to be very unusual in the field of TCNE chemistry; only one similar example has previously been reported in the literature.[8] In the complex $[(CO)(PPh_3)_2M(TCNE)]$, M = Rh, Ir, the TCNE is reduced to $TCNE^{2\ominus}$ and subsequently bonded to the metal through the nitrogen. Under certain conditions a dimer is formed, which is converted by cleavage of two $CN^{\ominus}$ groups into hexacyanobutenediide.

The salt **3**, which can be prepared in reasonable yield (ca. 40%) in a one-pot synthesis, is stable toward water and oxygen. Due to the five cyano groups the salt is supposedly a strong electron acceptor toward donor molecules.[9]

The anion **2** or the readily obtainable acid $C_{11}N_7H_3$ can be used in combination with the tetrathiafulvalene cation ($TTF^{\oplus}$) or TTF, respectively, to give new organic metals.[10] Preliminary studies have shown that a novel salt exhibiting interesting electrical properties is formed by metathesis of $NaC_{11}N_7H_2$ with $[(TTF)_3(BF_4)_2]$.[11]

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CAS Registry numbers:
2, 96096-48-9; **2** · Na, 96096-50-3; **2** (protonated), 96096-51-4; **3**, 96096-49-0; $Ti(bpy)_3$, 22143-19-7; $AsPh_4Cl$, 507-28-8; TCNE, 670-54-2.

[1] B. C. McKusick, *Trans. N. Y. Acad. Sci. 27* (1965) 719.
[2] First synthesis of $Ti(bpy)_3$: S. Herzog, R. Taube, *Z. Anorg. Allg. Chem. 306* (1960) 159.
[3] Experimental: TCNE (0.32 g; 2.5 mmol) was added under stirring at −80°C to a suspension of $Ti(bpy)_3$ (1.30 g; 2.5 mmol) in 50 mL tetrahydrofuran under N_2. The black suspension was allowed to warm to room temperature. After four hours it was cooled again to −80°C and CH_3NO_2 (50 mL) was added from a syringe with stirring under N_2. The final solution was allowed to warm to room temperature. The solvent was then evaporated at reduced pressure and the black-violet residue was washed with toluene (200 mL) and the undissolved residue filtered off. The solid was treated with acetone (200 mL) and the undissolved residue filtered off. $As(C_6H_5)_4Cl$ (1.05 g; 2.5 mmol) in H_2O (50 mL) was added to the violet solution. After concentration, the salt $[As(C_6H_5)_4 \cdot C_{11}N_7H_2]$ **3** separated as air-stable golden microcrystals, which were recrystallized from acetone-toluene (0.26 g; yield *ca.* 40%). **3** and the corresponding sodium salt have been characterized by their UV, IR, ^1H- and ^{13}C-NMR spectra and cyclic voltammograms. The molecular ion of the acid $C_{11}N_7H_3$, prepared from the sodium salt by acidification (H_2SO_4, 1 M) and extraction with ether, has been determined by MS ($m/z = 233.048 \pm 0.003$ ($C_{11}N_7H_3^{\oplus}$)).
[4] A resonance at $\delta = 67.8$, assigned to the C-7 carbon atom, strongly supports the existence of the carbanion **4**, bearing a high charge density on that atom (R. B. Bates, S. Brenner, C. M. Cole, E. W. Davidson, G. D. Forsythe, D. A. McCowly, A. S. Roth, *J. Am. Chem. Soc. 95* (1973) 926).
[5] **1** is not stable at room temperature: its IR spectrum slowly changes with time even when it is stored in a dry-box under nitrogen.
[6] O. W. Webster, W. Maheler, R. E. Benson, *J. Am. Chem. Soc. 94* (1962) 3678.
[7] Most of the chemistry of reduced TCNE is controlled by the *facile* elimination of cyanide (O. W. Webster, *J. Am. Chem. Soc. 86* (1964) 2898).
[8] W. Beck, R. Schlodder, K. H. Lechler, *J. Organomet. Chem. 54* (1973) 303.
[9] H. Meier, *Top. Curr. Chem. 61* (1976) 85.
[10] a) F. Wudl, *Acc. Chem. Res. 17* (1984) 227; b) M. R. Bryce, L. C. Murphy, *Nature 309* (1984) 119.
[11] F. Wudl, *J. Am. Chem. Soc. 97* (1975) 1962.

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Transformation of $[\{(CO)_5W\}_3Sn]$ into $[\{(CO)_5W\}_3Te_2]$, a Compound Containing Unusually Bonded Ditellurium**

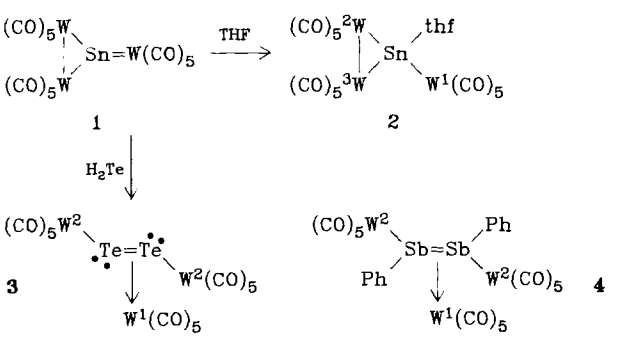
By *Olaf Scheidsteger, Gottfried Huttner,* Kurt Dehnicke,* and *Jürgen Pebler*

The complex **1** was recently synthesized. It is the first Sn analogue[1] of the class of complexes discovered by *Weiss* et al.,[2] which contain elements of the 4th main group that are trigonally planar coordinated by metals. We report here the Mössbauer spectrum of **1** as well as the use of **1** for the synthesis of the ditellurium complex **3**, in which a Te_2 unit is stabilized as a 2π-4σ ligand, a novel form of coordination.

The description of **1**[1] as a complex[3] of an unusual metallacyclic stannanediyl is supported by comparison of the ^{119}Sn Mössbauer spectrum ($IS = 2.56(4)$ mm s^{-1} relative to SnO_2; $EQ = 4.60(4)$ mm s^{-1}; asymmetry parameter $\Gamma = 0.88(5)$ mm s^{-1}; T (γ-source (SnO_2)) = 293 K; $T_{(sample)} = 84$ K; Lorentz fit) of **1** with the Mössbauer values of $[R_2SnM(CO)_5]$, M = Cr, Mo.[3a] Quadrupole splittings similar to those in **1** are only observed for stannanediyl complexes.[3a]

1 is very reactive due to the coordinatively unsaturated tin. It reacts with THF to give the expected base adduct **2** in which the Sn is tetrahedrally coordinated.[4] In the adduct, all Sn–W bonds are somewhat longer than those in **1**.

The reaction of **1** with the Lewis base H_2Te leads to **3**, in which, instead of Sn as in **1**, a Te_2 unit is coordinated in an unusual manner (Scheme 1).



Scheme 1. Synthesis of **3** and comparison of the structure of **3** with that of the distibene analogue **4** [8] (bond distances [pm], angles [°]): **3**: Te–Te 268.6(4), Te–W1 288.1(3), Te–W2 273.9(2); Te–Te–W2 106.7(1); W2–Te–Te–W2 140.0, W2–Te–Te–W1 110.0; **4**: Sb–Sb 270.6(4), average Sb–W1 288.8(19), average Sb–W2 276.2(4); average Sb–Sb–W2 129.5(11); W2–Sb–Sb–W2 124.5, W2–Sb–Sb–W1 117.

A brown-black suspension is formed from the orange-colored solution of **1** in the presence of Al_2Te_3[5] upon acidification with HCl; **3** is separated from this mixture chromatographically on diatomite. The black crystals of **3**[6] are stable in air at 20 °C and decompose only at 135 °C. **3** is insoluble in *n*-pentane but dissolves in toluene with a black-violet color, and is even more soluble in CH_2Cl_2. According to the X-ray structure determination,[4] **3** contains a Te_2 unit; the lone electron pairs on each tellurium terminally bind a $W(CO)_5$ group and, in addition, a further $W(CO)_5$ group is coordinated via the Te–Te π-system (Scheme 1).[7]

In this kind of bonding, the Te_2 unit is, in the broadest sense, isoelectronic with RSb=SbR. The comparison of the structure of the distibene complex **4**[8] with that of **3**, given in Scheme 1, makes this analogy clearer. In each case, the distance between the main-group elements is shorter than that of a single bond, despite the lengthening due to the side-on coordination. The Te–Te distance in **3** lies between the bond length of free $Te_{2(g)}$ (261 pm)[9] and that of hexagonal $Te_{(s)}$ (283.5 pm).[9] The "open" structure of **3** compared with the "closed" star-like structure of the complex $[\{(CO)_5W\}_3X_2]$ (X = As,[10] Sb,[8] Bi[11]) is a consequence of the different numbers of electrons in the diatomic ligands Te_2 and X_2, respectively.

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CAS Registry numbers:
1, 96427-23-5; **2**, 96412-24-7; **3**, 96412-25-8; Sn, 7440-31-5; W, 7440-33-7; Te, 13494-80-9.

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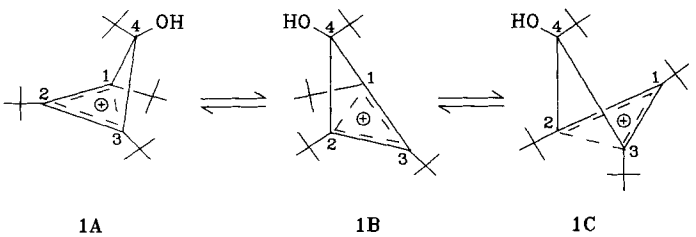
[**] This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.

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[3] a) J. D. Cotton, P. J. Davidson, M. F. Lappert, J. D. Donaldson, J. Silver, *J. Chem. Soc. Dalton Trans. 1976*, 2286; b) P. Jutzi, W. Steiner, E. König, G. Huttner, A. Frank, U. Schubert, *Chem. Ber. 111* (1978) 606.
[4] **2**: $P2_1/c$, $a = 902.0(4)$, $b = 1833.4(9)$, $c = 1907.7(9)$ pm, $\beta = 121.84(3)°$, $V = 2680 \cdot 10^6$ pm^3, $Z = 4$, 2350 independent reflections ($I > 2\sigma(I)$), $R_1 = 0.04$. Important bond lengths [pm]: Sn–W1 271.3(2), Sn–W2 279.4(2), Sn–W3 279.0(2), Sn–O(thf) 229(2).—**3**: $P4_12_12$, $a = 1068.8(3)$, $c = 2094(1)$ pm, $V = 2392 \cdot 10^6$ pm^3, $Z = 4$, 1574 independent reflections ($I > 2\sigma(I)$), $R_1 = 0.052$. The crystals were obtained by addition of *n*-pentane to the surface of a CH_2Cl_2 solution. **3** has crystallographic C_2 symmetry. Further details of the crystal structure investigation are available on request from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2, by quoting the depository number CSD 51191, the names of the authors, and the journal citation.
[5] G. Brauer: *Handbuch der Präparativen Anorganischen Chemie. Bd. II*, Enke, Stuttgart 1978.
[6] An orange-colored solution of **1** (1.9 g, 1.8 mmol) [1] in 100 mL of CH_2Cl_2 is treated successively with 1.2 g of Al_2Te_3 and 5 mL of 4 M HCl at 20 °C. After 5 h, the resulting brown-black suspension is treated with 10 g of Na_2SO_4 and filtered through a fritted disk, $\varnothing = 4.5$ cm, layered with 4 cm diatomite/2 cm Na_2SO_4. Removal of the solvent affords a crude black product containing more than 75% (IR) **3**. Chromatography on diatomite (−30 °C, eluent CH_2Cl_2, $\varnothing = 3$ cm) affords violet-black **3**, which was crystallized by trituration with *n*-pentane. Yield: 430 mg (19% from **1**). Correct elemental analysis. IR (CH_2Cl_2): 2105 (m), 2065 (s), 2060 (s), 2008 (m), 1948 (vs). MS: Under EI conditions, the mass spectrum exhibits only decomposition products ($W(CO)_6$); m.p. = 135 °C (decomp.).
[7] The structure of the compound $[(\eta^5\text{-}C_5H_5)(CO)_2Mn]_3Te_2$ is unknown. A structural analogy to **3** is probable: M. Herberhold, D. Reiner, D. Neugebauer, *Angew. Chem. 95* (1983) 46; *Angew. Chem. Int. Ed. Engl. 22* (1983) 59; *Angew. Chem. Suppl. 1983*, 10.
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[11] G. Huttner, U. Weber, L. Zsolnai, *Z. Naturforsch. B 37* (1982) 707.

Walk Rearrangement in the 1,2,3,4-Tetra-*tert*-butylhydroxycyclobutenylium Ion**

By *Günther Maier,** *Rolf Emrich,* and *Hans-Otto Kalinowski*

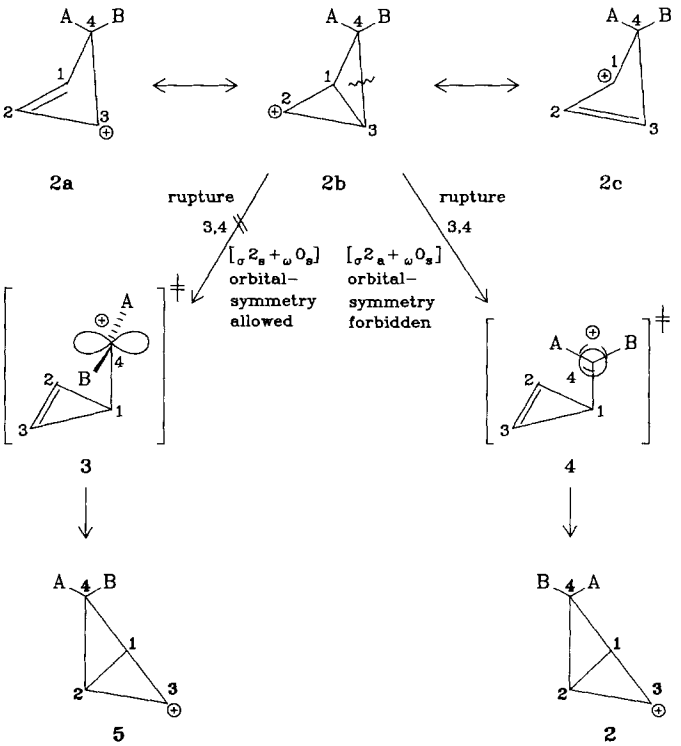
The oxidative ring-opening of tetra-*tert*-butyltetrahedrane leads to stable and crystalline isolable homocyclopropenylium salts.[1] The ion **1** thus obtained, the structure of whose hexafluoroantimonate has been confirmed by an X-ray structure analysis, shows temperature-dependent NMR spectra. In the ^{1}H-NMR spectrum, only three singlets are observed at $\delta = 1.10$ (9H, *t*Bu on C-4), 1.54 (27H, *t*Bu on C-1/2/3) and 4.60 (OH) at room temperature. On cooling, the signal at 1.54 becomes broader and finally splits at +1°C into two signals in the intensity ratio 2:1 (at −10°C: $\delta = 1.50$ and 1.58). The other two singlets remain unchanged.



1A 1B 1C

In the room-temperature ^{13}C-NMR spectrum of **1** only four signals are recorded, at $\delta = 29.3$ (CH_3, *t*Bu on C-4), 30.9 (CH_3, *t*Bu on C-1/2/3), 41.2 (quaternary, *t*Bu on C-4), and 101.2 (C-4). All other absorptions (C-1/2/3 and quaternary C of *tert*-butyl groups attached thereto) are hidden under these conditions because of poor signal-to-noise ratio as a result of exchange processes. Below +17°C, the signal for the *tert*-butyl groups on C-1/2/3 separates into two signals. In this temperature range, absorptions also gradually emerge for C-1/2/3 and the quaternary C-atoms of the *tert*-butyl groups attached thereto. At −20°C the expected spectrum could finally be observed: $\delta = 29.1$ (CH_3, *t*Bu on C-4), 30.6 (CH_3, *t*Bu on C-1/3), 31.3 (CH_3, *t*Bu on C-2), 34.9 (quaternary, *t*Bu on C-2), 38.1 (quaternary, *t*Bu on C-1/3), 40.9 (quaternary, *t*Bu on C-4), 101.0 (C-4), 161.5 (C-1/3), 184.9 (C-2).

The reversible changes in the spectra demand a dynamic process in which the olefinic ring positions in **1** are equilibrated, while C-4 and the substituents attached to it do not, however, experience any change. The simplest interpretation of this process is the occurrence of the walk rearrangement **1A** ⇌ **1B** ⇌ **1C**. From the coalescence temperatures (determinable on the signals of the methyl groups in the ^{1}H- and ^{13}C-NMR spectra; a measurement of the coalescence spectrum for C-1/2/3 and the neighboring C-atoms was not possible, owing to technical reasons and because of the instability of **1**) and the magnitude of the splitting in the low temperature spectra, an activation barrier of $\Delta G^+ \approx 15$ kcal/mol could be calculated for the observed rearrangement.



Such an isomerization is known in the case of methyl-substituted homocyclopropenylium salts.[2] Still unclear, but of particular interest,[3] is the stereochemistry of this reaction. According to theory[4] the rearrangement of the homocyclopropenylium ion **2** would violate the Woodward-Hoffmann rules. Of the two alternatives—**3** and **4** represent the corresponding eclipsed and bisected transition states, respectively—not the orbital symmetry allowed reaction via **3**, but the route via **4** with inversion at the migrating C-atom is to be expected. Accordingly, the substituents A and B would always retain their orientation. This prerequisite coincides with experiment, for the signals of C-4 and of the substituents on C-4 in the coalescence spectra remain sharp over the whole temperature range. Their chemical shifts likewise remain unaffected. The presence of equal amounts of the *endo-exo*-isomeric ions and a very rapid rearrangement into each other can therefore be ruled out. There remain three possibilities: a) Because of the size of the *tert*-butyl groups the "least-motion" process is favored. b) Ring inversion leads very rapidly to an *endo,exo* equilibrium that lies totally on the side of **1** (*endo-tert*-butyl group). c) An unusually strongly pronounced secondary orbital interaction[4] ensures that the Woodward-Hoffmann rules no longer hold in this instance. We consider the latter mentioned explanation not only to be the most attractive but also the most likely.

The above example can be compared with the Berson-Willcott rearrangement of norcaradienes, which, according to investigations by *Klärner* et al.,[5] likewise proceed contrary to the requirements of the rules of conservation of orbital symmetry with inversion at the migrating C-atom.

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[**] Small Rings, Part 56. This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.—Part 55: G. Maier, M. Hoppe, K. Lanz, H. P. Reisenauer, *Tetrahedron Lett.* 25 (1984) 5645.

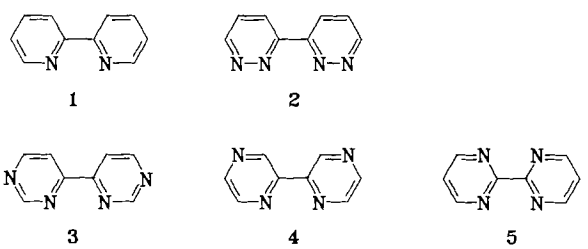
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d^6-Metal Complexes of 4,4′-Bipyrimidine, an Ambident Ligand with High π-Acceptor Ability**

By *Sylvia Ernst* and *Wolfgang Kaim**

Owing to the importance of ligands of the 2,2′-bipyridine type **1** in inorganic and analytical chemistry[1a] and especially in the photochemistry of coordination compounds[1b] there have been numerous attempts at purposefully modifying this system. Besides the substitution at the heterocyclic rings[2a] and the enlargement of the α-diimine π-system,[2b] the incorporation of further nitrogen centers in **1** has recently also attracted interest;[3–5] coordination compounds of 3,3′-bipyridazine **2**,[3] 2,2′-bipyrazine **4**,[4] and 2,2′-bipyrimidine **5**[5] have been described in connection with the use of corresponding ruthenium(II) complexes as photocatalysts.[1b]

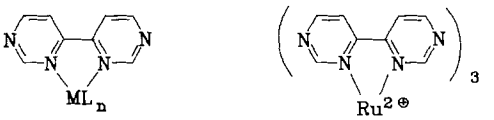


1 **2** **3** **4** **5**

We have now carried out Hückel MO calculations for all symmetrical bidiazines with α-diimine structure, including the remaining isomer 4,4′-bipyrimidine **3**.[6] Such calculations surprisingly revealed that the hitherto neglected[7] complex ligand **3** is the most π-electron deficient compound: $\varepsilon_{LUMO}^{HMO} = -0.583$ (**2**), -0.460 (**3**), -0.515 (**4**), and -0.518 (**5**).

In accordance with the specific properties of the pyrazine system,[8] 2,2′-bipyrazine **4** was considered to be a ligand with an especially low-lying π* level;[3,4] however, the π-acceptor activity expected to operate towards d^6 metal centers is compensated by the strongly reduced σ basicity of this 1,4-diazine ligand.[4b–d]

Since pyrimidines are stronger bases than pyrazines, we prepared **3** according to the method of *Effenberger*,[9a] found the pK_{a_1} to be 1.50 (pK_{a_1} (**4**) = 0.45[4c]), and were in fact able to establish a distinct red shift of the metal-to-ligand charge transfer (MLCT) absorptions for the chelate complexes **6**[9b] with tetracarbonylchromium, -molybdenum, and -tungsten and with ruthenium(II) fragments. Table 1 lists these data and some redox potentials; in Table 2, the tris(α-diimine)ruthenium(II) complexes of 2,2′-bipyridine and of the bidiazine series are compared.



6a: $ML_n = Cr(CO)_4$ **6e**
6b: $ML_n = Mo(CO)_4$
6c: $ML_n = W(CO)_4$
6d: $ML_n = [Ru(1)_2]^{2\oplus}$

Table 1. Long-wavelength absorption maxima λ(MLCT) [nm] [a] and redox potentials E [V vs SCE] [b] of d^6-metal complexes of 4,4′-bipyrimidine.

Complex	λ(MLCT) (lgε)	E(ox)	$E(red_1)$	$E(red_2)$
6a	630 (3.46)	0.64	−0.80	−1.56
6b	580 (3.72)	[c]	−0.71	−1.45
6c	608 (3.67)	[c]	−0.69	−1.40
6d [d]	522 (3.56)	1.45	−0.58	−1.19
	503 (sh)			
	427 (3.76)			
6f	460 (2.89)	[c]	−0.66	[c]

[a] Measurements in tetrahydrofuran (THF), except in the case of **6d** (acetonitrile). [b] Measurements in dimethylformamide (DMF)/0.1 M $Bu_4N^{\oplus}ClO_4^{\ominus}$, cyclovoltammetry at a glassy carbon electrode; potentials in acetonitrile are ca. 0.1 V more negative. [c] Irreversible steps. [d] Bis(hexafluorophosphate).

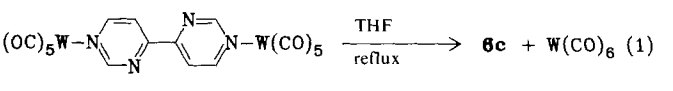
Table 2. Long-wavelength absorption maxima λ(MLCT) [nm] and redox potentials E [V vs. SCE] of tris(2,2′-bipyridine)- and tris(bidiazine)ruthenium(II) complexes [a].

Complex	λ(MLCT) (lgε)	$E_{ox}^{3\oplus/2\oplus}$	$E_{red}^{2\oplus/\oplus}$	$E_{red}^{\oplus/0}$	$E_{red}^{0/\ominus}$	E_{red}^{Ligand}
$[Ru(1)_3]^{2\oplus}$ [3]	452 (4.15)	1.27	−1.34	−1.53	−1.78	−2.18
$[Ru(2)_3]^{2\oplus}$ [3]	444 (4.06)	1.58	−1.00	−1.25	−1.54	−1.84
	410 (4.08)					
$[Ru(3)_3]^{2\oplus}$	496 (4.28)	1.75	−0.57	−0.71	−0.90	−1.38
	461 (sh)					
$[Ru(4)_3]^{2\oplus}$ [4b]	443 (4.18)	1.95	−0.71	−0.89	−1.16	−1.76
$[Ru(5)_3]^{2\oplus}$ [4d]	454 (3.93)	1.69	−0.91	−1.08	−1.28	−1.99 [b]
	418 (3.91)					

[a] Measurements on bis(hexafluorophosphates) in acetonitrile. [b] Irreversible reduction [4d].

Intermediates could be isolated during the formation of complexes with the ambident, potentially bridging (N^1, $N^{1'}$) or chelate-forming (N^3, $N^{3'}$) ligand **3**. Thus, the primary coordination of photolytically generated $THF \cdot W(CO)_5$ initially takes place at the peripheral nitrogen centers N^1 and $N^{1'}$[9c] before a conversion into the chelate complex occurs [Reaction (1)].

Consistent with the HMO calculations, both the ligand **3** as well as its complexes exhibit markedly more positive reduction potentials than corresponding coordination com-



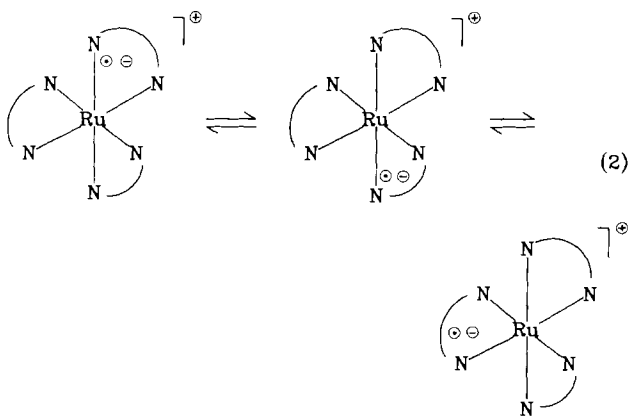
6f

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pounds of the ligands **1**,[4b] **2**,[3] **4**,[4b] and **5**;[4d] on the other hand, a comparison of the $Ru^{2\oplus}/Ru^{3\oplus}$ potentials (Table 2) indicates that **3** is a stronger σ-donor than **4**. The special position of the ligand **3** is nicely illustrated by the parameter $\Delta = E_{ox} - E_{red(1)}$, i.e. the difference between oxidation potential and reduction potential of tris(ligand)ruthenium(II) complexes, which correlates with the long-wavelength charge-transfer absorption (Table 2). In the case of **6e** there is only a difference of 2.32 V, whereas for all other complexes $\Delta = 2.62 \pm 0.04$ V.

In accord with the cyclovoltammetrically observed reversibility of the first electron uptake, the respective radical reduction products of all the 4,4′-bipyrimidine complexes described here can be generated and characterized by ESR spectroscopy.[10] In the case of compound **3d**, the partially resolved ESR spectrum of a reduced polyazineruthenium(II) complex could be obtained for the first time (Fig. 1, A). Because of the correlation between MLCT excited and reduced states of such systems (one unpaired electron in the ligand π* orbital) the formulation of such radical complexes was the subject of several studies,[11] in which ESR line-broadening caused by rapid exchange according to reaction (2) was postulated for singly reduced tris(ligand) complexes.[11b]



Due to the vastly different reduction potentials of **1** and **3** (Table 2), the unpaired electron in the reduced mixed complex $\mathbf{6d}^{\odot\ominus}$ is localized almost entirely in the π system of the bipyrimidine (Fig. 1, A and B). However, the ESR line width remains relatively large when compared to the better resolved spectrum of the tetracarbonylmolybdenum complex radical (Fig. 1, C), presumably as a result of the superposition of numerous small and unresolved hyperfine couplings with the protons and ^{14}N nuclei of the 2,2′-bipyridine ligands.[12]

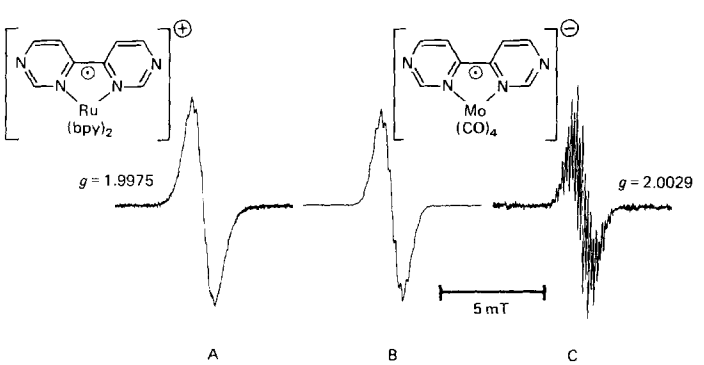


Fig. 1. Room temperature ESR spectra of the reduced complex $\mathbf{6d}^{\odot\ominus}$ in acetonitrile (A) and of the tetracarbonylmolybdenum radical complex $\mathbf{6b}^{\odot\ominus}$ at low (B) and high resolution (C) in THF. The similarity between A and B implies a localization of the unpaired electron in the π-system of the 4,4′-bipyrimidine, in accord with the formulation $[Ru^{2\oplus}(\mathbf{1})_2(\mathbf{3}^{\odot\ominus})]^{\oplus}$. Counterions $ClO_4^{\ominus}$ ($\mathbf{6d}^{\odot\ominus}$), $K^{\oplus}$ ($\mathbf{6b}^{\odot\ominus}$), modulation amplitudes 0.02 (A, C), 0.3 mT (B).

Undoubtedly, the ruthenium(II) complexes **6d**,**e** are distinguished by their ready reducibility (Tables 1 and 2); comparable effects have otherwise only been achieved after using ligands with a substantially larger π-system.[2b] Photochemical and photophysical investigations should therefore furnish information about the suitability of these complexes as photocatalysts; in any case, the 4,4′-bipyrimidine represents a relatively small but particularly π-acidic α-diimine ligand.

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6a, 96211-89-1; **6b**, 96211-90-4; **6c**, 96211-91-5; **6d**, 96211-93-7; **6e**, 96211-95-9; **6f**, 96211-96-0; $[Ru(\mathbf{3})_3]^{3\oplus}$, 96211-97-1; $[Ru(\mathbf{3})_3]^{\oplus}$, 96211-98-2; $[Ru(\mathbf{3})_3]$, 96211-99-3; $[Ru(\mathbf{3})_3]^{\ominus}$, 96212-00-9; $Cr(CO)_5THF$, 15038-41-2; $Mo(CO)_5THF$, 53248-43-4; $W(CO)_5THF$, 36477-75-5; $Ru(L)_2Cl_2$, 15746-57-3; $RuCl_2(DMSO)_4$, 11070-19-2.

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[6] $h_{N(diimine)} = h_{N'} = 0.5$; over the whole range of $0 < h_{N(diimine)} < 1$, **3** exhibits the lowest unoccupied molecular orbital (LUMO).

[7] J. J. Lafferty and F. H. Case (*J. Org. Chem. 32* (1967) 1591) have reported the reaction with $Fe^{2\oplus}$; *Kitamura* et al. [3] used a dimethyl derivative.

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[9] F. Effenberger, *Chem. Ber. 98* (1965) 2250; b) **6a**—**c** were obtained by thermal reaction of photolytically generated $THF \cdot M(CO)_5$ with **3** in THF (M = Cr, Mo, W); in the case of **6a** and **6b** this reaction already takes place at room temperature, whereas in the case of **6c** prolonged heating under reflux is necessary. **6d** and **6e** were prepared by heating a mixture of *cis*-$[Ru\mathbf{1}_2Cl_2] \cdot 2H_2O$ or $[RuCl_2(DMSO)_4]$ (DMSO: dimethyl sulfoxide), respectively, and excess **3** in ethylene glycol followed by precipitation in water with KPF_6 as the bis(hexafluorophosphates). All the compounds were purified by column chromatography on Florisil or Al_2O_3 (ruthenium complexes) and afford correct elemental analyses (isolated yields 20—40%). IR (THF; ν(CO) [cm^{-1}]): **6a**: 2000, 1910, 1900 sh, 1855; **6b**: 2010, 1910, 1900 sh, 1855; **6c**: 2000, 1900, 1895 sh, 1850. ^1H-NMR ([D_6]acetone): **6a**: δ = 8.66 (d, 2H), 9.14 (d, 2H), 9.81 (s, 2H); **6b**: δ = 8.75 (d, 2H), 9.20 (d, 2H), 9.74 (s, 2H); **6c**: δ = 8.81 (d, 2H), 9.22 (d, 2H), 9.86 (s, 2H). ^1H-NMR (CD_3CN): **6d**: δ = 7.4 (m, 4H), 7.70 (d, 2H), 7.80 (d, 2H), 8.05 (d, 2H), 8.11 (d, 2H), 8.5 (m, 8H), 9.06 (d, 2H); **6e**: δ = 8.56 (d, 6H), 8.61 (s, 6H), 9.11 (d, 6H); c) preparation of **6f** from **3** and 2 equivalents of $THF \cdot W(CO)_5$ at room temperature in THF, column chromatographic purification, 15% yield. IR (THF; ν(CO) [cm^{-1}]): 2065, 1935, 1907. ^1H-NMR (C_6D_6): δ = 7.12 (d, 2H), 7.96 (d, 2H), 8.87 (s, 2H).

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Synthesis and Structure of New Potassium-Gold-Tellurium Polyanions: $[KAu_9Te_7]^{4\ominus}$, $[K_2Au_4Te_4(en)_4]^{2\ominus}$, and $[K_2Au_4Te_4(dmf)_2(CH_3OH)_2]^{2\ominus}$

By *Robert C. Haushalter**

In the Au–Te binary system, one congruently melting compound is known, $AuTe_2$,[1] as well as the minerals calverite[2] and krennerite[3] (both $AuTe_2$) as a thermally metastable mineral montbrayite, Au_2Te_3.[4] Apparently, the only structurally characterized synthetic Au–Te compounds are the gold(III) chalcogenide halides AuTeI[5] and $AuTe_2X$ (X = Cl, Br, I).[6] However, several thioaurates like $[AuS_9]^{\ominus}$,[7] $[Au_2S_8]^{2\ominus}$,[8] and $[Au_{12}S_8]^{4\ominus}$[9] have recently been characterized. We have now obtained several novel K–Au–Te polyanions from the extraction of ternary K–Au–Te alloys. In this report, we describe the structures of the following salts:

$[Ph_4P]_4[KAu_9Te_7]$ **1**

$[Ph_4P]_2[K_2Au_4Te_4(en)_4]$ **2**

$[Ph_4P]_2[K_2Au_4Te_4(dmf)_2(CH_3OH)_2]$ **3**, dmf = dimethylformamide

During our investigation of ternary K–Au–Te alloys, we have prepared a yellow-brown material of nominal composition K_3AuTe_2, **4**, by heating a 5% excess of K with $AuTe_2$. Whereas K_3AuTe_2 dissolves readily in deoxygenated water, methanol solutions give a black precipitate on standing. However, if **4** is treated with methanol in the presence of Ph_4PBr, an orange crystalline precipitate, **5**, is immediately obtained. Dissolution of **5** in dimethylformamide (DMF), followed by dilution with additional Ph_4PBr in methanol, gives two products: red, triangular plates of **1** and red prisms of **3**.

The structure of the anion in **1**, viewed almost parallel to the pseudo threefold axis containing the unique Te and K, is shown in Figure 1 and can be approximately described as a derivative of an $[M_{12}X_8]^{4\ominus}$ cube, with one corner and three edges missing.[10] The structure of the intact thiocubanes $[M_{12}S_8]^{4\ominus}$ are known for M = Au[9] and Cu.[11] The Au_9Te_7 skeleton in the anion of **1** is distorted from a fragment of a perfect cube by compression along the pseudo threefold axis containing the unique Te and the missing corner. This compression is apparently due to a bonding interaction among the Au centers. Except for two longer contacts (367 and 338 pm), the Au–Au distances within the Au_3 triangles range from 303.9(2) to 322.1(2) pm with an average distance of 313 pm. These can be compared to Au–Au distances[12] of 288 pm in Au metal and 363 pm for the contacts in a hypothetical $[Au_{12}Te_8]^{4\ominus}$ cube with an Au–Te distance of 257 pm. The Au–Au distances between the Au_3 triangles are much longer with an average distance of 389 pm. The nine Te–Au–Te angles are close to 180° (range 173° to 180°, average 176°) as expected for Au^{I}. The compression of the cubic fragment is also reflected in the Au–Te–Au angles which fall into two groups: a) those involving the three Te atoms capping the Au_3 triangles, which are less than 90° (average angle = 77°), and b) the remaining Te atoms with average Au–Te–Au angles greater than 90° (average = 99°).

An interesting feature of the anion in **1** is the $K^{\oplus}$ imbedded in the cluster. This atom was identified as $K^{\oplus}$ as follows: 1) X-ray fluorescence analysis of **1** indicated the presence of K; 2) the observed charge of $4\ominus$ ($9\,Au^{\oplus} + 7\,Te^{2\ominus} + K^{\oplus}$); 3) satisfactory refinement of the thermal parameters, using values for K, in the X-ray data refinement. As observed in the only other structurally characterized K–Au–Te clusters, **2** and **3** (vide infra), the K–Au distances are shorter than the K–Te distances, which could be due to the fact that Au is more electronegative than Te (2.4 vs. 2.1).[13] The average of the nine K–Au contacts (364 pm) is longer than the average in the anions in **2** or **3** (359 and 349 pm, respectively) or the distances in K–Au intermetallic compounds like KAu_5,[14] which has K–Au contacts of 327 and 364 pm. $K^{\oplus}$ appears too large to be encapsulated by an intact $[Au_{12}Te_8]^{4\ominus}$ cube based on the observed Au–Te and K–Au distances.

In the solid state, the tetragonal compound CsAuO[15] has been prepared by the oxidation of CsAu. The important structural unit in CsAuO is an eight-membered $[Au_4O_4]^{4\ominus}$ ring, which is constrained to be exactly square-planar by the space group $I\bar{4}$ in which the structure was

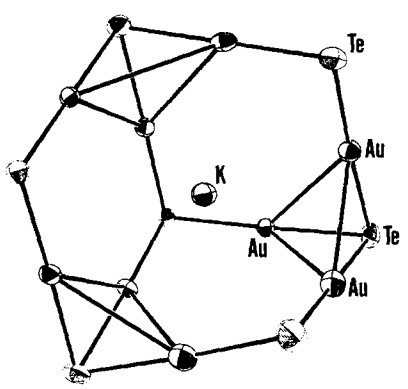


Fig. 1. Structure of the anion $[KAu_9Te_7]^{4\ominus}$ in **1** [10].

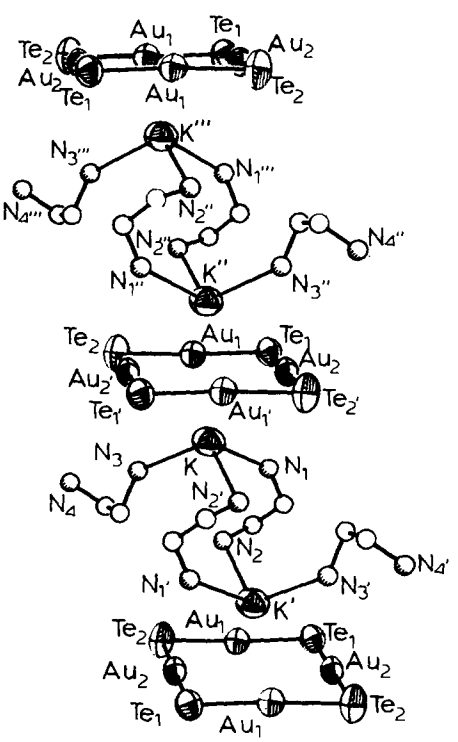


Fig. 2. Structure of the anion $[K_2Au_4Te_4(en)_4]^{2\ominus}$ in **2** [10].

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solved. We have found planar $[Au_4Te_4]^{4\ominus}$ rings, capped by $K^{\oplus}$ on each face, in the compounds **2** and **3**, which were prepared by the extraction of ternary K–Au–Te alloys.

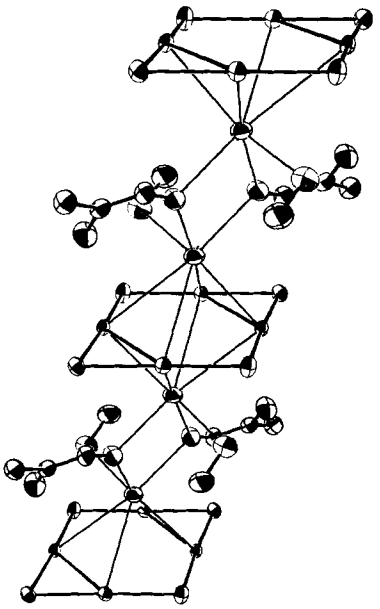


Fig. 3. Structure of the anion $[K_2Au_4Te_4(dmf)_2(CH_3OH)_2]^{2\ominus}$ in **3** [10].

Compound **2** was prepared in high yield by dissolving the alloy KAuTe (prepared from the fusion of equimolar amounts of K and a melt of nominal composition AuTe) in ethylenediamine (en) followed by treatment with Ph_4PBr in ethylenediamine, while **3** forms as a coproduct in the synthesis of **1**. Both compounds are dark red.

Compounds **2** and **3** crystallize in the triclinic space group $P\bar{1}$[10] and exhibit similar unit cell packings. The structures of the anions in **2** and **3** are shown in Figures 2 and 3, where the similarities of the structures are obvious. Both consist of planar $[Au_4Te_4]^{4\ominus}$ rings to which two $K^{\oplus}$ ions are coordinated on opposite faces. Solvent molecules, which occupy two of the $K^{\oplus}$ coordination sites, either en in **2** or DMF in **3**, bridge the $[K_2Au_4Te_4]^{2\ominus}$ moieties into one-dimensional strings. A third $K^{\oplus}$ coordination site is occupied by en in **2** or CH_3OH in **3**. As observed in $[KAu_9Te_7]^{4\ominus}$, the shortest potassium-metal contacts are the K–Au, not the K–Te distances. The coordination mode of K to Au is slightly different in **2** and **3**. In **2**, the four K–Au contacts are approximately equal (346.3, 350.1, 343.2, 351.3 pm), whereas in **3** there are two longer (387.4, 387.3 pm) and two shorter contacts (351.2, 348.3 pm). In CsAuO, KCuO,[16] and KAgO,[17] the K–O contacts are much shorter than the K–M (M = Au, Ag, Cu) distances as expected.

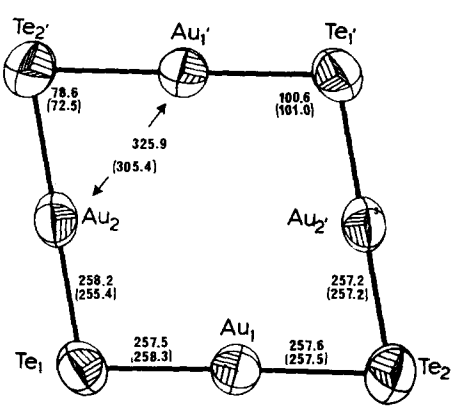


Fig. 4. Distances [pm] and angles [°] in the $[Au_4Te_4]^{4\ominus}$ rings in **2** and **3**. The values in parentheses are those of **3**.

Unlike the $[M_4O_4]^{4\ominus}$ rings in CsAuO[15] or KAgO,[17] which are perfect squares, the $[Au_4Te_4]^{4\ominus}$ rings in **2** and **3** have a rhombohedral distortion (Fig. 4). Presumably this distortion is due to the pairwise attractive interaction between the Au atoms and results in a pair of short Au–Au contacts and a pair of longer non-bonding contacts in both structures.

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1, 96211-78-8; **2**, 96211-81-3; **3**, 96211-83-5; **4**, 96211-76-6; $AuTe_2$, 12006-61-0; K, 7440-09-7; KAuTe, 96211-75-5.

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[10] Crystal data for **1**: monoclinic, $P2_1/c$ (No. 14), $a = 2609.6(9)$, $b = 1576.9(7)$, $c = 2504.8(4)$ pm, $\beta = 99.33(2)°$, $-107°C$, $Z = 4$; $Mo_{K\alpha}$ ($\lambda = 71.07$ pm), 5036 reflections, $R = 0.054$.—**2**: triclinic, $P\bar{1}$, $a = 1006.1(4)$, $b = 1295.8(5)$, $c = 1369.3(6)$ pm, $\alpha = 83.09(3)$, $\beta = 104.07(3)$, $\gamma = 98.75(3)°$, 20°C, $Z = 1$, $Mo_{K\alpha}$ ($\lambda = 71.07$ pm), $R = 0.051$ for 2727 reflections, solved by direct methods.—**3**: triclinic, $P\bar{1}$, $a = 972.3(3)$, $b = 1333.1(4)$, $c = 1336.6(8)$ pm, $\alpha = 81.01(4)$, $\beta = 73.95(4)$, $\gamma = 74.07(3)°$, $-108(1)°C$, $Z = 1$, $Mo_{K\alpha}$ ($\lambda = 71.07$ pm), $R = 0.034$ for 4497 reflections, solved by direct methods. Further details of the crystal structure analysis can be obtained from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2, by quoting the depository number CSD 51286, the name of the author, and the journal citation.
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Synthesis and Structure of New Hg–Te Polyanions: $[Hg_4Te_{12}]^{4\ominus}$, a Cluster Containing $Te^{2\ominus}$, $Te_2^{2\ominus}$, and $Te_3^{2\ominus}$ Ligands and $[Hg_2Te_5]^{2\ominus}$, a New One-Dimensional Inorganic Polymer

By *Robert C. Haushalter**

The binary compounds HgX (X = S, Se, Te) are known to have extremely low solubilities in aqueous solutions. Al-

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though it is possible to solubilize HgS in the presence of $S^{2\ominus}$,[1] apparently only one structurally characterized binary tellurium compound, $[HgTe_2]^{2\ominus}$, has been isolated and structurally characterized.[2] We would like to report the syntheses and structural characterization of **1** and **2** from the extraction of ternary K–Hg–Te alloys with ethylenediamine (en).

$[n\mathrm{Bu_4N}]_4[Hg_4Te_{12}]$ **1** $[PPh_4]_2[Hg_2Te_5]$ **2**

The only previously known HgTe anion is contained in the yellow [crypt·K]$_2$[$HgTe_2$], which was prepared by the extraction of an alloy of composition KHgTe with ethylenediamine. The alloy KHgTe was prepared by quenching a sealed tube initially containing equivalent amounts of K, Hg, and Te at 600 °C. We have observed that, under 1 atmosphere of helium, Hg boils out of a melt of nominal composition $K_2Hg_2Te_3$ (prepared from the fusion of 1.5 equivalents of Te with KHg), at temperatures well below 600 °C. It was necessary, therefore, to keep the temperature of the melt below the boiling point during the synthesis of K–Hg–Te alloys in order to prepare compositions richer in Hg than K_2HgTe_2.

Unlike KHgTe, which is reported to give yellow ethylenediamine solutions, the alloy $K_2Hg_2Te_3$ dissolves in ethylenediamine to give very dark brown-orange solutions. Treatment of these dark extracts with solutions of $n\mathrm{Bu_4NBr}$ in methanol (MeOH) furnishes dark brown **1** in high yields. **1** was identified by elemental analysis[3] and a single-crystal X-ray structure determination.[4]

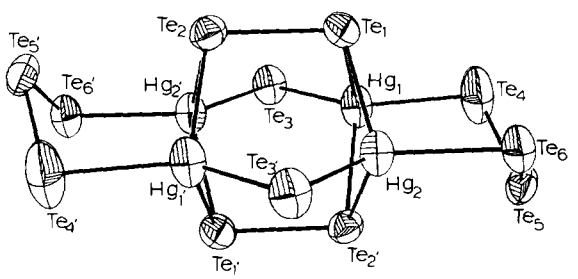


Fig. 1. The structure of the $[Hg_4Te_{12}]^{4\ominus}$ anion in **1** [4].

1 contains the novel $[Hg_4Te_{12}]^{4\ominus}$ anion which resides on a crystallographic inversion center (Fig. 1). The four Hg atoms, which are coplanar, are coordinated in a distorted tetrahedral fashion to an array of two $Te^{2\ominus}$-, two $Te_2^{2\ominus}$-, and two $Te_3^{2\ominus}$-ligands. There are no Hg–Hg bonds, as the nearest contacts are 394 pm (Hg1–Hg2) and 370 pm (Hg1–Hg2'). The Hg–Te bond lengths fall into two groups: shorter distances involving Hg to two-coordinate Te (270.6 to 277.6, average = 273.7 pm) and longer distances from Hg to three-coordinate Te (292.5 to 298.3, average 295.4 pm). These Hg–Te distances can be compared to those found in [crypt·K]$_2$[$HgTe_2$][2] (258.9 pm) and in [HgTe][5] (279 pm).

During the refinement of the X-ray data, it was observed that there is some disorder in the $Te_3^{2\ominus}$-ligand. The central Te atom (Te5) in the $Te_3^{2\ominus}$-ligand refined to an occupancy factor of ~75% while the remaining electron density (~25% of that expected for Te) was located along the line connecting Te4 and Te6. A possible explanation may be that a $Te_2^{2\ominus}$-ligand occupies the position of the $Te_3^{2\ominus}$-ligand ~25% of the time.

Using the cation $PPh_4^{\oplus}$ instead of $Bu_4N^{\oplus}$ has allowed us to isolate a different Hg–Te polyanion, $^1_\infty[Hg_2Te_5]^{2\ominus}$, a new one-dimensional inorganic polymer. Several examples of one-dimensional tellurium-containing polyanions have recently been structurally characterized. These include ternary systems such as K_2SnTe_5,[6] $LiGeTe_2$,[7] and K_2GeTe_4,[8] and binary systems like Rb_2Te_5[9] and Cs_2Te_5.[10] The ternary materials contain tetrahedral atoms bridged by Te atoms,[6–8] while Rb_2Te_5 and Cs_2Te_5 contain two variants of the $^1_\infty[(Te_4Te_{2/2})]^{2\ominus}$ chain.[9, 10]

2 was prepared from the same ethylenediamine extract, of an alloy of nominal composition $K_2Hg_2Te_3$, used for the preparation of $[Hg_4Te_{12}]^{4\ominus}$. Compound **2** forms black, spear-shaped needles with curved crystal faces, when the aforementioned $K_2Hg_2Te_3$ solution and an ethylenediamine solution of PPh_4Br are allowed to diffuse slowly (3 weeks) into each other in an H-tube.

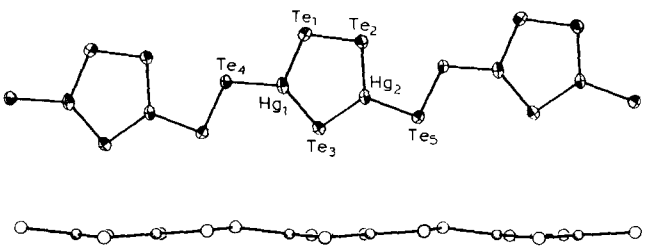


Fig. 2. Top: Structure of three repeat units of the polymeric anion $^1_\infty[Hg_2Te_5]^{2\ominus}$ of **2** [4]. Bottom: An edge-on view of the same structural unit.

The X-ray structure analysis of **2** shows that the new polymeric anion $^1_\infty[Hg_2Te_5]^{2\ominus}$ runs in one-dimensional strings parallel to the crystallographic *a* axis (Fig. 2, top). The anion chain is approximately planar (Fig. 2, bottom).

In **2**, the two crystallographically independent Hg atoms have essentially trigonal planar environments with Hg1 10 pm out of the Te1, Te2, Te3 plane and Hg2 50 pm from the Te2, Te3, Te5 plane. Although rare, other examples of species containing trigonal planar coordinated Hg atoms are known, such as $Hg_3O_2Cl_2$[11] and $(Me_3S)[HgI_3]$.[12] The average of the six Hg–Te distances in **2** is 271 pm, which can be compared to the average of the Hg to two-coordinate Te contacts in $[Hg_4Te_{12}]^{4\ominus}$ (274 pm) or the short Hg–Te distance in $[HgTe_2]^{2\ominus}$ of 259 pm. The Te–Te distances are similar to those found in many other polytellurides. The chains of $^1_\infty[HgTe_5]^{2\ominus}$ are isolated from one another in **2** by $Ph_4P^{\oplus}$ cations and there are no interchain contacts.

It should be noted that the structures of $^1_\infty[Hg_2Te_5]^{2\ominus}$ and $[Hg_4Te_{12}]^{4\ominus}$, which were prepared by extracting the same starting alloy, are somewhat related. The five-membered Hg_2Te_3 ring, with two Te atoms exocyclic to the Hg atoms, is present in both $[Hg_4Te_{12}]^{4\ominus}$ and $^1_\infty[Hg_2Te_5]^{2\ominus}$. Thus, $[Hg_4Te_{12}]^{4\ominus}$ is a face-to-face dimer of the repeat unit of $^1_\infty[Hg_2Te_5]^{2\ominus}$ with two additional Te atoms present per dimer.

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1, 96129-10-1; **2**, 96129-12-3; $K_2Hg_2Te_3$, 96129-13-4.

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[3] Calcd. for $C_{64}H_{144}N_4Hg_4Te_{12}$: C 23.26, H 4.36, N 1.70, Hg 24.29, Te 46.38%; found: C 23.75, H 4.78, N 1.89, Hg 24.12, Te 45.83%.
[4] Crystal data for **1**: Monoclinic, space group $P2_1/n$, $a = 1665.3(6)$, $b = 2688.8(6)$, $c = 2706.8(6)$ pm, $\beta = 90.72(3)°$ at 20°C, $Z = 2$, $Mo_{K\alpha}$ ($\lambda = 71.07$ pm), $R = 0.057$ for 2207 reflections, solved by direct methods.—**2**: monoclinic, $P2_1$, $a = 1040.0(2)$, $b = 1732.4(4)$, $c = 1374.2(3)$ pm, $\beta = 94.02°$, 20°C, $Mo_{K\alpha}$ ($\lambda = 71.07$ pm), $R = 0.057$, 3939 reflections.—Further details of the crystal structure investigations are available on request from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2 (FRG), on quoting the depository number CSD 51287, the name of the author, and the full citation of the journal.
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BOOK REVIEWS

Cyclophanes, Vols. 1 and 2. Edited by *P. M. Keehn* and *S. M. Rosenfeld,* Academic Press, New York 1983. Vol. 1: xxx, p. 1—358, bound, $ 65.00, ISBN 0-12-403001-7/Vol. 2: xxx, p. 359—725, bound, $ 60.00, ISBN 0-12-403002-5.

This set appears as part of the excellent series of monographs chosen by its editor *H. H. Wasserman*. There may be an *embarras de richesse* in updating reviews of the chemistry of cyclophanes (a series edited by *F. Vögtle* comprising two volumes, albeit smaller, has recently appeared) but the present set is more encyclopedic.

The editors have done a fine job in choosing authors and in parcelling out the vast material to be covered. Inevitably there is some overlap but this is surprisingly minimal. I agree with the editors' claim that each chapter stands on its own. The set opens with a charming chapter by the father of the field; *Don Cram*'s personal account is a short overview, past, present, and future. The other chapters either emphasize synthesis and reactions, or properties and structure, or, in the best ones, there is a blend of the two. The more synthetic chapters are by *Rosenfeld* and *Chloe* ([n]cyclophanes, 46 pages), *Reiss* (condensed cyclophanes, 41 pages). *Hopf* (multibridged cyclophanes, 51 pages), *Misumi* (multilayered cyclophanes, 55 pages). Those emphasizing properties and structure are by *Liebman* (the conceptual chemistry of cyclophanes, 45 pages), *Keehn* (the crystal structure of cyclophanes, 169 pages), *Mitchell* (NMR properties and conformational behavior of cyclophanes, 71 pages). The chapters that, to my taste, blend all aspects and are thus the most useful in giving the reader an overall review before consulting the primary literature are those by *Paudler* and *Bezoari* (synthesis and properties of heterophanes, 82 pages) and *Itô, Fujise,* and *Fukuzawa* (non-benzenoid cyclophanes, 35 pages). Biological applications are given in two chapters by *Odashima* and *Koga* (cyclophanes in host-guest chemistry, 49 pages), and by *Sutherland* (cyclophanes as synthetic analogs of enzymes and receptors, 46 pages). The first doesn't touch upon, the second emphasizes crown ether hosts.

I have a bone to pick with *Don Cram*'s statement: "It seems that the selection of certain research problems is dominated by a subliminal aesthetic judgment." Subliminal indeed! There is little doubt that symmetry motivates many chemists in their choice of subject, in full awareness, explicitly.

Liebman's excellent chapter covers chemical concepts which have been clarified through cyclophane chemistry. *Keehn*'s very useful chapter includes a wealth of structural information accompanied by general explanatory comments. *Mitchell*'s chapter is not as exhaustive but clearly shows how NMR techniques have been used to assign rigid stereochemistry or conformation in mobile systems. *Rosenfeld* and *Chloe* include the variegated approaches for synthesis of [n]cyclophanes. *Paudler* and *Bezoari* do a good job in covering all aspects of heterophane chemistry but *Reiss* covers only synthesis of condensed benzenoid cyclophanes. Although he mentions in telegraphic style, e.g., that electronic spectra have been measured, his omission of more detail gives short shrift to important aspects of the work of *Staab* and his group. On the other hand, the *Itô* et al. chapter, albeit shorter, covers non-benzenoid cyclophanes in a much better way following *Hamlet*'s invocation: "There are more things in heaven and earth, Horatio, than are dreamt of in your philosophy." *Reiss* can learn from this. *Hopf*'s chapter, though essentially synthetic, is a gem in its general approach and pedagogic clarity. *Misumi*'s chapter covers his subject's manifold aspects. Both biochemical chapters are excellent, well-coordinated reviews with no unnecessary overlap between them.

Many of the authors (and the editors who did not correct them) do not know that one converts **52** into **51**, not to **51**. It is amusing to note that the Japanese authors (or those who do not describe synthetic steps) do not err in this respect; they do not use the word in their constructions.

This set on cyclophanes is a must in every library; even those suffering from the steep rise in Journal prices would be well advised to buy them, as would all wealthy individuals interested in the subject.

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Chemical Dynamics via Molecular Beam and Laser Techniques. By *R. B. Bernstein*. Oxford University Press, Oxford 1982. ix, 362 pp, paperback, £ 10.95.

This book is based on the Hinshelwood lecture series delivered by the author in Oxford in 1980. An introductory discussion of problems of reaction dynamics is followed by treatment of the following topics: The connection between reaction cross section and rate constant, the principle of microscopic reversibility, jet stream properties,

state-specific excitation and detection of educt and product molecules by laser and electrical multipole techniques, potential models for elastic and inelastic scattering and the classical deflection function, "glory" and "rainbow" effects, the concept of the scatter phase in the quantum theory of elastic scattering, reactive scattering problems such as product angular distributions in the laboratory and center of mass systems in complex and direct reactions, "opacity" (reaction probability as a function of the impact parameter) and "excitation functions" (reaction cross section as a function of collision energy), orientation effects, the influence of vibrational, rotational, and translational excitation on reaction velocity, and nonadiabatic (proceeding by various electronic potential surfaces) reactions. The text ends with a section covering the author's own field, the information-theoretical analysis of chemical dynamics and a survey of promising new fields such as the spectroscopy of transition states and the laser analysis of catalytic effects.

Such an enormous range of material can only be discussed in highlights in the space of 360 paperback pages. Exceptions, for example an interesting and detailed calculation for the determination of the degree of excitation of particles in molecular beams by laser techniques, only prove the rule. Thus, *Bernstein*'s book provides (aside from its price) a welcome guide for the rather confused student through the flood of specialized texts in this field.

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Biotechnology. A Comprehensive Treatise in 8 Volumes. Edited by *H. J. Rehm* and *G. Reed*. Vol. 5: **Food and Feed Production with Microorganisms.** Edited by *G. Reed*. Verlag Chemie, Weinheim 1983, 631 pp., bound, DM 425. ISBN 3-527-25767-5.

This series[*] from Verlag Chemie is a welcome addition to the repertoir of resources for people in the biotechnology and allied fields. Volume 5, in some respects, continues where Volume 3 left off in the area of food related fermentations. One should look to Vol. 3 for the production of ethanol, bakers' yeast, edible mushrooms, starter cultures, acetic acid, citric acid, gluconic acid, lactic acid, amino acids and extracellular polysaccharides—all food related topics. This underlines one of the problems the editors must have faced in organizing the series. I would just caution the reader that this Volume alone will not cover the area described by its title.

It begins with a contribution by *G. Spicher*, who presents a thorough discussion on the technology of baked goods, in particular bread. *S. Lafon-Lafourcade* gives an excellent review of the science of wine and brandy production. She has included some fine photomicrographs of the yeast and bacteria involved. This chapter however, like several others in this volume, does not emphasize the commercial aspects such as production technology, economics, and regulatory information. Nevertheless, what is covered is covered well. Later on in this volume is included a discussion on distilled beverages other than brandy, i.e., whiskey, rum, vodka, tequila by *L. Bluhm*.

W. A. Hartwick describes the technology of beer including its history in a very readable chapter. The next two chapters relate to the dairy industry. *E. R. Vedamuthu* and *C. Washam* deal with cheese technology. The chapter appears to be not well integrated. For example, the involvement of microorganisms and enzymes is discussed twice in the chapter. Despite this, the chapter has a lot of good information including excellent summaries of changes occurring during the manufacture of seven different kinds of cheeses.

A very fine review of the technology of yogurt production and of lactic acid bacteria in fermented dairy products is given by *V. Bottazzi*.

The importance of lactic acid bacteria in food biotechnology is recognized through two additional chapters. One on cabbage and cucumbers *(J. R. Stamer)* and the other on olives *(M. J. Fernández Díez)*.

Starter cultures in sausage and ham production are discussed by *H.-U. Liepe*. The emphasis here is on the use of starter cultures and not on the production of the cultures. *H. Ebner* and *H. Follmann* continue their chapter on acetic acid from Vol. 3 by focussing on how raw vinegar is treated before sale. Regulatory aspects are also reviewed.

A commendable addition to the selections in this volume is made by *L. R. Beuchat* via a presentation on "Indigenous Fermented Foods". This one provides you with a chance to learn about the real "classical biotechnology" as practiced for centuries the world over. A good review of the literature on cocoa fermentation, with a somewhat sloppy section on page 556, is presented by *D. W. Lehrian* and *G. R. Patterson*. The Volume is concluded with three short chapters. These provide introductions to the manufacturing of tea *(G. W. Sanderson)*, coffee fermentation *(J. Castelein* and *H. Verachtert)*, and of fermented feeds and feed supplements *(H. J. Peppler)*. I would have preferred to see a greater consistency in the emphasis and orientation from one chapter to another, a better coverage of regulatory issues, of economic issues and of manufacturing and engineering aspects. The subjects of single cell protein for both food and feed production and solid state fermentations for feed production could have been covered here. However, the editors have a very difficult job and it seems to me they have succeeded in bringing together a great deal of useful information in this third volume released.

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New Books

The following books have been received by the editor. All the publications listed are available through W & P Buchversand für Wissenschaft und Praxis, Boschstrasse 12, D-6940 Weinheim (Federal Republic of Germany). Tel. (06201) 606-0, Telex 465516 vchwh d, Telefax (06201) 602328.

Oxygen Radicals in Chemistry and Biology. Proceedings of the Third International Conference, Neuherberg, July 10—15, 1983. Edited by *W. Bors, M. Saran*, and *D. Tait*. Walter de Gruyter, Berlin 1984. xix, 1029 pp., bound, DM 250.00.—ISBN 3-11-009704-4

[*] Cf. Angew. Chem. *95* (1983) 758; *Angew. Chem. Int. Ed. Engl. 22* (1983) 893.

Progress in Clinical and Biological Research, Vol. 157: Recognition Proteins, Receptors, and Probes: Invertebrates. Proceedings of a Symposium on Recognition and Receptor Display: Lectin Cell Surface Receptors and Probes, held in Philadelphia, Pennsylvania, December 28, 1983. Edited by *E. Cohen*. Alan R. Liss, New York 1984. 228 pp., bound, $ 38.00.—ISBN 0-8451-5007-3

Gesundheitsschädliche Arbeitsstoffe. Toxikologisch-arbeitsmedizinische Begründung von MAK-Werten. Edited by *D. Henschler*. A publication of the Deutsche Forschungsgemeinschaft. 9th installment. Verlag Chemie, Weinheim 1984. 336 pp., loose-leaf edition, DM 140.00.—ISBN 3-527-25978-3

Analytische Methoden zur Prüfung gesundheitsschädlicher Arbeitsstoffe. Edited by *D. Henschler*. A publication of the Deutsche Forschungsgemeinschaft. Verlag Chemie, Weinheim. **Sammlung 1: Luftanalysen.** 4th installment. 1984. 104 pp., loose-leaf edition, DM 48.00 (installments 1—4 in file: DM 430.00; further installments will follow), **Sammlung 2: Analysen in biologischem Material.** 7th installment. 1984. 208 pp., loose-leaf edition, DM 94.00 (installments 1—7 in file: DM 785.00; further installments will follow).—ISBN 3-527-27602-5

Datensammlung zur Toxikologie der Herbizide. Edited by the Arbeitsgruppe Toxikologie der Kommission für Pflanzenschutz-, Pflanzenbehandlungs- und Vorratsschutzmittel der DFG. A publication of the Deutsche Forschungsgemeinschaft. Verlag Chemie, Weinheim. 5th installment. 1984. Ca. 180 pp., loose-leaf edition, ca. DM 82.00 (installments 1—5 in file: ca. DM 635.00; further installments will follow).—ISBN 3-527-27606-8

Methodensammlung zur Rückstandsanalytik von Pflanzenschutzmitteln. Edited by the Arbeitsgruppe Analytik der Kommission für Pflanzenschutz-, Pflanzenbehandlungs- und Vorratsschutzmittel der DFG. A publication of the Deutsche Forschungsgemeinschaft. Verlag Chemie, Weinheim. 7th installment. 1984. 108 pp., loose-leaf edition, DM 54.00 (installments 1—7 in file: DM 668.00; further installments will follow).—ISBN 3-527-27604-1

Kosmologie heute. By *J. Meurers*. Wissenschaftliche Buchgesellschaft, Darmstadt 1984. xii, 339 pp., paperback, DM 81.00 (for members DM 54.00).—ISBN 3-534-07020-8

Einführung in die Thermodynamik der Irreversiblen Prozesse. By *H. Baur*. Wissenschaftliche Buchgesellschaft, Darmstadt 1984. x, 231 pp., paperback, DM 39.00 (for members DM 26.00).—ISBN 3-534-07323-1

Mit dem Salz durch die Jahrtausende. By *H.-H. Emons* and *H.-H. Walter*. VEB Deutscher Verlag für Grundstoffindustrie, Leipzig 1984. Ca. 264 pp., bound, ca. DM 30.00.—Order No. 541-839-8

Progress in Tryptophan and Serotonin Research. Proceedings of the Fourth Meeting of the International Study Group for Tryptophan Research ISTRY, Martinsried, April 19—22, 1983. Edited by *H. G. Schlossberger, W. Kochen, B. Linzen,* and *H. Steinhart*. Walter de Gruyter, Berlin 1984. xix, 889 pp., bound, DM 240.00.—ISBN 3-11-009760-5

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Enzymes Hosted in Reverse Micelles in Hydrocarbon Solution

By Pier Luigi Luisi*

Reverse micelles are spheroidal aggregates formed by certain surfactants in apolar media. In contrast to normal micelles in water, the polar head groups of the surfactant molecules are directed towards the interior of the aggregate and form a polar core which can solubilize water (the "water pool"); the lipophilic chains are exposed to the solvent. The water of the water pool exhibits properties that (depending on the mole ratio of water to surfactant) differ from those of bulk water. Surprisingly, these reverse micelles are able to solubilize in hydrocarbon solvents hydrophilic molecules, e.g., enzymes and even plasmids, that are much larger than the original water-pool diameter. These biopolymer-containing reverse micelles can be viewed as novel microreactors, whose physical properties can be controlled through the water content. Remarkable is the ability of enzyme-containing micelles to react with water-insoluble, hydrocarbon-soluble substrates, as in the example of lipoxygenase with linoleic acid.

1. Introduction

This review presents the work carried out over the last few years on enzymes solubilized in apolar solvents with the help of reverse micelles. The basic properties of reverse micelles will be described first, followed by a discussion of the physical and chemical properties of enzymes solubilized in reverse micelles.

Some common surfactants that form such aggregates in apolar solvents are summarized in Table 1. As is well known, other types of aggregates can be found in aqueous solution,[1] such as bilayers, vesicles, and liposomes; these, however, will not be considered here. Figure 1 gives an idea of the structure of normal (aqueous) and reverse micelles, as well as of the surfactant AOT, which has been mostly used in our studies. Most important is the fact that reverse micelles exhibit relatively ordered structures, characterized by a definite (although average) radius, molecular weight, and packing density. Micelles are an ideal subject of investigation for those chemists who are interested

Table 1. Aggregation of amphiphilic molecules in hydrocarbon solvents. n = average aggregation number [a].

Amphiphilic molecule	Solvent	T [°C]	Conc. range [wt.-%]	n
dodecylammonium propionate	benzene	25	0.09–0.21	3
dodecylammonium propionate	cyclohexane	20	0.023–0.034	5
dodecylammonium benzoate	benzene	25	0.20–0.33	3.6
dodecylammonium benzoate	cyclohexane	20	0.8–3	3.6–9
sodium 1,2-bis(2-ethylhexyloxycarbonyl)-1-ethanesulfonate (AOT)	cyclohexane	28	1–3	45–66
sodium 1,2-bis(2-ethylhexyloxycarbonyl)-1-ethanesulfonate (AOT)	benzene	28	1–3	23
lithium dinonylnaphthalenesulfonate	benzene	35	0.5–6	7
lithium dinonylnaphthalenesulfonate	cyclohexane	35	0.5–6	8
α-monoglyceryl oleate	benzene	20	0.01–0.06	19
lecithin	benzene	20	0.001–0.01	80
lecithin	benzene	25	0.07–1	73

[a] Table adapted from [1].

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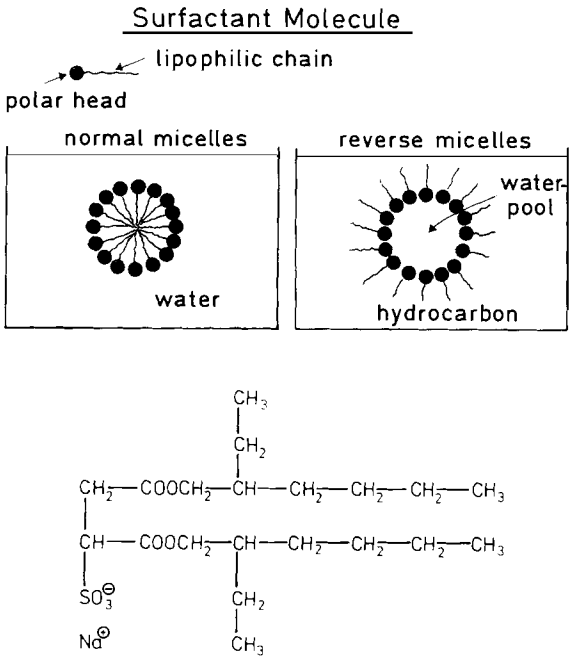


Fig. 1. An idealized representation of normal (aqueous) and reverse micelles in cross section. The structure of sodium 1,2-bis(2-ethylhexyloxycarbonyl)-1-ethanesulfonate (AOT) is also shown. Typical conditions for reverse micelles: isooctane (2,2,4-trimethylpentane), 25—100 mM AOT, 0.5—2% water. Reverse micelles are fairly monodisperse, dynamic aggregates, which can solubilize relatively large (ca. 10%) amounts of water. For mole ratios $w_0 = [H_2O]/[AOT] \gtrsim 7$, the term microemulsion should be used (see text).

in the spontaneous formation of ordered structures. Figure 1 should not, however, convey the idea that micelles are rigid structures: on the contrary, they are characterized by several dynamic processes.[2-4] For example, one important characteristic of reverse micelles is their coalescence upon collision.[4] This is assumed to take place through a "transient dimer" having a communication channel that permits rapid exchange of material. This is illustrated in Figure 2, along with the significance of this phenomenon for the enzymatic activity cycle (see Section 4).

Of considerable importance is the interaction of reverse micelles with water. Due to their polar core, reverse micelles can solubilize water in apolar solvents. This solubilized water is usually referred to as a "water pool".[2]

The reverse micelles formed by sodium 1,2-bis(2-ethylhexyloxycarbonyl)-1-ethanesulfonate (AOT) will now be considered more closely. The system we will mostly be dealing with is AOT/isooctane/water. An important parameter is the molar ratio of water to surfactant, $w_0 = [H_2O]/[AOT]$. This ratio, more than the absolute amount of water or surfactant present in the hydrocarbon solvent, determines most of the structural and physical properties of reverse micelles.[1,5,6] The water in the water pool is partly "bound" to the polar wall, and is relatively "free" only above a certain critical concentration. In the case of AOT, it appears that the molecules of water up to perhaps $w_0 = 6-8$ are tightly bound to the head groups of the surfactant[6,7] and that only above this value does "free water" exist in the water pool. In fact, reverse micelles swell when the water content increases.[5,6] Figure 3 (solid line)[5,6] illustrates this phenomenon with enzymes as guest molecules (see Section 3).

Particularly at low w_0 values, where the micelles are smaller and a relatively high amount of water is bound to

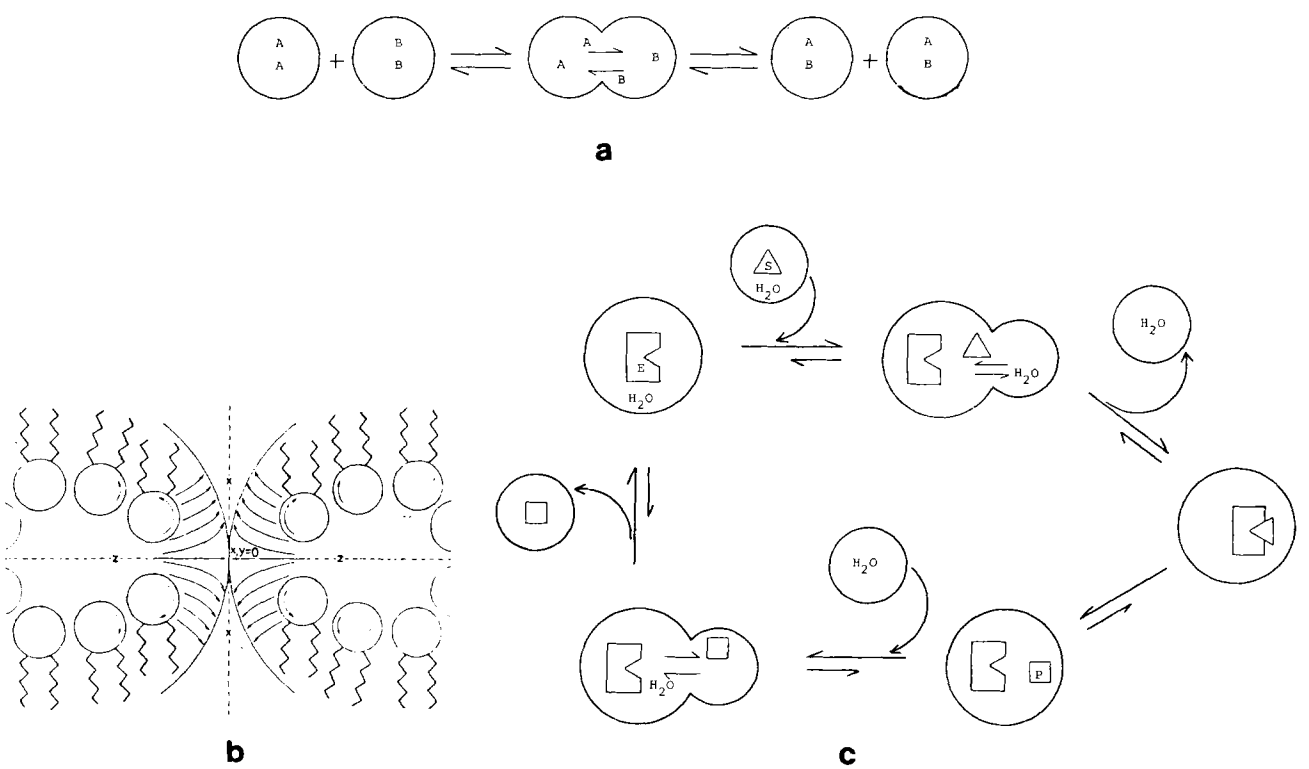


Fig. 2. Dynamic properties of reverse micelles. a) Exchange of materials between two reverse micellar solutions, which is the prerequisite for the reaction between A and B (from [2]). Coalescence between micelles and exchange of reagents takes place through a transient dimer, a concept elaborated by *Eicke* et al. [4a]. b) Schematic representation of the site of contact of two reverse micelles prior to coalescence (from [4a]). c) The proposed steady-state cycle of an enzymatic reaction in reverse micelles (from [24]).

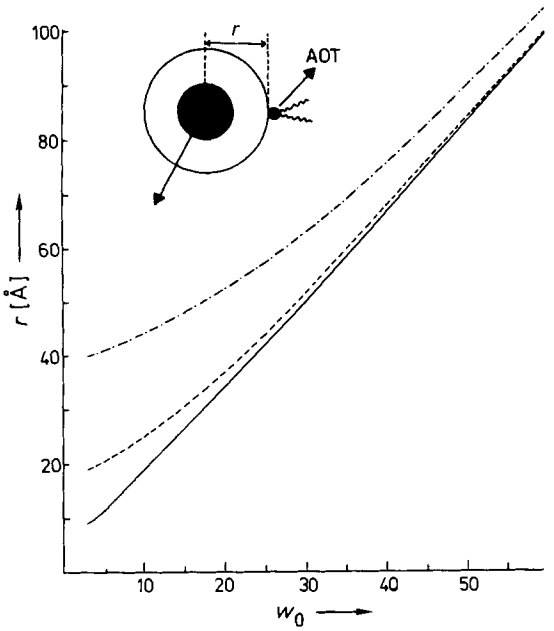


Fig. 3. The radius r of the AOT reverse micelles as a function of $w_0 = [H_2O]/[AOT]$. (—): "empty" micelles, i.e., micelles containing only water. This curve corresponds to the data of *Eicke* et al. [5, 6] (from [24]). (– – –): protein = ribonuclease (RNase); (– · –): protein = liver alcohol dehydrogenase (LADH). All data in this figure and in the following figues refer to room temperature if not otherwise stated.

the micelle walls, water in reverse micelles behaves "anomalously"—i.e., its physical properties are somewhat different from those of bulk water.[8–10] With increasing water content, the physical properties of the water pool asymptotically approach those of pure water. However, even at relatively large w_0 values, small differences may remain.

The w_0 region where water becomes free is usually taken as the dividing line between micelles and microemulsions. Microemulsions can indeed be visualized as distinct droplets of water in oil (hydrocarbon), whereas micelles form a homogeneous system, the water being used only to solvate the surfactant molecules. This distinction is usually disregarded since we generally study a large w_0 range and it would be too confusing to switch nomenclature depending upon the w_0 value—furthermore, the dividing line is not so clear. However, the difference between micelles and microemulsions should be kept in mind, because the physical properties of the system (e.g., mass transport, dynamics, reactivity and structure of guest molecules) may be different in the two w_0 ranges.

The discussion above suggests that the reactivity and conformation of biopolymers solubilized in reverse micelles changes as a function of the micellar parameters, in particular as a function of w_0. Since, with increasing w_0, the physical properties of the water pools approach those of the bulk water, the enzyme-containing micelle can be viewed as a microreactor, whose physical properties can be continuously changed by simply regulating the amount of water present in the micellar system. These new biopolymer aggregates may be of biotechnological use and may provide chemists with some basic information about the interaction of proteins with water and with membrane-like surfaces.

2. Experimental Problems

Figure 4 shows the three techniques that have been applied until now to prepare enzyme-containing micellar solutions. The first method (Fig. 4a) is the one we first used in our group for peptides[11,12] and defined as the "phase transfer" method. According to this method, the protein is present initially in an aqueous solution, which is covered with a layer of the micellar solution of AOT. Upon gentle stirring, a part of the protein is slowly transferred from the aqueous phase into the hydrocarbon phase (the process can be followed spectrophotometrically, for example at 280 nm). This method is relatively slow, but has the advantage that the final system is in thermodynamic equilibrium and the final hydrocarbon micellar solution, containing the biopolymer, is generally stable. This point is better understood if one compares the phase transfer method with the so-called injection method (Fig. 4b), whereby a few microliters of the concentrated stock solution of the protein are injected into the hydrocarbon solution of AOT (no sonication is used in this or in the other solubilization methods). If the hydrocarbon solution becomes oversaturated with protein, so that the micellar solution is metastable, a decrease of the protein absorption with time might be observed, which is indicative of protein precipitating out of the micellar system. However, the method is so fast and simple that it has become the method of choice. In most cases, we have been able to obtain stable micellar solutions of the proteins up to $w_0 = 5-30$ by simply injecting an aqueous stock solution of the protein in the pH range 7—10 into the hydrocarbon solution of the surfactant at room temperature.

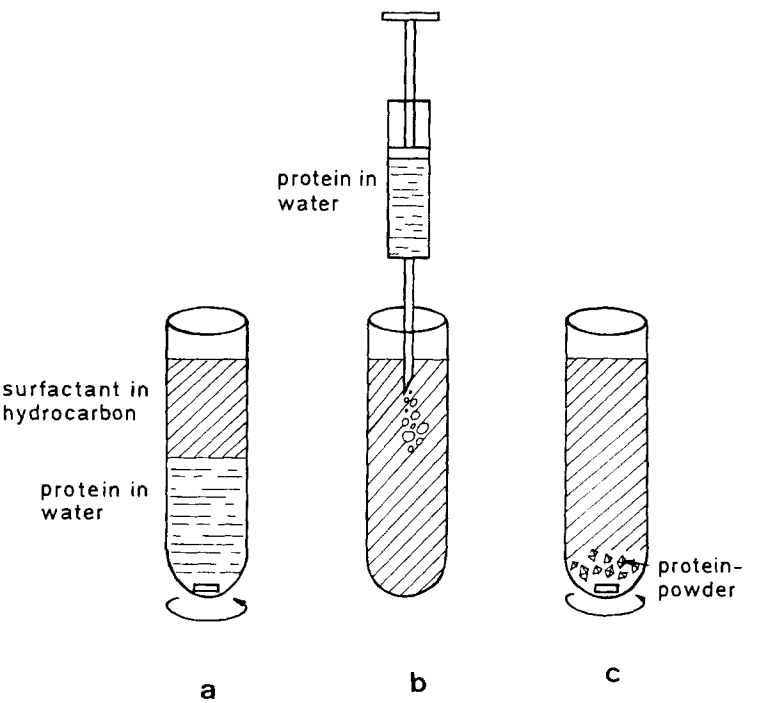


Fig. 4. The three methods used up to now to solubilize proteins in reverse micelles: a) "phase transfer" method; b) the most commonly used "injection method"; c) method for water-insoluble proteins.

Generally, it is important to characterize the stability domain of the protein-containing reverse micellar system. A simple, relatively rapid way to accomplish this is shown in Figure 5, which shows the regions of temperature and of water content in which the enzyme micellar system is thermodynamically stable. We usually do not work with micellar solutions of proteins unless they are completely transparent; an operative criterion is to measure the scattering at 330 nm and to discard all solutions having an optical density greater than 0.1.

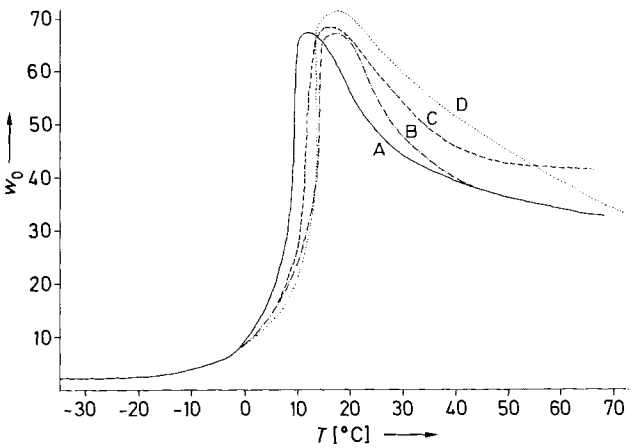


Fig. 5. Stability diagram of AOT reverse micelles in isooctane with and without enzymes. The area underneath the curve represents the stability region where hydrocarbon micellar solutions are clear. Outside this region, the preparation of micellar solutions results in cloudy and/or unstable systems. A (—) Stock solution: 0.05 M AOT with 50 mM borate buffer, pH 8.5; B (-·-·) stock solution with lipoxygenase (0.16 μM); C (----) stock solution with ribonuclease (175 μM); D (····) stock solution with ribonuclease (17.5 μM).

The methods illustrated in Figures 4a and 4b are appropriate for water-soluble proteins. Of great advantage and interest is the ability of reverse micelles to solubilize water-insoluble proteins. This is accomplished according to the method illustrated in Figure 4c, where the insoluble protein, as a powder, is gently stirred with the hydrocarbon micellar solution containing already a certain amount of water (for example, $w_0 = 3-30$). This solubilization phenomenon can perhaps be understood on the basis of the already mentioned fact that water in reverse micelles may have different physical properties from those of bulk water, so that its solubilizing ability may be changed. This method can be useful for water-insoluble membrane proteins, because the protein-containing micelles may mimic to some extent the protein-containing lipid membranes. This area of research, however, has not yet been investigated intensively, and there are to the best of our knowledge no systematic investigations on water-insoluble membrane proteins in reverse micelles. *Waks, Carol* et al. (CNRS, Paris) have been able to solubilize the Folch-pi proteolipid (or lipophyline) (Fig. 6) and are presently studying the interaction of this protein with the water-soluble myelin basic protein.[13] Both proteins ensure the lamellar structure of myelin. By the use of reverse micelles it is possible to study the interaction between the two proteins, one of which is soluble, the other insoluble in water.

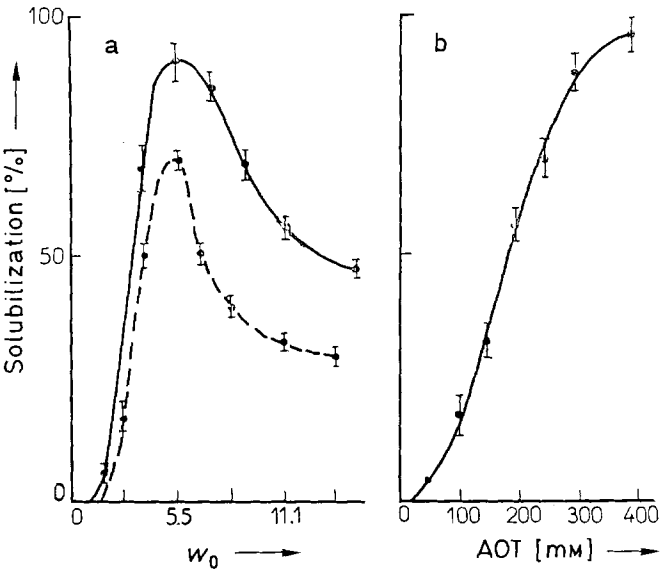


Fig. 6. Solubilization of the Folch-pi proteolipid in isooctane-AOT-water reverse micelles. The overall concentration of the proteolipid in the assay was 20 μM (20 nmoles/mL). A micellar solution of this concentration corresponds to 100% solubilization. a) The percent of solubilization plotted against $w_0 = [H_2O]/[AOT]$ at 300 (—) and 200 (---) mM AOT. b) The percent of solubilization against AOT concentration at $w_0 = 5.56$ (the bars represent experimental error) (from [13]).

Table 2 summarizes the main studies that have appeared until now on proteins solubilized in reverse micelles. The main groups active in this area at the present are those of *Martinek* in the USSR, *Robinson* in the UK, *Laane* in the Netherlands, and *Balasubramanian* in India. Several groups in France (*M. P. Pileni, M. Waks, J. F. Biellmann*) are studying related problems. Table 2 will be referred to again in Sections 4 and 5.

Although we have been able to solubilize almost all kinds of proteins, difficulties are still encountered with the heme-containing proteins: for example, hemoglobin and myoglobin are not stable in AOT/isooctane reverse micelles, probably because the heme group dissociates rapidly once the protein is solubilized in reverse micelles. Also, using AOT, we could not get reproducible data for the activity of cytochrome P-450.

An interesting practical problem concerns the definition and determination of the pH in the water pool. The difficulty stems from the fact that one cannot reliably use a glass electrode in an isooctane solution containing as little as 1% water; even if this could be done, no reliable value could be obtained, because the water of the water pool, particularly at low w_0 values, is a novel solvent with unknown properties and for which no pH calibration is available. Problems are probably less severe at high water contents (cf. [14–17]). In general, it appears that the pH of reverse micelles cannot be determined with certainty. We proposed[16] an empirical calibration based on ^{31}P-NMR data (measurement of the phosphate ion concentration on the basis of its chemical shift)—but, to obtain pH values from these experiments, we had to assume that the pK of the phosphate ion in reverse micelles is the same as in water—an arbitrary, although quite reasonable, assumption.

Another practical problem concerns the definition of the concentration of guest molecules inside reverse micelles.

Table 2. A schematic representation of the activity of various groups in the field of enzymes in reverse micelles.

Group	System	Most important studies, main results
Martinek et al. (1978) [55]	α-chymotrypsin and peroxidase in AOT/octane	activity studies, enzymes remain active
Levashov et al. (1980) [56]	α-chymotrypsin and other enzymes in AOT/octane or CTAB/octane/$CHCl_3$ [a]	determination of k_{cat} and K_m, theoretical considerations of enzyme kinetics in reverse micelles
Martinek et al. (1981) [37]	chymotrypsin in AOT/octane	ultracentrifuge studies on "filled" and "unfilled" micelles
Martinek et al. (1982) [35]	peroxidase in AOT/octane	activity of enzyme much higher than in water
Malakhova et al. (1983) [57]	pancreatic lipase in AOT/octane horse liver alcohol dehydrogenase	substrate specificity determined change of relative substrate specifity
Misiorowski, Wells (1974) [58]	phospholipase A_2 in phosphatidylcholine/ether/MeOH	kinetic studies, surfactant acts as substrate
Fletcher et al. (1984) [59]	α-chymotrypsin in AOT and $C_{12}E_4$/octane [b]	kinetic studies with various substrates, k_{cat} similar to bulk water values
Kumar, Balasubramanian (1980) [60]	α-chymotrypsin and bovine serum albumin in various surfactants	spectroscopic studies and activity measurements
Menger, Yamada (1979) [29]	α-chymotrypsin in AOT/heptane	investigation of activity as a function of pH and w_0
Douzou et al. (1978) [61]	cytochrome P-450 in sorbitan tristearate	cryoenzymology in reverse micelles
Douzou et al. (1979) [62]	trypsin in AOT/heptane	activity comparable to water, cryoenzymology
Ramakrishnan et al. (1983) [63]	rhodopsin in phospholipids/hexane	model for the protein in reverse micelles
Darszon et al. (1979) [64]		enzyme remains photochemically active
Schönfeld et al. (1980) [65]	reaction centers from *Rhodopseudomonas*	centers remain photochemically active
Hilhorst et al. (1982) [66]	hydrogenase in CTAB/octane/$CHCl_3$ [a]	photosensitized hydrogen formation with sensitizers in the interface
Hilhorst, Laane, Veeger (1983) [39]	hydrogenase in CTAB/octane/hexanol [a]	multi-enzyme system with progesterone as substrate in organic phase
Delahodde et al. (1984) [13]	Folch-Pi-proteolipid in AOT/isooctane	solubilization of a water-insoluble protein in reverse micelles, spectroscopic studies
Pileni (1981) [67]	cytochrome in AOT/isooctane	reduction of cytochrome by photoelectron transfer
Luisi et al. (1977–79) [42, 12]	α-chymotrypsin, trypsin, pepsin, glucagon in methyltrioctylammonium chloride/cyclohexane	transport of enzymes into organic phase, spectroscopic properties investigated, loss of enzymatic activity
Wolf, Luisi (1979) [23]	ribonuclease in AOT/octane	spectroscopic properties similar to water, enzyme remains active
Meier, Luisi (1980) [25]	horse liver alcohol dehydrogenase in AOT/isooctane	spectroscopic investigations and activity studies
Bonner et al. (1980) [24]	various enzymes in AOT/isooctane	ultracentrifuge studies and the proposal of water-shell model
Barbarić, Luisi (1981) [19]	α-chymotrypsin in AOT/isooctane	activity and spectroscopic properties as function of w_0 and pH
Grandi et al. (1981) [22]	lysozyme in AOT/isooctane	

[a] CTAB = hexadecyltrimethylammonium bromide. [b] $C_{12}E_4$ = tetraethyleneglycol monododecyl ether.

For simplicity, let us consider one mole of a compound A that is soluble only in water and is present in one liter of a hydrocarbon reverse micellar solution containing 1% water ($F_w = 0.01$). The "overall" concentration (relative to the total volume, i.e., hydrocarbon plus water) is $[A]_{ov} = 1$ M; but its water-pool concentration (relative to the water "microphase" alone) is $[A]_{wp} = [A]_{ov}/F_w = 100$ M (cf. [18]). Velocities, and all other properties having dimensions of concentration, can be expressed by two different numbers. Which one is physically relevant? This question is not simply semantic, but involves the physics itself of reverse micelles. For example: is the concentration of Na^+ (the counterion of the sulfonate group) in reverse micelles 50 mM or (50/F_w) mM? This question is also important because it may generate confusion when comparing different data in the literature. In some simple instances, however, it is a moot question and the difference in the final physical property disappears when the proper normalization is consistently used throughout. An example is the Michaelis-Menten constant in enzyme kinetics.[36]

Last but not least among the practical problems is the purity of the surfactant. Three kinds of impurities are usually present, to a greater or lesser extent, in most commercial preparations of AOT. There are one or more still unidentified impurities that absorb in the ultraviolet region (Fig. 7). In addition, commercial preparations of AOT often contain an acid impurity. This may produce a significant decrease in the pH of the water pool with respect to that of the stock aqueous solution used to prepare the micelle water pools. We have found two efficient ways to considerably reduce the UV-absorbing species: HPLC and an extraction procedure.[20] The acid impurity can also be eliminated,[34] and certain commercial preparations are much better than others to start with in this regard. *Robinson* et al.[18] have pointed out another source of difficulty with AOT preparations: AOT can partly hydrolyze at alkaline pH. Finally, commercial AOT preparations may contain an indeterminate amount of common salt, which is an important determinant for the conformation of guest biomolecules.[10] In principle, therefore, one should do routine conductometric measurements to check the ionic strength of a standard aqueous AOT stock solution.

These questions of chemical purity are now more important than in the past, due to the increased level of sophistication of the research (spectroscopy, enzymatic activity, conformational properties), and should be taken into account in order to make possible the comparison of data from different laboratories. We would like to end this discussion with one example. Figure 8 shows the pH-activity profiles of α-chymotrypsin in water and in two different AOT micellar hydrocarbon solutions. The first pH-activity profile is taken from our first investigation,[19] when we were not yet completely aware of the acid impurities in the

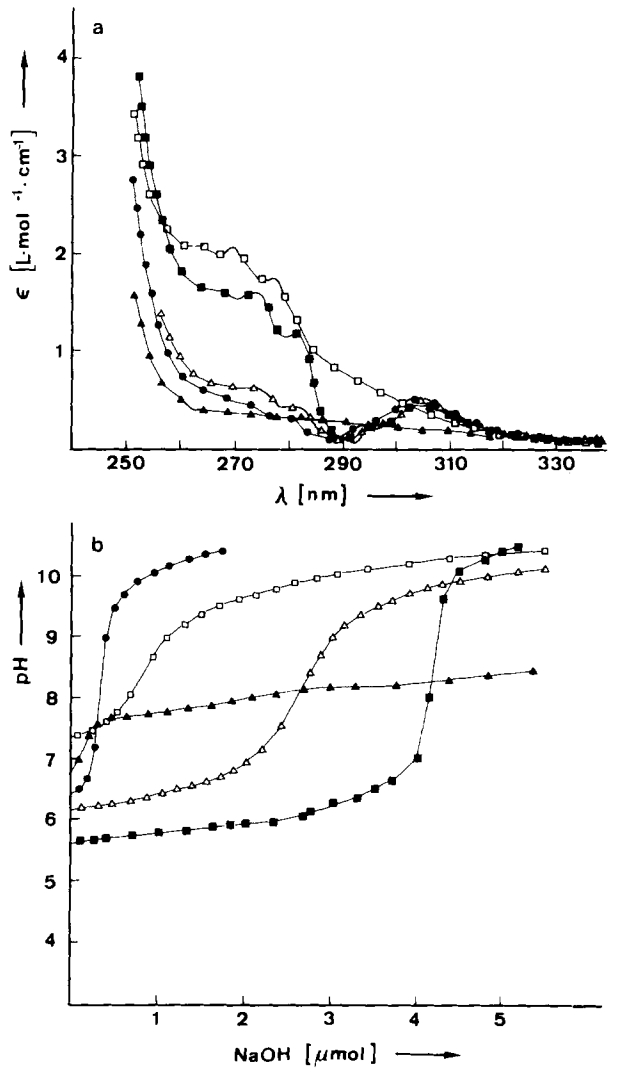


Fig. 7. UV absorption (a) and potentiometric titration (b) profiles of various AOT samples. The spectra were obtained using 50 mM AOT solutions in UV-grade isooctane, and titrations were performed with 10 mL of a 1 : 1 (v/v) water-methanol solution containing ca. 2.2 mmol of AOT, using 0.1 N NaOH as the titrating agent. The extinction coefficient, ε, was calculated as if the absorption were due only to AOT. Thus, an ε of 1 L mol^{-1} cm^{-1}, for example, refers to an absorbance of 0.05 in a 1-cm cell. (□—□): commercial AOT (SERVA); (△—△): purified according to [34]; (■—■): purified according to [54]; (●—●): see text for purification procedure; (▲—▲): purified by HPLC (from [20]).

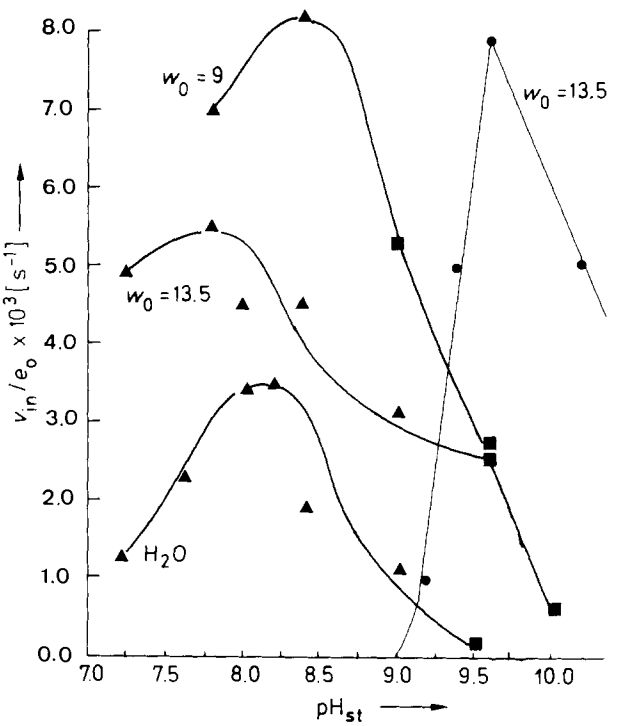


Fig. 8. The effect of AOT purity on the pH profile of enzymatic reactions: α-chymotrypsin catalysis of the hydrolysis of *N*-glutarylphenylalanine-*p*-nitroanilide. The curve on the right ($w_0 = 13.5$) is taken from our earlier work [19], in which AOT was purified according to the existing literature procedure. The two curves on the left ($w_0 = 9$ and $w_0 = 13.5$) are obtained with HPLC-purified AOT (prepared by *P. Lüthi* [30]; cf. [20]). Another such example is shown in [20]. pH_{st} = pH value of stock solution; v_{in}/e_0 = initial rate/initial enzyme concentration.

commercial preparations of AOT and only used the purification procedure described in the literature. In this case, there is a sizeable shift of the pH-activity profile towards more alkaline values, which can be explained (all or in part) by the presence of an acid impurity. The other curve is with an HPLC-purified AOT preparation;[20] in this case, the micellar solution gives about the same pH-activity profile as the aqueous solution. The result cannot, however, be generalized: lysozyme and ribonuclease, for example, continue to exhibit a shift of the pH optimum even with the purified AOT preparations.[20,21] In the case of α-chymotrypsin, the presence of acid impurities in our old AOT preparations does not seem to affect the conformational properties (e.g., enhancement of the helical structure) or the peculiar enhancement of k_{cat} at low w_0 over the value found in aqueous solution.[19]

3. Structural Aspects

Where and how is the biopolymer situated inside the reverse micelle—or more generally—what can be said about the structure of the protein-containing reverse micelles? This question is not completely clarified as yet. In fact, as depicted in Figure 9, different models are conceivable, and the answer to the above question may be different for different enzymes. We believe that most of the data for hydrophilic proteins can be interpreted on the basis of the so-called water shell model (see Fig. 9a), according to which the protein is confined to the middle of the water pool and is protected by a layer of water from the charged inner wall of the micelle and from the external organic milieu.[22,24] The evidence for this model is still indirect. For example, the conformation and activity of enzymes depend on w_0,[22-27] which indicates that the enzyme is sensitive to the amount of water surrounding it. This would not be so if the enzyme adhered with its active site region to the internal wall of the reverse micelle, or if the enzyme were predominantly exposed to the hydrocarbon solvent. In the latter case, most enzymes would be denatured. Finally, circular dichroism data for some enzymes, for example, horse liver alcohol dehydrogenase, ribonuclease, and lipoxygenase, indicate rather similar conformations in the reverse micelle and in bulk water.[25,28,23] However, lysozyme and other enzymes show marked differences.[23,19]

Additional indirect evidence in favor of the water shell model is provided by the fact that the kinetic behavior of

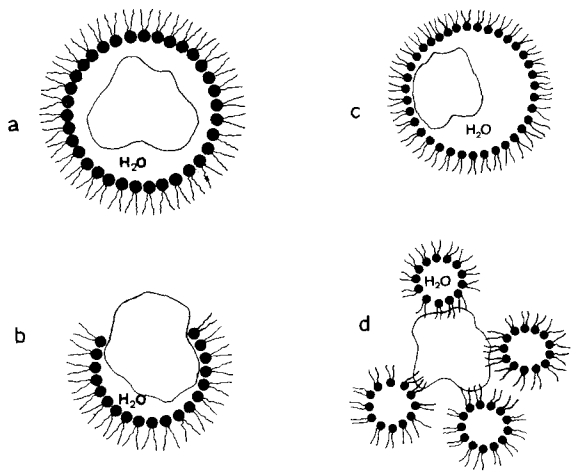


Fig. 9. Possible models for a protein hosted in a reverse micelle (see text): a) the water-shell model, in which the protein is located in the middle of the water pool and is protected from the micelle wall by a layer of water; b) the protein has a very lipophilic part, which tends to interact directly with the bulk hydrocarbon; c) the protein is adsorbed to the micelle wall; d) the protein is solubilized by several small micelles, whose hydrocarbon tails interact with the hydrophobic portions of the protein.

enzymes in reverse micelles appears to be essentially the same as in aqueous solution.[22-27] Furthermore, the pH-activity profile for enzymes in reverse micelles, although somewhat shifted with respect to bulk water, forms a very similar bell-shaped curve.[22,27,29] If the enzyme adhered to the inner wall of the micelle by electrostatic effects, one would expect rather dramatic changes of activity when the enzyme, becoming more negatively charged, dissociates from the micelle wall. For α-chymotrypsin, further circumstantial evidence comes from fluorescence studies: the fluorescence properties of α-chymotrypsin in reverse micelles for $w_0 \gtrsim 7$ (i.e., when "free" water is present) are very close to its fluorescence properties in bulk water,[19] indicating that the environment of the active protein is essentially aqueous.

Using the water shell model, we have developed a scheme, partly based on ultracentrifuge experiments,[24] which enables us to approximate the dimensions of the protein-containing micelles and to estimate the micellar parameters characterizing such aggregates. This model was based on several assumptions, the most important being that the volume of the protein-containing micelle is the algebraic sum of the volume of the protein and the volume of water molecules originally present in the "empty" micelle, and that w_0 does not change. The two dashed curves in Figure 3 show the dimensions of the protein-containing micelles as a function of w_0 according to our model.[24] Noticeably, for small proteins such as ribonuclease, there is very little difference in size between "empty" (containing only water) and "filled" micelles (containing the protein) for $w_0 \gtrsim 15$. In contrast, for small values of w_0, the protein induces an enlargement of the reverse micelles (with the consequent mass redistribution in the micellar solution). In the case of a larger enzyme like horse liver alcohol hydrogenase ($M_r = 80000$), the micelles that contain guest molecules will always be larger, even at large w_0 values, than the empty micelles. It is now doubtful whether the first approximation model is valid for all enzymes. The group of *Martinek* has presented a model, also based on ultracentrifuge studies, according to which the uptake of α-chymotrypsin does not produce any significant increase in size of the host reverse micelle.[26,31] Our own studies using neutron scattering (carried out at Oak Ridge National Laboratory in collaboration with *L. Magid*) appear, on the contrary, to give dimensions for the lysozyme-containing micelles that are at least 30% larger than those predicted by our original model. The situation is therefore still in a state of flux.

4. The Reactivity of Enzymes in Reverse Micelles

The preceding discussion provides the basis for understanding qualitatively which kind of micellar parameters may affect the activity of an enzyme hosted in reverse micelles. When there is enough "free" water (namely at $w_0 > 7-8$), the activity should be very similar to that found in bulk aqueous solution, and the steady-state cycle may be represented simply according to Figure 2c: enzyme and substrate molecules form an active complex that eventually decays to products which dissociate from the enzyme. The difference with respect to water solution is that in micellar solution each bimolecular step requires micellar collision and coalescence.[24]

At lower w_0 values, when most of the water molecules are bound to the inner surface of the AOT micelles, one may expect some interaction between the protein surface and the inner wall of the reverse micelles, which may affect the mechanism. Also, at low w_0 values, deviations from the normal activity profile can be expected because the water in the water pool is a novel solvent. Another effect that may influence the enzyme activity in this regard is the local pH. The transport rate of the substrate into the reverse micelles or the transport rate of the product out of them can also, in principle, play a role. Depending upon the structure of the micelle or upon the relative concentration of micelles and substrate molecules, these events can possibly become the rate-limiting step.

With all this in mind, we will now consider some of the enzymes studied to date. Figure 10 shows the activity of lysozyme as a function of pH in water and in reverse micelles. Notice that the maximal velocity is at about $w_0 = 10$ and not at the maximal water content. This is surprising and can be generalized to all hydrolases. Notice also the shift of the pH-optimum with respect to water, which can possibly be ascribed to a difference in pK of the amino acid residues involved in the catalysis. The turnover number at the optimal pH is not much different from that in water; it appears therefore that lysozyme, apart from the pH-shift of the activity, behaves quite normally in reverse micelles. However, things are not so simple if the conformation of the protein in reverse micelles is considered. As shown in Figure 11, there are large differences in the circular dichroism (CD) spectra on going from water to micellar solutions.[22,21] As is well known, the circular dichroism spectrum in the near-ultraviolet region reflects the environment of the aromatic amino acid residues of the protein, while the CD spectrum in the far-ultraviolet region, particularly around 220 nm, reflects the secondary structure of the protein. The near-UV region will be considered first.

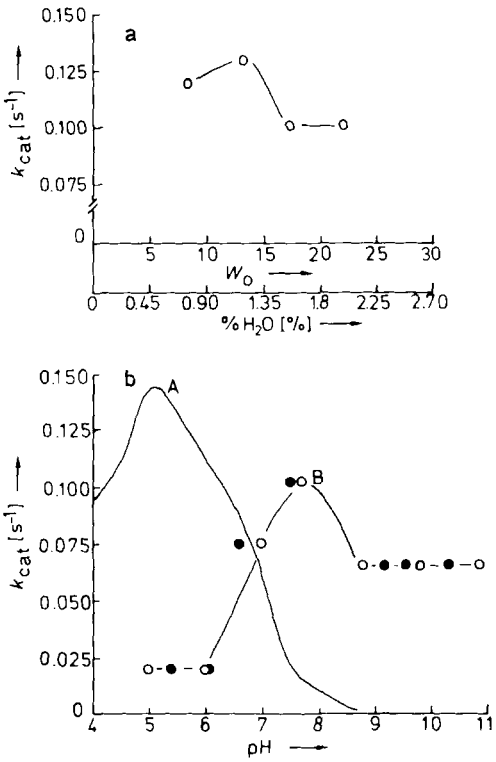


Fig. 10. Degradation of chitin with lysozyme in micellar solutions prepared from 50 mM AOT/isooctane; dependence of the rate constant k_{cat} on the water content (a) and pH (b). Curve A, for comparison, represents an aqueous solution. Curve B refers to the micellar solutions. ○: pH of the stock solutions used to prepare the reverse micelles (pH = pH_{st}); ●: pH values measured directly in the reverse micellar solutions using ^{31}P-NMR at $w_0 = 16.8$ (from [16] and [22]).

Since the ultraviolet absorption spectra of lysozyme in this region are the same in water and in reverse micelles,[22] the changes observed in the CD spectrum can be safely ascribed to conformational changes. The orientation of several aromatic side chains of lysozyme is therefore probably different in water and in reverse micelles. The CD spectrum in the lower wavelength region, where the ultraviolet absorption spectra of micellar solutions also show an increase in intensity, can be interpreted in terms of an increase in the helical structure. Thus, the CD spectra of Figure 11 show that the enzyme has lost its conformational specificity without loosing activity. In order to interprete this apparent paradox, we have proposed that the changes in the enzyme's conformation may only involve peripheral regions[22] rather removed from the active site. However, one should recognize that lysozyme has three of its five tryptophan residues adjacent to or within the active site; it is thus hard to conceive that the conformation of these aromatic residues is changed without affecting the overall active-site geometry. We are presently carrying out CD studies on the enzyme in reverse micelles in the presence of inhibitors and/or substrates in order to clarify this point[*].

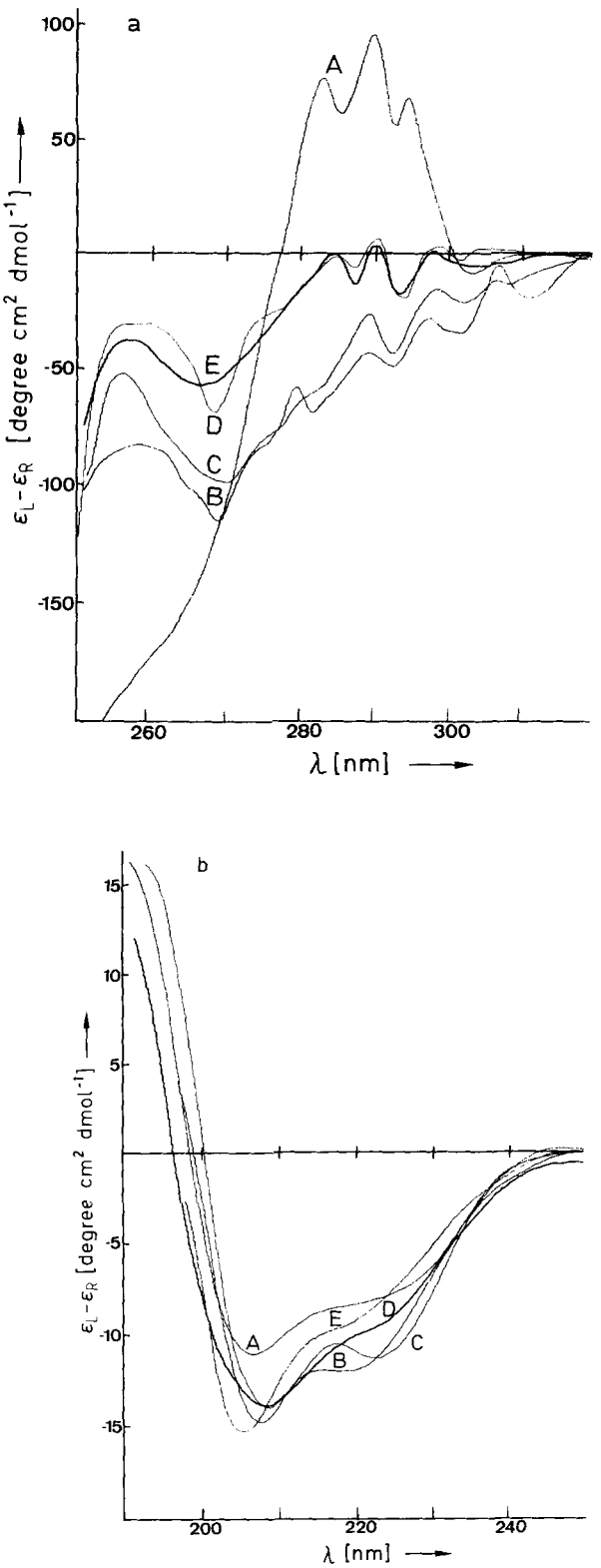


Fig. 11. Near- (a) and far- (b) ultraviolet circular dichroism spectra of lysozyme in water (A) and in AOT reverse micelles at $w_0 = 3$ (B), $w_0 = 6$ (C), $w_0 = 16$ (D), and $w_0 = 25$ (E).

[*] Note added in proof: The problem has now been clarified. The CD spectra of lysozyme in reverse micelles formed by AOT in isooctane do not change significantly with respect to water when NAG (*N*-acetylglucosamine) or NAG_3 is bound. By inference, the conformation of the enzyme in AOT reverse micelles remains the same (or nearly the same) as in aqueous solution when the substrate is present. Without the substrate, AOT brings about a rapid denaturation of the enzyme (lysozyme appears to be the only enzyme where this happens thus far), with the CD spectrum changing as shown in Figure 11. In other words, the lysozyme in the reverse micelles of Fig. 11 is denatured. The reason why our earlier investigation failed to notice this is due to the fact that the enzyme was added to a reverse micellar solution already containing the substrate, so that the enzyme did not have time to denature (B. Steinmann, P. L. Luisi, in preparation).

The situation with chymotrypsin is also very interesting. As apparent from Table 2, this case has been studied by at least four different groups. *Menger* and *Yamada*,[29] the first to study this enzyme in reverse micelles, initially failed to find activity with an ester substrate at a nominal pH of 7. The reason was that the micellar environment had markedly changed the pH-activity profile of the enzyme. In fact, they found a very good activity in the alkaline pH range. We found that, with *N*-glutarylphenylalanine-*p*-nitroanilide, the turnover number is larger at low w_0 values than in water.[19] Although the effect is not extremely large, it is certainly worthy of attention. Of particular interest in this case is the relationship between the activity and the conformation of the main chain of the enzyme, as determined again by circular dichroism. Here, too, there is an enhancement of the ellipticity at 220 nm, which can again be interpreted as an increase of helical content. The activity enhancement has been interpreted[19] by postulating that in reverse micelles the conformational equilibrium of α-chymotrypsin is shifted towards the more active form of the enzyme. α-Chymotrypsin is not the only example of "superactivity". An increase has also been found for ribonuclease and lysozyme,[21,23,24] again at low w_0 values. *Martinek* et al.[27,35] have reported a large increase of activity for peroxidase (Fig. 12).

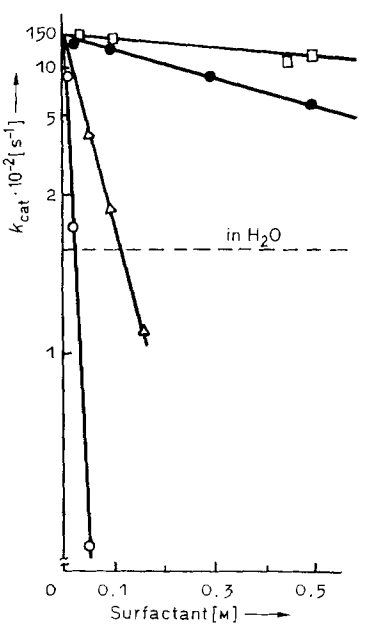


Fig. 12. Dependence of the first-order rate constant k_{cat} for peroxidase oxidation of pyrogallol on the concentration of surfactant (from [2]). (□—□): AOT in octane, 0.1 M imidazole buffer; (●—●): AOT in octane; (△—△): dodecylammonium propionate in diethyl ether/benzene (1:2); (○—○) egg yolk lecithin in methanol (2.5% v/v)/pentanol (5% v/v)/octane. 26°C, $w_0 = 13$, 0.025 M aqueous buffer (phosphate-borate-acetate), pH 7.0. The kinetic assay was carried out as described in [37].

Dehydrogenases are particularly interesting from the point of view of preparative bioorganic chemistry. As is apparent from Table 2, horse liver alcohol dehydrogenase has been investigated by several groups. In addition to the reduction of acetaldehyde, the reduction of a highly lipophilic substrate (decanal) and of a steroid hormone has also been tested.[25] An interesting finding has been reported by the Russian group of *Martinek*: the relative specificity of alcohols in reverse micellar solutions appears to be different from that found in aqueous solution.[35]

Concerning the kinetic parameters, an important question is whether K_m in reverse micelles is different from that in water. We have already indicated[36] that K_m in reverse micelles should be expressed as $K_{m,ov}$ in order to be properly compared with the values in aqueous solution. Table 3 lists typical K_m values in water and reverse micelles. Generally, there is a close agreement between the K_m values in water and in reverse micelles. The efficiency of the enzymes (usually expressed by k_{cat}/K_m) is also not impaired, therefore, when enzymes are solubilized in reverse micelles. The stability of enzymes in reverse micelles is important for kinetic studies and is also of direct relevance for the biotechnological applications (see Section 5). To date, there have been few systematic studies on this important subject. In the case of chymotrypsin,[19] the time stability depends on w_0; at low w_0, the enzyme can be more stable and more active than in water. *Martinek* et al. have studied the stability of several enzymes in reverse micelles formed by different surfactants and/or organic solvents.[37]

Table 3. Kinetic parameters for enzymatic reactions in reverse micelles (isooctane/AOT/water). pH_{st} = pH value of the stock solution [a].

System	K_m^S [μM] [b]	K_m^{NADH} [μM]	v/e [s^{-1}]
LADH in water [c], pH 7.1	110—375	10—11	114
LADH in water, pH 9	400	3	5
LADH in micelles, $w_0 = 42$, $pH_{st} = 8.8$	300	23	80
LADH in micelles, $w_0 = 19$, $pH_{st} = 9.2$	—	20	30
lysozyme in water [d], pH 5.1	10	—	0.14
lysozyme in micelles, $w_0 = 22.2$, $pH_{st} = 7.6$	2	—	0.10
α-chymotrypsin in water [e], pH 7.9	600	—	0.7
α-chymotrypsin in micelles, $w_0 = 13.5$, $pH_{st} = 9.8$	450	—	2.3
α-chymotrypsin in micelles, $w_0 = 9$, $pH_{st} = 11.8$	400	—	4.2

[a] Adapted from [53]. For further details see [19, 22, 25]. [b] Expressed as "overall" concentration. The numerical value of $K_{m,ov}$ depends on the water content of the micellar system. [c] Horse liver alcohol dehydrogenase, with acetaldehyde as substrate. [d] Chitin oligomers as substrate. [e] *N*-glutarylphenylalanine-*p*-nitroanilide as substrate.

5. Biotechnological Relevance

Until now we have considered hydrophilic enzymes with their water-soluble substrates. A very interesting aspect of enzyme-containing reverse micelles is their ability to accept and transform water-insoluble, hydrocarbon-soluble substrates. An example is lipoxygenase. The enzyme, although lipophilic, is readily soluble in water (and insoluble in hydrocarbons) and, as such, is probably hosted in the water pool of reverse micelles. The fact that its kinetic behavior corresponds closely to that observed in water supports this view. The substrate linoleic acid is not, or only very sparingly, soluble in water at neutral or acidic pHs. It is soluble, however, in isooctane, and can be added in its pure liquid form to a micellar solution containing lipoxy-

genase. Spectrophotometric analysis of the solution reveals that the substrate is enzymatically converted into the expected products.[28] Typical data are shown in Figure 13. The important point here is that the substrate dissolved in

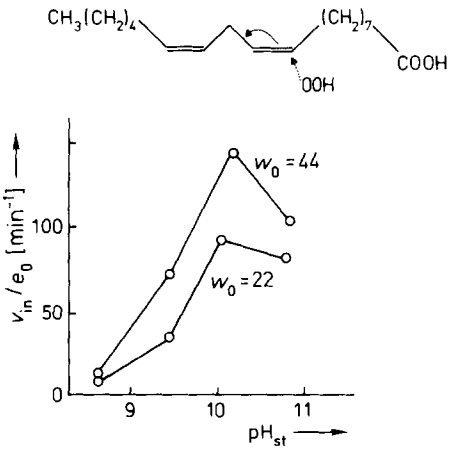


Fig. 13. pH-activity profile of the lipoxygenase reaction. Enzymes in reverse micelles react with both water-soluble and water-insoluble (hydrocarbon-soluble) substrates. An example is the oxidation of linoleic acid with lipoxygenase. [enzyme] = 2.5×10^{-8} M, [substrate] = 4×10^{-4} M, [AOT] = 10×10^{-3} M, isooctane. Overall concentrations are given (v_{in}/e_0 as in Fig. 8).

the bulk hydrocarbon finds its way to the enzymatic active site in the reverse micelle, i.e., through the layer of water that surrounds the enzyme. How this can happen is not yet clear. It may be that the particular physical properties of the water in the reverse micelles, for example, a lower dielectric constant, result in a better solubility of lipophilic substrates. The other possibility, particularly in the case of linoleic acid or analogous substrates, such as arachidonic acid, is that they are incorporated into the micellar interface as cosurfactants and that the enzyme interacts dynamically with the interior micellar wall. The solubility of lipophilic substances in reverse micelles is, however, not restricted to fatty acids; steroids,[25,39] long-chain aldehydes,[25] or water-insoluble peptides[40] are also readily accepted as substrates by their respective enzymes in reverse micelles. The fact that the mechanism of this uptake is not yet clarified does not decrease the biotechnological relevance of the finding that water-insoluble, hydrocarbon-soluble substrates can be enzymatically converted into their products (for a review on the few results available, see [28]). This may open the way to a new application of enzymes in organic chemistry and biotechnology. The interest is increased by the observation that almost all enzymes tested until now can be solubilized in reverse micelles—it is therefore a general method (by contrast, the use of enzymes in biphasic systems, for example, does not appear to be so general, since many enzymes rapidly denature under such conditions). Preliminary work involving the use of α-chymotrypsin for the synthesis of peptide bonds should also be mentioned: acetylalanylphenylalanine ethyl ester and leucinamide are coupled enzymatically to yield the water-insoluble, isooctane-soluble, protected tripeptide AcAla-Phe-LeuNH$_2$, which, after synthesis in the water pool, is expelled into the bulk hydrocarbon. The reaction is carried out in an enzyme reactor[40] with hydrocarbon-resistant, semipermeable, hollow fibers, in which the enzyme-containing reverse micelles are entrapped. Thus, the product can be obtained in pure form and physically separated from the enzyme and reagents.

Although such reactions may be interesting in organic synthesis, until now there has been no example of relevant practical applications of enzymes in reverse micelles. As apparent from Table 2, *Hilhorst, Laane,* and *Veeger*[39,41] in Wageningen (Netherlands) have come closest to such a goal. They were able to solubilize three enzymes in reverse micellar solution at the same time; in a chain reaction, these enzymes reduce regioselectively a ketosteroid. As shown in Figure 14, molecular hydrogen is transferred by a hydrogenase (H_2ase) to methyl viologen (MV), which in turn is able to recycle the system NAD/NADH with the help of lipoamide dehydrogenase (LipDH). Finally, NADH reduces the ketosteroid in a reaction catalyzed by a specific steroid dehydrogenase (HSDH).

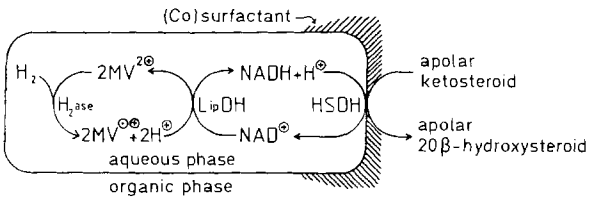


Fig. 14. The scheme of *Hilhorst, Laane,* and *Veeger* [39]: three enzymes in reverse micelles cooperate to selectively reduce a water-insoluble ketosteroid in a chain reaction (see text).

The enzymatic conversion of lipophilic substrates is not the only field where reverse micelles can be used for biotechnological applications. Another interesting aspect stems, for example, from the phase transfer of proteins and nucleic acids. Indeed, our interest in the whole field originated in the transfer of amino acids and peptides, and later polypeptides and proteins, from an aqueous to a hydrocarbon solution containing the surfactant.[11,12,42] Figure 15 shows the three possibilities of phase transfer (cf. [46]). In the "forward transfer", the protein is transferred from an aqueous solution to the supernatant micellar solution. In the "backward-transfer", the enzyme, solubilized in hydrocarbon, is recovered as an aqueous solution. In the "dou-

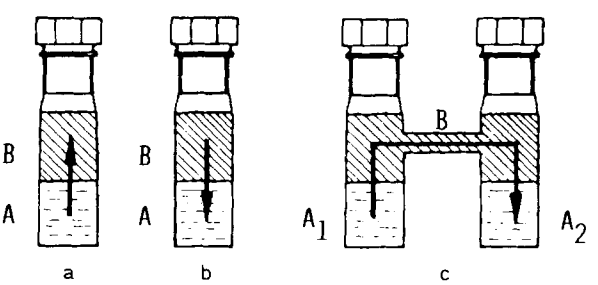


Fig. 15. Phase transfer processes. a) In the "forward-transfer" the protein is transferred from the water phase A into the micellar solution B; b) in the "backward transfer," the protein is transferred from the hydrocarbon micellar solution into the aqueous solution; c) in the "double transfer" method, the protein is vectorially transported from a first water phase A_1 into a second water phase A_2 via reverse micelles present in the hydrocarbon bridge. The vials are gently shaken during the experiment. The shaking is interrupted periodically for the removal of small aliquots to monitor the concentration of the transported biopolymer.

ble transfer" experiments, the biopolymer is present initially in an aqueous phase, and is then transferred into a second aqueous phase, which is separated from the first by a hydrocarbon bridge containing the reverse micelles. In all cases, the transfer of the protein is carried out by the micelles. We have presented until now only preliminary data, but it appears that the method can possibly be used as a chromatographic separation technique for biopolymers. There are already several groups engaged with such projects.[43,44] The separation of proteins and nucleic acids should also be possible, since the transfer of DNA is much slower than that of proteins.

The use of reverse micelles as a drug delivery system by *Speiser*'s group[45] should also be mentioned (cf. [46]).

The biotechnological relevance is actively being explored, but we will have to wait a few years to see whether and to what extent the present expectations are fulfilled.

6. Nucleic Acids

The internal wall of AOT reverse micelles is negatively charged, and although there is a stoichiometric amount of positively charged sodium ions, the solubilization of negatively charged polyelectrolytes such as RNA or DNA was somewhat of a surprise. In fact, the solubilization of nucleic acids in hydrocarbon micellar solutions occurs readily[47] and is actually easier at alkaline pHs. The mechanism of this uptake is not clear yet. We know that the solubilization of high-molecular-weight DNA can only take place at relatively high w_0 values (for example, above 14). Proteins, on the other hand, behave differently.

Does the structure of a high-molecular-weight nucleic acid change upon insertion into the reverse micelles? The solubilization is attended by a decrease of absorbance in the 260-nm region, with a corresponding increase of ellipticity.[47] This can be interpreted as an increase in the base-pair interactions (more hydrogen bonds are formed), which brings about an increase in the UV hypochromic effect and an increase in the macromolecular conformational rigidity. The picture is thus not unlike that proposed for proteins. The effect is more pronounced for RNA, which is more flexible in water solution, than for DNA, which exists already as a rigid double helix; it is not significant for low-molecular-weight oligonucleotides.

Of particular interest is the observation that the plasmid pBR 332 ($M_r = 2.7 \times 10^6$) can also be solubilized in isooctane/AOT/water reverse micelles. We are still investigating the structure of such aggregates. It is really not easy to imagine how a small micelle can accept such a large molecule. Certainly, the uptake involves an enlargement of the original micelle, with a redistribution of its components. The interest in this solubilization experiment also stems from the fact that the CD spectra of the plasmid-containing reverse micelles (Fig. 16) belong to the so-called ψ family.[48] Such spectra in turn are supposed to be diagnostic for superpackaged DNA, like that present in vivo when the long macromolecules are obliged to condense into a geometrically very restricted environment (e.g., a virus head or chromatin). The spectroscopic study of such structures in reverse micelles should be facilitated by the fact that the hydrocarbon medium does not interfere spectroscopically with water or nucleic acids. Studies in this direction are in progress in our group.[69]

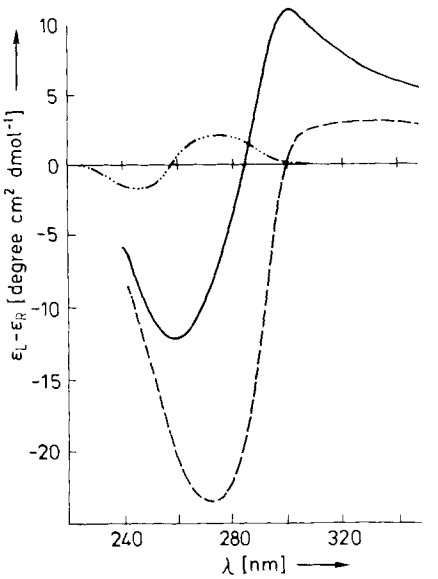


Fig. 16. CD spectra of the DNA of the plasmid pBR 322 in AOT reverse micelles (ψ-spectra). (· · · — · · ·): borate buffer; (——): AOT/isooctane, $w_0 = 18.5$; (– – –): AOT/isooctane, $w_0 = 14.8$ [69].

7. Concluding Remarks

Biopolymer-containing reverse micelles are not only interesting because of their biotechnological relevance, but also because such structures may exist in vivo in biological membranes.[49-52] Perhaps the first hint of this derives from the well-known hexagonal structure that is occasionally formed by phospholipids. The group of *de Kruijff* in Utrecht[49,50,52] has presented very convincing arguments in favor of the biological relevance of reverse micelles. However, the question of the biological relevance of reverse micelles in membrane structure remains to be definitly answered (cf. [38]). The question of the possible existence of reverse micelles in vivo bears upon the more general one of whether and to what extent reverse micelles can be considered as proper models for biological membranes. The term "biological model" is a misused one, as pointed out elsewhere (cf. appendix to [36]) and we do not want to dwell here further on this question.

Despite the uncertainty about the biological and biotechnological relevance of biopolymers in reverse micelles, this review demonstrates the fascination of the field. It stretches over quite different areas, from biotechnology to pure biology, from basic enzymology to nucleic acid structures, and touches upon a variety of important physical aspects. These include the transfer of macromolecules across interphases, or the transfer of low-molecular-weight materials across interfaces, as well as the structure and stability of novel aggregates of biopolymers.

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Combination of Chromatographic Separation Methods with Mass Spectrometry—a Modern Technique for Studying Metabolism

New Analytical Methods (26)

By Gerhard Spiteller*

Powerful separation methods developed during the past few decades, in particular glass capillary gas chromatography (GC) and high performance liquid chromatography (HPLC), can be combined with sensitive methods of detection such as mass spectrometry (MS) to provide new insights into metabolic processes. Research in a field that was long thought to be exhausted has thus been revitalized. New perspectives have been opened up for studying the metabolism of foods, spices and flavorings, drugs, and compounds produced in the body as well as for establishing the way in which the organism rids itself of harmful substances or how and when these compounds can interfere with the metabolic processes occurring in the body.

1. Introduction

If biological material is investigated with modern analytical methods, it soon becomes apparent that our knowledge of this field is still alarmingly fragmentary. Some compounds that are excreted in urine in relatively large amounts (milligrams per day) have still not been identified. The situation is even worse in the case of trace compounds, only a few of which are known.

This review shows how these compounds can be detected and identified by combining different chromatographic techniques with mass spectrometry and how chromatographic methods can contribute to solving biological and medical problems, and, moreover, demonstrates the difficulties involved in establishing this type of "biological profile."

This field is so extensive that an arbitrary selection has to be made from the wide range of literature available.

2. General Comments on the Work-Up of Biological Fluids and the Characterization of Their Individual Components

Urine and other biological fluids represent very complex mixtures that contain low- and high-molecular-weight substances with very different polarities. Only some of them can be extracted with organic solvents and are thus readily accessible for analysis. Many of the less polar substances occur in the form of "conjugates," i.e., as esters of sulfuric or glucuronic acid. If these polar conjugates are to be extracted, they must be subjected to enzymatic hydrolysis before work-up.

Polar compounds can, however, also be adsorbed onto added adsorbents, ion exchange columns, or "reversed phase" columns (Sep Pak columns) and subsequently separated after elution by HPLC. The eluates are often later cleaved enzymatically and roughly separated into acidic, neutral, and basic fractions, which are then chromatographed.

Since the individual components of a class of substances usually occur in amounts that differ by several orders of magnitude, only the most predominant compounds can be identified by means of a single chromatographic method while many trace substances escape detection (Fig. 1). The necessary enrichment of the trace substances can only be achieved by the use of a combination of different chromatographic separation methods.

With these combined separation procedures, almost all substances with molecular weights of up to about 2000 (or even higher) that are found in biological materials can be sufficiently enriched to characterize them and to elucidate their structures; the substances must, however, be convertible into volatile derivatives to allow gas chromatographic

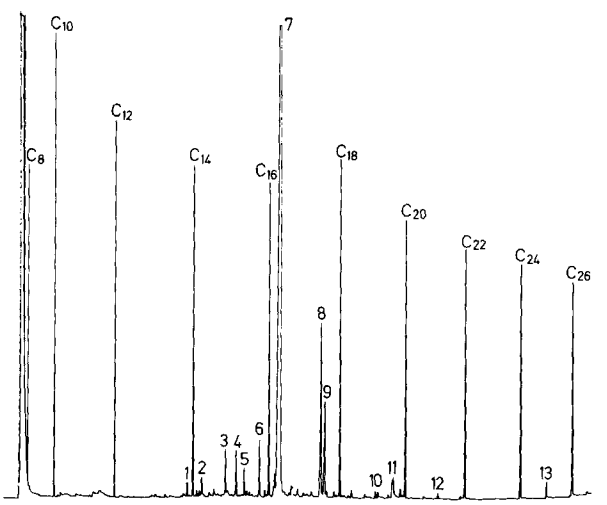


Fig. 1. Glass capillary gas chromatogram of the total acid fraction of a urine sample taken from a healthy woman (28 years old) after extraction with chloroform and reaction with diazomethane. The numbered peaks are the mono-, di-, or trimethyl esters of the following acids: 3-methoxyphenylacetic acid (1) (from 3-hydroxyphenyl acetic acid), citric acid (2), 2,4-dimethyloctanedioic acid (3), nonanedioic acid (4), *N*-acetyl-2-aminooctanoic acid (5), 3,4-dimethoxyphenylacetic acid (6), hippuric acid (7), indoleacetic acid (8), *N*-methylhippuric acid (9) (an artifact formed when hippuric acid is treated with diazomethane), palmitic acid (10), phthalic acid (11), stearic acid (12), and di(*n*-butyl) phthalate (13). Experimental conditions: Carlo Erba Fractovap 4160 gas chromatograph with a WCOT glass capillary (33 m × 0.3 mm, OV 101); hydrogen flow-rate: 2 mL/min; injector temperature: 275 °C; oven temperature: 80—280 °C (5 min isothermally, then 2 °C/min); flame ionization detector (FID); C_8, C_{10}, C_{12}, etc., are *n*-alkanes.

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separation. The separation may require a great deal of time and complex instrumentation and may also necessitate experience and skill.

Quantitative detection of the individual substances has not been solved as satisfactorily. Losses are incurred during every separation step and add up if several separation steps are involved. The losses of an individual compound can be kept to a low level by skilled experimental organization, but it is generally difficult to simultaneously quantify the large number of compounds usually found in biological fluids due to their different properties.

The relationships between peaks in a chromatogram do not necessarily reflect the true relationships between substances, not only because different losses of substances have to be taken into account during the work-up, but because the peak intensities also depend on the properties of the substances concerned. If, for example, a flame ionization detector is employed to detect a substance in a GC separation, the peak height depends on the oxygen content of the compound[1]—the higher the oxygen content, the smaller the peak. Quantitative measurements thus require admixture of several standards.

Fortunately, individual substances do not always have to be quantified exactly because metabolic disorders generally produce such massive changes (sometimes reaching several orders of magnitude) in the quantities of the individual metabolic products that they cannot be overlooked.

A compound can always be clearly identified if it can be separated in the form of an appropriate derivative by gas chromatography on capillary columns and its mass spectrum is then recorded. The mass spectrum and retention index usually suffice for identification, even if isomers are present.

It is much more difficult to characterize compounds that, on account of their polarity, can only be separated by HPLC, because such compounds can only be characterized by their retention times. Attempts have been made to combine HPLC with mass spectrometry but the results obtained do not seem very convincing.[2]

GC or HPLC chromatograms of mixtures obtained from biological fluids are called "biological profiles," a term proposed by *Horning* et al.[3]

3. Work-Up of Biological Fluids for Establishing Acid Profiles

The acid profiles of urine and other biological fluids low in protein (e.g., saliva) are the easiest to obtain. The biological fluid is first acidified and then extracted with an organic solvent. The acids so obtained are converted into their methyl esters with diazomethane[4] or they are trimethylsilylated,[5] and the derivatives are separated by gas chromatography.[3b]

Some very volatile acids (e.g., isovaleric acid) and strongly polar acids (e.g., citric acid) are, however, lost during this procedure; most compounds cannot be identified by such a simple separation and only become evident after the main products have been separated (Fig. 2).

If mainly volatile acids are to be determined, the sample is acidified and subjected directly to a GC separation.[6] The acids can, however, also be obtained by vacuum distillation[7] or extraction.[8] *Zlatkis* et al.[9] and *Politzer* et al.[10] have published reviews on the investigation of volatile substances.

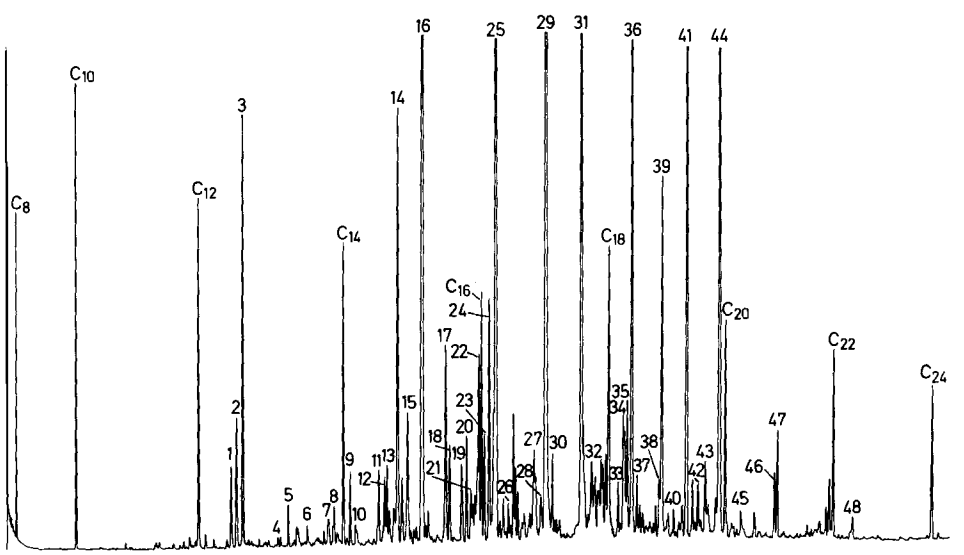


Fig. 2. Glass capillary gas chromatogram (for conditions see Fig. 1) of a fraction (methylated with diazomethane) obtained by column chromatography of the total acid fraction shown in Figure 1. The main acid components (e.g., hippuric and citric acids) have been separated and products appear that occur in small amounts in urine. The following acids in the form of their mono-, di-, or trimethyl esters represent a selection of the numbered peaks: 2-methylhexanedioic acid (1), 3-methylhexanedioic acid (2), 2-hydroxyphenylacetic acid (3), 3,5-dimethyloctanedioic acid (15), nonanedioic acid (16), 3,4-dimethyloctanedioic acid (17), hexanedioic acid (24), 5-decynedioic acid (25), 3-methylfuran-2,5-dipropanoic acid (29), 2-(3-carboxy-4-methyl-5-*n*-propylfuranyl)-*n*-propanoic acid (31), 2-(3-carboxy-4-methyl-5-*n*-pentylfuranyl)-*n*-propanoic acid (41).

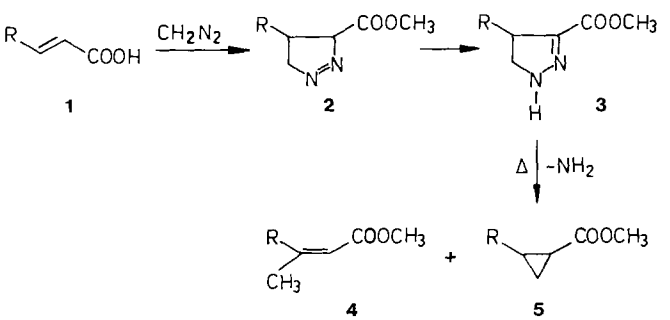
Conjugates that contain mainly phenolic acids are rapidly cleaved by β-glucuronidase/arylsulfatase.[11] The free acids can then be extracted.

Polar acids can be obtained by adsorption of the compounds present in the biological fluid onto an ion exchanger,[12] and, after desalting, elution with an organic solvent;[12] the type of solvent used has a marked effect on the appearance of the profile.

When serum and protein-rich biological fluids are processed, the peptides must first be separated because they would otherwise block the columns. Since acids are sometimes coprecipitated during precipitation, it is advisable to remove the protein by one-step[13] or, preferably, two-step[14] ultrafiltration. The filtrates can then be easily processed similarly to urine.

Complications also arise during the separation of urine on ion exchange columns. Highly polar compounds are very strongly bound to ion exchangers and gradually co-elute in subsequent runs. Complete elution of trace components that are adsorbed onto a column may require washing with many liters of solvent and may take up to 14 days.[15]

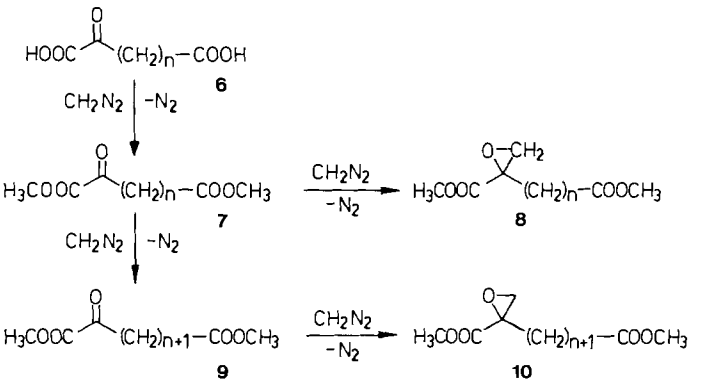
Further difficulties are encountered in the derivatization steps required for gas chromatographic separation. If diazomethane is used for esterification,[4] not only do the acidic and phenolic groups react to form the desired esters and ethers, respectively, but the nitrogen atoms of some amino acid conjugates are also methylated—e.g., hippuric acid is converted into methyl *N*-methylhippurate (Fig. 1). Diazomethane can also add to the double bonds of any α,β-unsaturated acids present[16] (Scheme 1).



Scheme 1. Reaction of an α,β-unsaturated carboxylic acid with diazomethane.

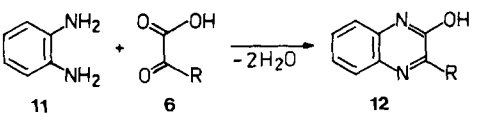
The 4,5-dihydro-3*H*-pyrazoles **2** produced from the α,β-unsaturated acids **1** rearrange to give the isomers **3**. The latter may undergo partial decomposition in the gas chromatograph to form the α,β-unsaturated esters **4**, substituted with a methyl group at the 3-position, or the cyclopropane derivatives **5**.[17]

When the α-oxo acids **6** are treated with diazomethane, they form not only the corresponding methyl esters **7** but are also converted into the epoxy compounds **8** and the homologous methyl esters **9** (Scheme 2). The resulting homologues **9** can react further with diazomethane in a similar fashion to yield **10**.[17] Accordingly, several reaction products are sometimes formed from one compound and acid profiles usually show more compounds than actually exist.



Scheme 2. Reaction of an α-oxo acid with diazomethane.

Other routes must be used if such artifacts are to be avoided. For example, the α-oxo acids **6** can be analyzed by reacting them with *o*-phenylenediamine **11** to give the quinoxaline derivatives **12** (Scheme 3), which are also highly suitable for quantitative gas chromatographic determinations.[18]



Scheme 3. Reaction of α-oxo acids **6** with *o*-phenylenediamine **11** to give the quinoxaline derivatives **12**.

Trimethylsilylation[5] is preferred, especially for the quantitative determination of known substances, due to the danger of side reactions that take place when diazomethane reacts with acids. However, compared with diazomethane derivatization, trimethylsilylation has the decisive disadvantage—in addition to the sensitivity of trimethylsilylated acids to hydrolysis—that the mass spectra of trimethylsilyl derivatives generally provide less information about the structure of a compound than the corresponding methyl esters; it is thus almost impossible to elucidate the structure of unknown compounds by this method and, in many cases, this is what is required.

Biological fluids usually contain so many acids that the peaks observed in the gas chromatograms correspond to several components if packed columns are used. Therefore, peaks cannot always be clearly identified even with the aid of mass spectrometry. Superimposed spectra can be subtracted from one another by recording a large number of spectra during the course of a run.[19] This procedure is still useful even if glass capillary columns are employed. In such cases, however, a further chromatographic method is now generally used (see Figs. 2 and 3).

4. Structure Elucidation of Unknown Compounds

The structure of unknown compounds can be deduced from the mass spectra of substances separated by GC if reference spectra are found in the large number of spectral catalogs that are available.[20] Computers can, of course, also be utilized for such searches.[21]

If a structure cannot be assigned with the aid of refer-

ence spectra, some information about the structure may usually be deduced from a spectrum, but complete structures can only be established in a small number of fortuitous cases. Generally, it can be assumed that the compound may already have been described in the literature. Since the empirical formula is needed for a literature search, it must be obtained by high-resolution mass spectrometry of the peaks observed in the gas chromatogram.[22] The measuring period for the individual ions of a peak obtained in glass capillary GC is, however, so brief that the instruments must be operated far below their optimal resolution[*] (e.g., with a "resolution of 3000" instead of a possible "resolution of 50000") in order to obtain adequate ion currents; determination of mass thus gives a large number of possible empirical formulas.[22]

Selection of the correct formula from a large number of possibilities requires a great deal of effort, a knowledge of additional parameters of the substance, and consideration of the possible routes of mass spectrometric decomposition. Despite time-consuming considerations, the empirical formula cannot always be obtained in this way. The substance then usually has to be enriched to such an extent that masses can be determined by "peak matching."[**]

Enrichment is performed by first separating the mixture of methyl esters by thin layer chromatography. The plates are arbitrarily divided into zones, the zones are then eluted, and each fraction is investigated by means of glass capillary gas chromatography. If necessary, the fraction containing the enriched, unknown compound can be located using mass spectrometry.[23] The next step involves further separation by HPLC and subdivision into arbitrary fractions which are also tested by means of gas chromatography to determine whether the separation was successful.

When the unknown compound is enriched to such an extent that it accounts for about 20% of the total material present and examination of the mass spectra of the accompanying substances shows that these contain key ions other than that of the unknown compound, the exact mass of the ions and hence the empirical formula of the compound can be determined from the mixture, and a literature search can then be made.

If the literature search proves to be unsuccessful, further information is often provided by determining the empirical formulas of the fragment ions. However, high-resolution data of the key ions obtained using a few micrograms of the enriched sample only allow structural determination in special cases.[24]

Proposed partial structures can then be confirmed or rejected by chemical reaction of the enriched sample on a microscale and subsequent analysis of the reaction products by GC/MS. Several micrograms of enriched material are sufficient for hydrogenation, addition of OsO_4[25] or H_3CSSCH_3[26] to double bonds, ozonolysis, acylation, methylation, etc. Approximately 5 to 10 times as much sample is required for the detection of a carbonyl group by oxime formation, for the identification of a methoxycarbonyl group by $LiAlH_4$ reduction, or for oxidative degradation reactions, because the polar reaction products formed are often strongly adsorbed.

Reactions in which the electron densities of specific parts of the molecule are modified considerably are especially advantageous, since the ionization and thus the initiation of fragmentation is shifted from one part of the molecule to another. In favorable cases, important information can first be obtained from the mass spectrum of one part of the molecule and then from that of the other.

In each of these microreactions contaminants are introduced via the solvents, filters, and materials used to coat the columns, by touching glass vessels with the fingers, and from the atmosphere,[27] etc.; the quantity of the introduced contaminants sometimes far exceeds that of the reacted sample. Separation of the contaminants by subsequent gas chromatography is thus an absolute prerequisite for the interpretation of spectra. It is often difficult to find the "right" reaction products in a gas chromatogram; many spectra have to be examined, since the smaller the reacted sample, the more often is the reaction product a small peak whose intensity is overshadowed by the much more intense peaks due to the contaminants.

It is, however, easy to establish that a reaction has failed if the starting compound remains unchanged. The retention index and the mass spectrum of this substance are known and therefore even traces of it can be recognized within the range of the known retention index by means of the key ions.

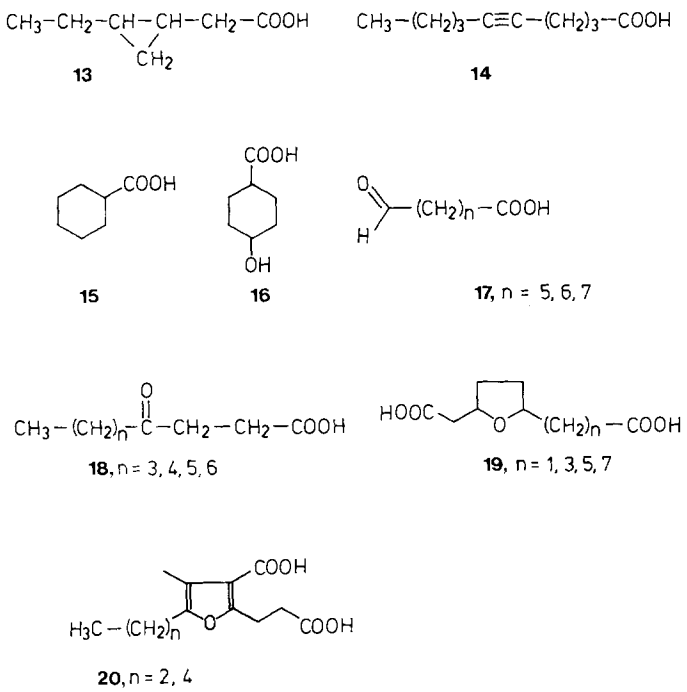
The structure of an unknown molecule can usually only be partially clarified with the aid of microreactions. For instance, the positions of substituents in aromatic and heterocyclic rings are seldom established from mass spectra. There is thus no alternative but to collect at least 1 mg of the sample of a sufficient purity to determine NMR and other spectroscopic data.

Nowadays this quantity of substance usually allows unambiguous structural determination provided that the molecule has a maximum molecular weight of about 2000, the necessary microchemical degradation experiments are carefully planned, and the reaction products (at least in the form of derivatives) can be separated by GC. The studies of *Bergström* et al. on prostaglandins are noteworthy examples of this type of structural determination[28] with the aid of microreactions.

In recent years a large number of unknown acids, some of which display unusual structures, have been identified in biological fluids. For example, the following compounds have been isolated from urine: the cyclopropanoic acid **13**,[29] the acetylene compound **14**,[30] cyclohexanecarboxylic acid **15**,[31] 4-hydroxycyclohexanecarboxylic acid **16**,[32] the aldehyde acids **17**,[33] the 4-oxo acids **18**,[33] the tetrahydrofuran acids **19**,[34] and the urofuran acids **20**[23] (Scheme 4). This indicates that we are still unaware of many metabolic pathways.

[*] Resolution means that two different masses are separated from one another by a "valley"—e.g., for a resolution of $R = M/\Delta M = 50000$, a mass of 500 daltons will be separated from a neighboring mass of 500.01 daltons by a valley. For a resolution of $R = 3000$, masses of 500.00 and 500.01 will no longer be separated; in this case, it is only possible to separate masses of 500.00 and 500.17 daltons.

[**] The substance to be determined is introduced into the mass spectrometer together with a reference compound that affords ions of known mass. The different acceleration voltages are then measured that are needed for "identical" focusing of a reference peak of known mass and the unknown peak. The voltage ratio is the same as the ratio of the two masses. The exact mass of the unknown ion (e.g., the molecular ion) can thus be calculated with a very small degree of error (< 5 ppm).



Scheme 4. Carboxylic acids recently discovered in human urine.

5. Acids as Degradation Products of Body Substances and Foodstuffs

It is not easy to decide whether a compound is synthesized in the body or whether it passes through the body as an unmodified constituent of food. This problem can be solved as follows: if the compound in question is found in the urine of babies fed exclusively on breast milk but does not exist in the breast milk itself, it can be concluded that the substance is produced by the body.[35]

The supposition that a substance comes from a specific food can be tested by selecting a diet that does not contain the food in question; disappearance of the compound from the urine supports the hypothesis. More definitive evidence is provided by examining the urine before, during, and after a starvation diet; substances that are not changed on passage through the body (e.g., 3,4-dihydroxybenzoic acid) are no longer found in the urine after only one day of starvation. Substances of exogenous origin that undergo metabolism are found in the urine for up to one week after beginning the starvation diet (e.g., piperine metabolites), whereas metabolic products formed from depots within the body are still excreted after longer starvation periods (e.g., **19**).[15]

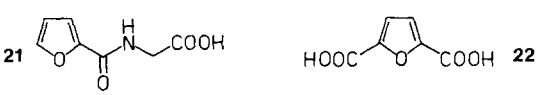
Up to now, physiologically active compounds were first identified on the basis of their activity and subsequently isolated so that their structures could be determined. It should now be possible to adopt the reverse approach. Physiologically active compounds are often synthesized in very small amounts and are then converted into inactive compounds which are excreted in the urine, where they accumulate. These degradation products can then be used to detect the active precursors.

Possible precursors can be synthesized in the search for active precursors. Animal experiments then show whether these compounds are degraded to the substances found in urine.[36] Attempts to find appropriate precursors in the liver, kidney, and other organs can, however, also be made.

Such studies have demonstrated, for example, that tetrahydrofurandiacetic acid **19** (n = 1) is formed by oxidative degradation of higher homologues that are synthesized by the body.[35] The search for physiologically active precursors seems to have paid off in this case. The aldehyde acids **17** are, however, less interesting; they are oxidation products of linolenic acid and probably enter the body in the food[37] as is also the case for cyclohexanecarboxylic acid **15**.[31]

To the best of our present knowledge, most of the acids excreted in the urine are derived from foodstuffs or from spices and flavorings. Only a small proportion of the acids excreted are products that can be synthesized by the body. Our future interest should be centered on research into these compounds since this will enable us to discover unknown metabolic processes. A prerequisite for such studies is a knowledge of the substances contained in foodstuffs, but our understanding in this area is still as fragmentary as that of metabolism. Modern analytical methods are often employed to examine aroma and flavoring substances but are hardly ever used to determine all of the constituents of plant foods.

The acid contents of individual foodstuffs vary appreciably,[38] which means that mere ingestion of different foods can lead to considerable differences between the profiles. On the other hand, acids derived from food can be integrated into the metabolism of the body; an equilibrium is then set up between the ingested and the excreted acids. Few studies have been performed on this subject;[39] it is known that a diet rich in vegetables promotes the excretion of aromatic acids.[40] In spite of this, some of these acids (e.g., homovanillic acid and vanillinmandelic acid), which are also produced from catecholamines, have been employed to deduce the concentrations of these amines.[40,41] 2-Furoylglycine **21** and 2,5-furandicarboxylic acid **22** (Scheme 5) also enter the body via the food.[42]



Scheme 5. 2-Furoylglycine **21** and 2,5-furandicarboxylic acid **22**.

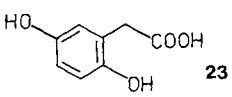
Since definitive results have not been obtained, the acid excretion rates of individuals are determined and these mean values are regarded as "normal profiles."[43] It would certainly be better to differentiate the acids already present in the body from the acids ingested with the food and to use only the former to determine the "normal values."

The determination of a "normal profile" implicitly assumes that acid excretion in one and the same individual does not change on a regular basis and that it is not affected by external conditions; this is, however, not always the case. Thus, marked changes in acid excretion are observed after physical exertion. The amount of propylurofuranic acid **20**, for example, decreases within three hours to 1/5th of its original amount.[44] Detailed studies in this field are, however, lacking.

6. Investigation of Metabolic Diseases that are Associated with the Excretion of Unusually High Quantities of Acids

Acid profiles are crucial for recognizing inborn errors of metabolism because, in many cases, acidic metabolites are accumulated as a result of enzyme defects, thus resulting in the excretion of abnormally high amounts in the urine.

Some of these usually rare, genetically controlled metabolic diseases have been known since the turn of the century—e.g., alcaptonuria in which the patients suffer from a lack of homogentisic acid oxidase, resulting in the excretion of 4–8 g of homogentisic acid **23** (Scheme 6) in the urine per day.[45]



23

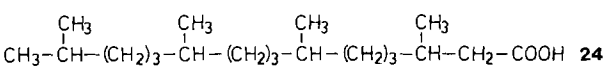
Scheme 6. Homogentisic acid **23**.

Many of the 1400 genetic metabolic diseases that are now known[26] soon cause serious physical and mental damage. If muscle spasms, uncontrollable vomiting, acidosis, etc., are observed after birth or in young babies, the patients should be thoroughly examined for metabolic defects.[47]

Nowadays GC/MS plays an important part in these investigations,[48] the urine profiles of the patients being compared with those of healthy individuals. Unusual peaks found in the gas chromatogram of the patient's urine may indicate a metabolic defect. Mass spectra of these peaks can then be used for structural determination.[49]

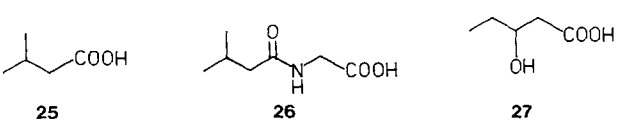
It is remarkable that an unknown metabolic product has often been discovered in this way but that subsequent, more precise studies show that the compound thought to be "specific" for the disease also occurs in the urine of healthy persons; the quantities involved are, however, so small that the compound can only be detected when special attempts are made to find it. The specific characteristic of the disease is thus not the compound itself but rather the extremely large quantities of it that are found.

GC/MS was first used in 1963 to investigate a lipid storage disease ("Refsum syndrome"); phytanic acid **24** was identified in the urine of the patient (Scheme 7).[50]


24

Scheme 7. Phytanic acid **24**.

In 1966 *Tanaka* et al. were able to demonstrate that large quantities of isovaleric acid **25**, its glycine conjugate **26**, and 3-hydroxyvaleric acid **27** (Scheme 8) were excreted in a previously unknown metabolic disease.[51]



25 **26** **27**

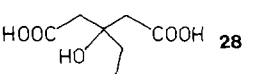
Scheme 8. Isovaleric acid **25**, its glycine conjugate **26**, and 3-hydroxyvaleric acid **27**.

Improvement of detection techniques led to the discovery of more new and unusual metabolites which are produced as a result of the isovaleryl coenzyme A dehydrogenase deficiency encountered in this disease, which has been called "isovaleric aciduria."[52]

A large number of unknown metabolic defects have been subsequently identified using GC/MS; these studies were initiated primarily by *Jellum* et al.[53a,c] These defects are all characterized by the excessive excretion of acids—e.g., methylmalonic aciduria,[53b,54] pyroglutamic aciduria,[53a] hydantoin-5-propionic aciduria,[55] propionic aciduria,[56] glutaric aciduria,[57] and glutaric aciduria II.[58] Further studies using improved methods have shown that in some cases a large number of unusual metabolic products are formed, for example, in propionic aciduria,[59] which is a result of a disorder in the metabolism of propionyl CoA, or in tyrosinuria, which is caused by a defect of tyrosine aminotransferase.[60] Disorders in the metabolism of the amino acid leucine are especially numerous; the various enzyme defects can cause a wide range of different diseases.[61]

A total of more than 50 previously unknown hereditary diseases have been shown to be caused by metabolic defects with the aid of GC/MS. Gas chromatography has proved to be a suitable method for definitively identifying an even larger number of such diseases.[62]

Acids that occur in the urine of patients suffering from metabolic diseases need not necessarily be a consequence of the disease. It was recently reported, for example, that 3-ethyl-3-hydroxyglutaric acid **28** (Scheme 9) is found in the urine of children suffering from propionic aciduria.[63]

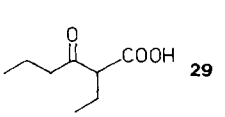


28

Scheme 9. 3-Ethyl-3-hydroxyglutaric acid **28**.

Such results should be assessed very critically for a number of reasons—packed columns were used for the gas chromatographic separations, the width of the peak indicates the presence of a mixture of compounds and the peak itself is not very large, and the same compound also occurs in the urine of healthy persons and probably originates from foodstuffs.[64]

It should also be carefully considered whether 2-ethyl-3-oxohexanoic acid **29**[65] (Scheme 10) found in the urine of diabetics is a metabolic product of the body or, instead, a degradation product of an artifact, since the corresponding alcohol is formed from dioctyl phthalate; the latter compound is an almost ubiquitous constituent of all biological materials and can reach the body via plasticizers. Diabetics still seem to have difficulty in further degrading 2-ethyl-3-oxohexanoic acid.



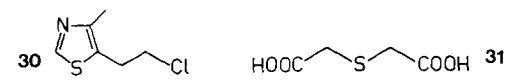
29

Scheme 10. 2-Ethyl-3-oxohexanoic acid **29**, which has been discovered in the urine of diabetics.

7. Investigation of Drug Metabolites

Acids are often produced during the metabolism of pharmaceuticals. If the profiles are compared before, during, and after administration of the drug, the acids formed from it can be recognized from the additional peaks that appear in the gas chromatogram of the methylated acid fraction of the urine obtained during treatment. This method can thus supplement metabolic studies with radioactively labeled compounds.

For example, the drug 5-(2-chloroethyl)-4-methylthiazole (Clomethiazol or Distraneurin®) **30**, which is often used to alleviate withdrawal symptoms in alcoholics, is degraded not only by oxidative attack at the carbon atoms of the side chain[66] but also by oxidation at C2 with subsequent ring cleavage. Since the labeled C-2 atom is thereby lost in the form of CO_2, some important metabolites escaped detection. Comparison of the profiles of untreated and treated individuals revealed, however, the presence of other metabolites that had lost the C-2 atom, e.g., thiodiacetic acid **31**[67] (Scheme 11).



Scheme 11. 5-(2-Chloroethyl)-4-methylthiazole (Distraneurin®) **30** and its metabolite thiodiacetic acid **31**, which is probably produced by reaction of the side chain with glutathione.

Saliva is, like urine, a biological fluid that is easy to obtain. Examination of its acids has shown that saliva contains the same metabolic products that are found in other body fluids.[68]

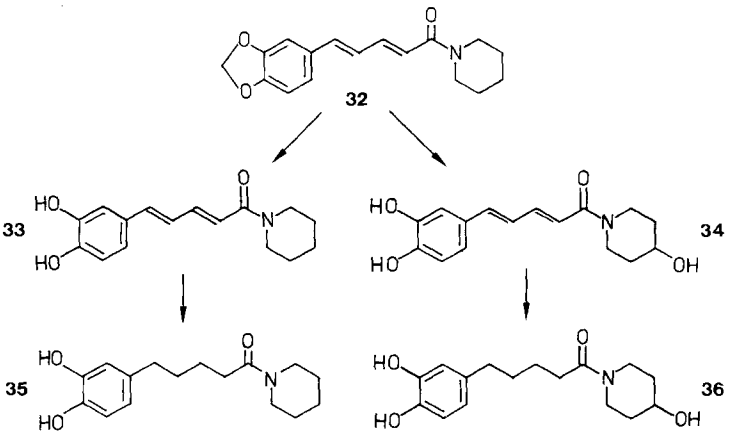
8. Steroid Profiles

Unlike acids, which are often of exogenous origin, the steroids of biological fluids are of endogenous origin so that one does not have to contend with the problem of whether these compounds are derived from foodstuffs or spices and flavorings. It is, however, more difficult to obtain the steroid fraction than the acid fraction because the steroids mainly occur in the form of conjugates.

In routine investigations free steroids are generally not separated from steroids that are excreted as sulfate and glucuronide conjugates.[69] The conjugates are usually hydrolyzed enzymatically and then extracted with an organic solvent, e.g., ethyl acetate or ether.

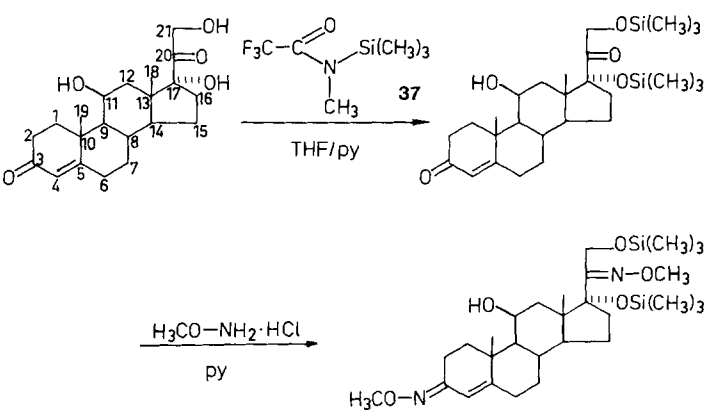
Even if the acids are removed by addition of hydrogen carbonate, neutral substances originating from food are still carried over into the steroid fraction. After ingestion of sweets containing liquorice, numerous peaks appear which are derived from flavanones. Oxindole is also a common interfering substance.[70] Urine steroid profiles almost always contain the degradation products of the pepper constituent piperine **32**, which enters the body in the food. It is interesting that the metabolites **35** and **36** are lacking in approximately every tenth person; these individuals excrete the precursors **33** and **34**[24] (Scheme 12).

Steroids and their conjugates can be isolated completely and under mild conditions by extraction with XAD resins.[71] The steroids can then be eluted from the ion exchanger with methanol and subjected to further work-up. Lipophilic Sephadex is also used for this purpose.[72] One of the disadvantages of these adsorption methods is the tedious washing procedure. This disadvantage can largely be overcome by applying the biological fluid to Sep Pak C-18 cartridges which adsorb all the steroids present.[73] This method can also be utilized to obtain steroids from serum and other biological fluids.[74]



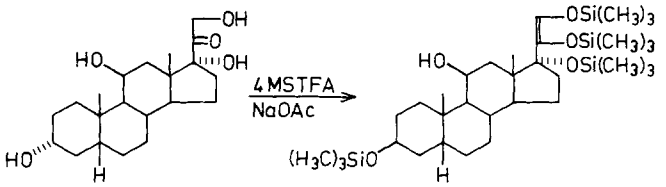
Scheme 12. Piperine **32** and its metabolites **33** and **34** or **35** and **36**, which are excreted in the urine.

A few polar steroids can be separated by gas chromatography without derivatization, as was first shown by *Horning* et al.,[75] but even simple hydroxysteroids decompose. Progress was made with the synthesis of trimethylsilyl derivatives.[76] This form of protection is not, however, sufficient to prevent steroids with hydroxyl groups at positions 17 and 21 from being decomposed to 17-oxosteroids.[77] Analysis of such steroids (e.g., cortisol) only became possible when their trimethylsilylated methoxime derivatives (MO-TMS derivatives) had been synthesized[78] (Scheme 13).



Scheme 13. Trimethylsilylation and methoxime formation of cortisol. THF: tetrahydrofuran.

Modern trimethylsilylation reagents, such as *N*-methyl-*N*-trimethylsilyltrifluoroacetamide (MSTFA) **37** or trimethylsilylimidazole (TMSI) **38**, now permit conversion to trimethylsilylenol ethers,[79] which display gas chromatographic properties that are equally as good as those of the MO-TMS derivatives (Scheme 14).



Scheme 14. Formation of the trimethylsilylenol ether of 5β-tetrahydrocortisol.

We use such derivatives almost exclusively. The introduction of glass capillaries, which have been employed since about 1970, also led to further important developments in the field of steroid analysis.[80]

Urine steroid profiles of healthy adults are distinguished by a characteristic double peak in the androgen range, which corresponds to androsterone and etiocholanolone,[78a,81] and by an equally intense peak corresponding to tetrahydrocortisone in the range of the corticoid metabolites[3a,81,82] (Fig. 3).

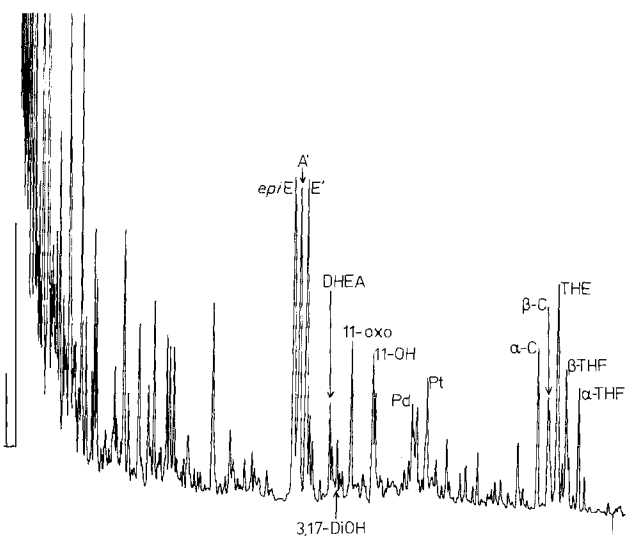
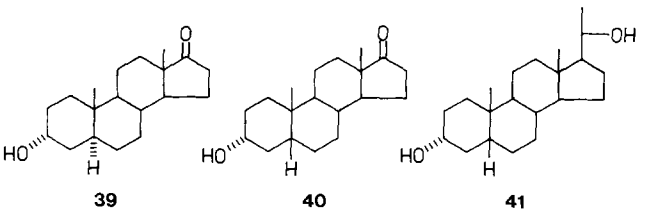


Fig. 3. Urine steroid profile of a healthy man (24 years old); *epi*-etiocholanolone (*epi*E) as an internal standard, androsterone (A'), etiocholanolone (E'), dehydroepiandrosterone (DHEA), 3,17-dihydroxyandrost-5-ene (3,17-DiOH), 11-oxoetiocholanolone (11-oxo), 11-hydroxyetiocholanolone (11-OH), pregnanediol (Pd), pregnanetriol (Pt), α-cortolone (α-C), β-cortolone (β-C), tetrahydrocortisone (THE), β-tetrahydrocortisol (β-THF), *allo*-tetrahydrocortisol (α-THF). Experimental conditions: Siemens L 402 gas chromatograph with a WCOT glass capillary (30 m × 0.3 mm, OV 101); hydrogen flow-rate: 2 mL/min; injector temperature: 270°C; oven temperature: 150–280°C (2°C/min); flame ionization detector (FID). The steroids were separated in the form of their trimethylsilylenol ethers.

If the intensity of the tetrahydrocortisone peak in profiles of healthy individuals is only a fraction of that of the androsterone and etiocholanolone peaks, it is likely that errors have been made during the work-up. This often applies to older studies.

It should be possible to differentiate steroid profiles according to sex. Although sex-specific differences are found in most cases[83]—in the urine steroid profiles of adult men, the peak for androsterone **39** is generally considerably greater than that for etiocholanolone **40** (Scheme 15), whereas in women the etiocholanolone peak is about twice as intense as the androsterone peak—the urine steroid profiles of some healthy men are similar to those of women and, moreover, women must not necessarily excrete more etiocholanolone than androsterone.[84]

In the second half of the menstrual cycle of women, there is a sharp increase in the excretion of pregnanediol **41** (Scheme 15), which is reflected in the steroid profile (Fig. 4).



39 **40** **41**

Scheme 15. Androsterone **39**, its isomer etiocholanolone **40**, and pregnanediol **41**.

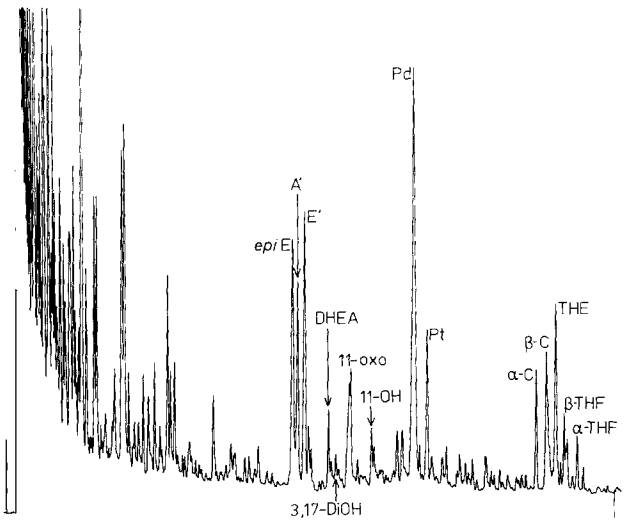


Fig. 4. Urine steroid profile of a healthy woman (27 years old, second half of the menstrual cycle). For conditions and abbreviations see Figure 3.

The change in hormonal balance during pregnancy can be recognized above all by a considerable increase in the excretion of pregnanediol.[85] The steroid metabolism of the fetus differs from that of the mother; the fetus passes its steroids back to the mother so that the 16-hydroxysteroids typical of the fetus can be used as a measure of the normal course of pregnancy.[86] The excretion of 6-hydroxylated pregnane derivatives is examined using GC/MS and is especially important during the last three months of pregnancy.[87]

The gradual development of a steroid metabolism in the first few months of life is reflected in the steroid profiles. The fetal zone of the adrenal cortex, which gradually recedes, produces other steroids than those typically found in adults. The steroid profiles of newborns and babies are thus characterized by the presence of steroids having a 3β-hydroxy-5-ene structure[88] and often possessing additional hydroxyl groups at positions 16, 18, and 21 as well as by corticoid metabolites with hydroxyl groups at positions 1 or 6. GC/MS has played an important part in the separation, structural examination, and elucidation of these steroids.[89]

As expected, only small amounts of androgens are excreted in the urine of children prior to puberty. Moreover, the aging process can be followed by means of the steroid profiles: the androgen content in older individuals decreases sharply in comparison with that of the corticoids.[85]

The steroid excretion rate of adults exhibits a circadian rhythm;[90] the mean excretion rate when awake is about ten times higher than when asleep. These differences can be offset by collecting "24-hour urine." This does not, however, compensate for the often large, day-to-day fluctuations in steroid excretion rates found in one and the same person, which may be as high as 50%[84] (Fig. 5).

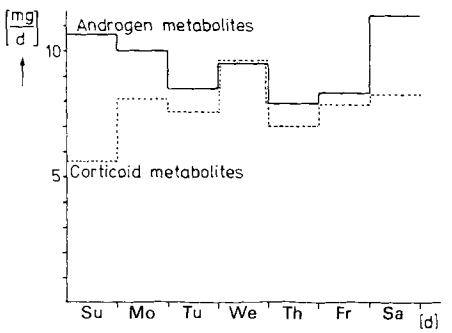
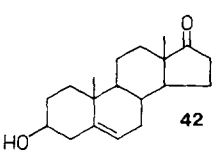


Fig. 5. Mean daily androgen and corticoid excretion rates of a healthy man (25 years old) over the course of a week.

Whereas the absolute quantities of steroids vary considerably, their relative amounts only display slight differences. In healthy individuals the ratio of androsterone to etiocholanolone remains almost constant over a period of years.[84]

In chronic diseases, however, the steroid levels can gradually change (see below). The body thus works like a chemical factory: if production is increased, the by-products are also formed in correspondingly larger quantities.

The steroid dehydroepiandrosterone (DHEA) **42** (Scheme 16) occupies an exceptional position with respect to the others. The excretion rate of DHEA in most people is only 1/10th that of the main androgens androsterone **39** and etiocholanolone **40** but increases up to ten- to twenty-fold during psychological stress.[91]

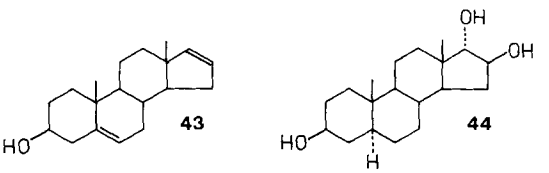


Scheme 16. Dehydroepiandrosterone (DHEA) **42**.

Approximately every tenth person excretes these high levels of DHEA continuously.[84] Women who suffer from hirsutism often excrete large amounts of DHEA.[92] Increased excretion of corticoids is also associated with psychological and emotional stress.

Steroids are excreted not only in the urine but also in the feces, where they are subjected, however, to attack by microorganisms in the intestines.[93] The excretion of steroids in the feces of normal and germ-free rats was studied in detail in order to establish what happens to steroids in the intestines.[94] It was concluded that steroids are released into the intestines and are then reabsorbed. 21-Hydroxysteroids are, for example, dehydroxylated by the internal bacterial flora of rats.[95]

In contrast to humans, rats exhibit major sex-specific differences as regards the hydroxylation of the D-ring of certain androstane derivatives, e.g., 5,16-androstadiene-3β-ol **43**. 5α-Androstane-3β,16β,17α-triol **44** (Scheme 17) predominates in the urine of male rats, whereas an analogous metabolite is not found in the urine of female rats.[96]



Scheme 17. 5,16-Androstadiene-3β-ol **43** and its main metabolite 5α-androstane-3β,16β,17α-triol **44** found in the urine of male rats.

The observation that rats display different steroid profiles depending on their sex was used by *Eriksson* and other workers to show that the liver enzymes responsible for corticoid metabolism are regulated by androgens and estrogens.[97] Metabolism of a steroid in the liver can be studied by allowing the steroid to react with rat liver microsomes and then examining extracts by means of GC/MS.[98]

Since bile metabolism is related to diseases of the gastrointestinal tract, GC/MS was used at a very early stage to investigate bile acids and their precursors, especially by *Sjövall* and his group.[99] Previously unknown bile acids and other steroids were discovered with this method and determined in bile and serum.[100]

As expected, disorders in the functioning of steroid-producing glands have an extremely marked effect on steroid excretion. Lack of 11β-hydroxylase, for example, causes diminished cortisol production and thus greatly reduces the excretion of tetrahydrocortisol. A functional defect in the adrenal cortex leads to a drastic decrease in corticoid production.

A reduced ability to cleave steroid sulfates is associated with pathologically prolonged pregnancy. Drastically elevated levels of steroid sulfates are excreted in cases of sulfatase deficiency; this defect can thus be differentiated from other possible causes of deficient estrogen excretion in pregnant women by analyzing the sulfate fraction of the urine.[101]

3β-Hydroxysteroid dehydrogenase deficiency is reflected by extremely high excretion of 3β-hydroxy-4-ene steroids.[102]

Hereditary hypofunctioning of the adrenal cortex causes greatly reduced excretion of 3-hydroxy-5-ene steroids in babies;[103] a tumor in the adrenal cortex leads to greatly increased excretion of all steroids, but especially of dehydroepiandrosterone, 16β-hydroxydehydroepiandrosterone, and androstenetriol. A lack of 21-hydroxylase can be recognized by markedly reduced excretion of corticoids and elevated excretion of 17β-hydroxysteroid metabolites such as pregnanetriol and pregnanetriolone.[104]

A deficiency of enzymes that oxidize 18-hydroxysteroids to aldehydes (the pathway of aldosterone synthesis) leads to increased excretion of these steroids.[105] A deficiency in 17-hydroxylase is reflected by low excretion of androgen and cortisol metabolites; instead, large amounts of corticosterone are excreted.[106]

Atlases have been compiled for the recognition of metabolic steroid disorders. They contain typical excretion patterns and thus allow identification of the individual disorders.[107]

Unexpectedly, disturbances of steroid metabolism are also encountered in chronic diseases. It has been shown that the main steroids found in the ultrafiltrates of blood from uremic patients are 11-oxidized androsterone derivatives (Fig. 6), while production of the normal androgens is greatly diminished and the ratio of androsterone to etiocholanolone is shifted increasingly in favor of etiocholanolone.[108] The increase in the 11-oxidized steroids roughly parallels the development of hypertension.[109]

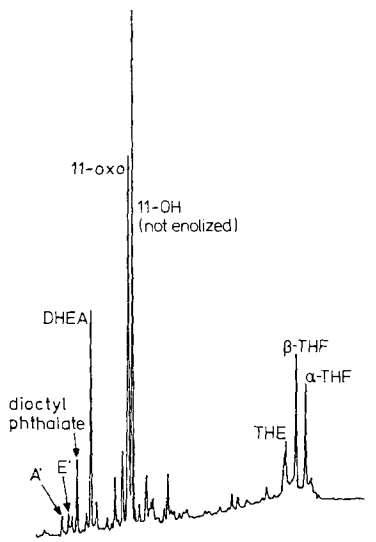


Fig. 6. Steroid profile of the ultrafiltrate of blood from a uremic patient (for conditions see Figure 3).

Interestingly, the blood steroid balance is different in uremia; the main steroid found in the blood of healthy individuals is, apart from cholesterol, dehydroepiandrosterone, whereas in uremia another main steroid is present—androst-5-ene-3β,17β-diol.[108]

Steroid metabolism also changes in diabetics[110] and persons suffering from liver diseases[111] (Fig. 7). Large quantities of the bile acid precursors are excreted in the form of steroid alcohols that are derived from cholesterol. They are normally only present in trace amounts.

Changes in steroid metabolism also seem to be typical of some skin diseases. For example, the blood steroid profiles of patients suffering from psoriasis resemble those of uremic patients.[112] Low levels of corticoid excretion in urine have been observed in a number of skin diseases such as psoriasis and neurodermitis;[113] this phenomenon may perhaps be related to the irritation of large areas of skin associated with such diseases.

External application of corticoid ointments should not affect the body's steroid metabolism. However, it has been

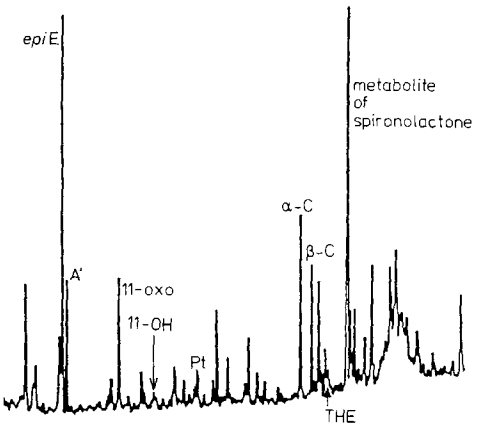
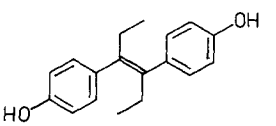


Fig. 7. Urine steroid profile in liver disease (Wilson's syndrome) (for conditions see Figure 3).

found that fluorocorticoids can apparently penetrate damaged skin[114] and thus simulate increased corticoid levels, which leads to a reduction of the body's own steroid production. The urine steroid profile then exhibits reduced steroid excretion.

GC/MS plays an important part in determining whether artificial estrogens such as diethylstilbestrol (Scheme 18) have been used to fatten livestock.[115] Traces of these substances can be detected in the bodies of animals by "selective ion monitoring"[116] or "selected metastable peak monitoring."[117]



Scheme 18. The synthetic steroid diethylstilbestrol detected in the urine of fattened beef cattle.

9. Profiles of Bases

Since biological fluids generally only contain very small quantities of bases, base profiles usually reflect the consumption of stimulants. The main peak of the base profile of urine obtained from smokers is nicotine while that for coffee drinkers is caffeine.

Polyamines such as putrescine **45**, cadaverine **46**, spermidine **47**, spermine **48**, and isoputreanine **49** (Scheme 19) are of importance for cell proliferation and growth, especially in their acetylated forms.[118]

$H_2N-(CH_2)_4-NH_2$ **45**

$H_2N-(CH_2)_5-NH_2$ **46**

$H_2N-(CH_2)_3-NH-(CH_2)_4-NH_2$ **47**

$H_2N-(CH_2)_3-NH-(CH_2)_4-NH-(CH_2)_3-NH_2$ **48**

$H_2N-(CH_2)_3-NH-(CH_2)_3-COOH$ **49**

Scheme 19. Putrescine **45**, cadaverine **46**, spermidine **47**, spermine **48**, and isoputreanine **49**.

A relatively large amount of spermidine **47** is found in young tissues and relatively little in aging tissues. Increased levels of polyamines are consequently released in

tumor diseases. It was therefore hoped that cancer could be diagnosed at an early stage by determining polyamines in urine. However, high levels of polyamines were also found in other diseases.[118] Furthermore, even if amine production is increased in tumor tissue, the quantity of tumor tissue is so small when compared with the body weight that it has little effect on the total excretion of polyamines.

Polyamines and their acetyl derivatives cannot easily be extracted from biological fluids because they are highly soluble in water. One method for obtaining these compounds consists of extracting the alkalized urine with butanol, reextracting after acidification, and adsorption of the amines onto a Dowex 50W-X8 ion exchanger, from which the amines can then be washed off with HCl.[119] In another procedure, the acetyl residues initially present are cleaved by acid hydrolysis, the hydrolysate is then concentrated, buffered, and applied to a Sep Pak column, and the amines are finally eluted with acidic methanol.[120] The polyamine fraction is derivatized by acylation with heptafluorobutyric anhydride for the subsequent gas chromatographic separation.

Profiles were obtained in this way using packed[119] and capillary columns.[120] The profiles revealed the presence of many other amines in addition to the known polyamines and purine bases; only one degradation product of spermidine[119] **47** and isoputreanine[120] **49** (Scheme 19) have so far been identified. Many polyamines still remain to be identified.[121]

Since isoputreanine **49** is excreted in much smaller quantities by healthy individuals than by patients who have been successfully treated for lymphomatosis, it has been suggested that this could provide a method for analytically studying the success of the therapy used to treat such diseases.[120]

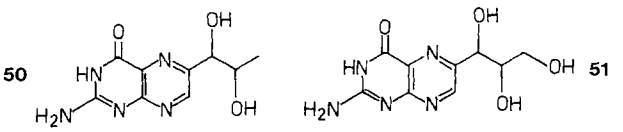
Neurophysiological processes are closely linked to the release of catecholamines. Determination of these compounds is important because the liberation of catecholamines is related to nervous diseases such as schizophrenia, Parkinson's disease, epilepsy, migraine, and depressive symptoms. Their concentrations in blood vary greatly with time. Measurement in urine is therefore often preferred because this gives the mean release values over longer periods of time.

The determination of many phenylethylamines is difficult due to their dipolar nature—they contain both basic amino groups and phenolic hydroxyl groups having acidic character. Their subsequent degradation products, such as vanillinmandelic acid, homovanillic acid, and 4-hydroxy-3-methoxyphenylethyleneglycol, are therefore often measured instead.[41a,b,122]

Many methods have been developed for measuring the catecholamines themselves.[123] The biogenic amines[124] can be determined by GC/MS or by HPLC using electrochemical detection to identify the components.[125]

Basic metabolites are often formed from pharmaceuticals. Since the amines normally present in the body hardly interfere with the base profile and usually only a few basic metabolites are produced from a single drug, GC/MS is highly suitable for routine measurements in pharmacokinetic studies even if packed columns are used.

The investigation of pterins has recently become of importance in connection with the growth of tumors. MS is very important for detecting and determining biopterin **50** and neopterin **51** (Scheme 20) in the form of their trimethylsilylated derivatives.[126]



Scheme 20. Biopterin **50** and neopterin **51**.

10. Amino Acid Profiles

Amino acids and low-molecular-weight peptides are obtained from biological fluids by acidification and adsorption on a cation exchanger. On rinsing with water, the amino acid and peptide fractions are retained by the ion exchanger and can then be eluted with NH_3. They can be separated into an amino acid fraction and a peptide fraction by using reversed phase octadecasilyl columns[127] or Chelex 100.[128]

For gas chromatographic determination of the amino acids, the amino acid fraction is esterified and acylated;[129] the butyl esters are usually prepared as suggested by *Gehrke* et al. and are then trifluoroacetylated in a subsequent step.[130] It is difficult to determine arginine, sulfur-containing amino acids, and tryptophan with this technique.[131] This problem can be surmounted, however, by preparation of the *N*-heptafluorobutyryl *n*-butyl ester derivatives.

The trifluoroacetylated amino acid butyl esters can easily be characterized by MS.[130a,132] Profiles of amino acid hydrolysates of differing biological origin were obtained using packed columns.[133] They display, in addition to the peaks corresponding to the 20 known amino acids present in proteins, other peaks corresponding to unknown basic substances.[134] Small quantities of, for example, acylated[135] and methylated[136] amino acids were identified. Since most of these studies were reported some time ago and capillary gas chromatography has only been employed recently in this field (Fig. 8),[137] little is known about the unidentified substances.

Unlike acid profiles, amino acid profiles remain highly consistent. Differences are observed between individuals but the profiles vary little with time. The quantities of the main amino acids that are excreted vary within one order of magnitude but are probably more dependent on diet than those of acids. It is known that ingestion of food rich in protein leads to an increase in the excretion of amino acids, particularly those that are branched. Stress has a similar effect in adults.[138] When meat and above all poultry are consumed, 1-methylhistidine is found in the urine;[139] homocitrulline occurs in the urine of children who drink a great deal of milk.[140] Small children excrete appreciably more glycine, histidine, glutamine, alanine, and lysine than adults.[141]

Amino acid excretion in individuals with hereditary diseases that affect amino acid metabolism[142] naturally differs considerably from that of healthy individuals.[138,141]

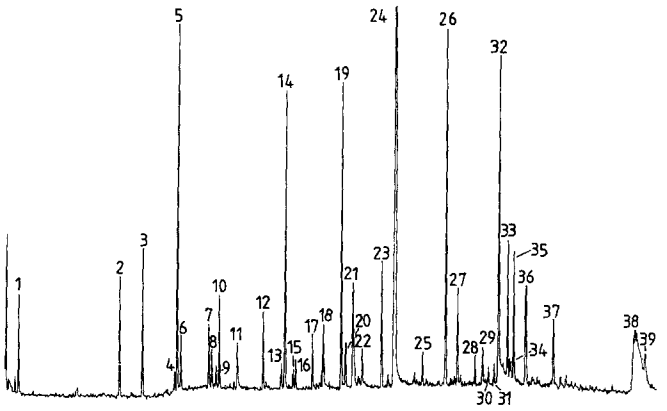


Fig. 8. Urine amino acid profile of a healthy man (29 years old). The amino acids were separated in the form of their *N*-heptafluorobutyryl *n*-butyl ester derivatives. Alanine (3), valine (4), glycine (5), threonine (6), serine (7), β-aminoisobutyric acid (8), leucine (9), isoleucine (10), cycloleucine, standard 1 (12), proline (13), cysteine (15), hydroxyproline (18), methionine (22), aspartic acid (and asparagine) (23), creatinine and phenylalanine (24), glutamic acid (and glutamine) (26), tyrosine (27), ornithine (30), 4-aminomethylenecyclohexanecarboxylic acid, standard 2 (33), arginine (34), lysine (35), 1-methylhistidine (36), 3-methylhistidine (37), histidine (38). (1), (2), (11), (14), (16), (17), (19), (20), (21), (25), (28), (29), (31), (32), and (39) are unknown. Experimental conditions: Carlo Erba Fractovap 4160 gas chromatograph with a WCOT quartz capillary (50 m × 22 mm with the chemically bound phase OV 1701); hydrogen flow-rate: 1.3 mL/min; injector temperature: 270°C; oven temperature: 130–260°C (3 min isothermally, then with 3°C/min); flame ionization detector (FID).

The kidney has the important function of resorbing much larger quantities of the essential amino acids than of other substances from the primary urine. The filter that is used for ultrafiltration of the blood of patients suffering from uremia is incapable of doing this. Consequently, uremic patients lose a much higher percentage of essential amino acids due to excretion in the urine than do healthy persons. Studies of the amino acid profiles show, for example, that the loss of methionine is 10 times higher, that of proline 100 times higher.[137b]

11. Peptides

Dipeptides can also be separated by gas chromatography in the form of trifluoroacylated butyl esters. The urine of healthy individuals contains small quantities of dipeptides.[143] Patients suffering from skin disease excrete relatively large amounts of proline-containing dipeptides.[144]

Determination of the structures of oligopeptides by mass spectroscopy proved to be unsuccessful due to the low volatility and high mass of these substances. The oligopeptides were therefore cleaved enzymatically with dipeptidyl aminopeptidases, and the mixture of dipeptides was then separated by gas chromatography after derivatization and the individual dipeptides were characterized by MS.[145] The main problem in all of these investigations was presented by the large number of dipeptides (about 400) that can be formed and whose GC and MS properties had to be known for purposes of identification. Furthermore, many dipeptide mixtures are difficult to separate on packed columns.[145d] Nevertheless, this procedure was finally applied successfully to study the *N*-terminus of spinach plastocyanin.[146]

Peptides can be sequenced by GC/MS using the method developed primarily by *Biemann*'s group. The peptides are split into smaller peptides by peptidases that act specifically on certain peptide bonds or by non-specific chemical hydrolysis. The mixture is then esterified, acylated, and reduced with $LiAlH_4$ ($LiAlD_4$) or B_2H_6 (B_2D_6). The resulting amino alcohols are trimethylsilylated and separated by gas chromatography. The structure of the hydrolysate peptides and thus of the original peptides can be deduced from the very characteristic mass spectra of the derivatized amino alcohols.[147]

Since this procedure initially required a relatively large amount of material, it could only compete with conventional sequencing procedures in special cases.[148] The many steps involved in preparing the derivatized amino alcohols can be reduced if the mixture of the esterified partial peptide hydrolysate is methylated.[149] However, C-methylation may also occur,[150] resulting in the formation of complex mixtures. This method can therefore only supplement classical degradation procedures.[151]

In recent years "soft" ionization methods, in particular "fast atom bombardment" (FAB)[152] and field desorption mass spectrometry,[153] have become increasingly important in the study of oligo- and polypeptides. In FAB-MS investigations a noble gas is ionized and the ionized atoms are then accelerated. If these atoms pass through a zone of intact gas molecules, they will transfer their charge but not their kinetic energy to these molecules. The beam of atoms then bombards a glycerol solution of the non-derivatized peptide. Peptides and solvent molecules that are hit by the beam are expelled and ionized. Protonated molecular ions are chiefly obtained. This method is thus especially suitable for determining molecular weights of even larger molecules—e.g., both fragments[155] and molecular ions were obtained from insulin[154] ($M_r \approx 6000$).

Attempts were made to determine the sequence of model peptides from the fragments formed. Basically, fragments were selected from those present whose formation could be accounted for by the given structure. Since additional ions (some being produced by reaction of the peptide with the matrix molecules) and missing ions confuse the fragmentation pattern, it is almost impossible to deduce the complete structure of unknown free peptides without supplementary information.

However, the tendency to form fragments can be greatly increased by introducing an electron-rich system into the peptide, as is demonstrated by comparing the FAB mass spectra shown in Figures 9 and 10. In the case of small peptides (up to ten amino acids), the introduction of an aromatic group containing bromine is particularly advantageous because the presence of the almost equally abundant bromine isotopes ^{79}Br and ^{81}Br in the fragments affords a label which allows simple recognition of the structurally specific fragments in the form of double peaks[155c] (Scheme 21).

Interpretation of the spectra can also be improved by establishing the decomposition pathways with the aid of the "linked scan technique."[156] After the primary production of ions, the ions of a defined mass that are to be studied are separated from the other ions by the electric field of the mass spectrometer and then excited by reaction with an

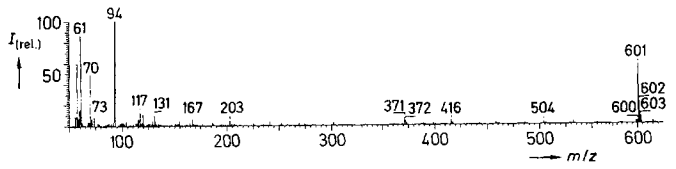


Fig. 9. FAB mass spectrum of the positive ions of the hexapeptide Pro-Pro-Gly-Phe-Ser-Pro in a glycerol matrix; m/z 601 (MH^+).

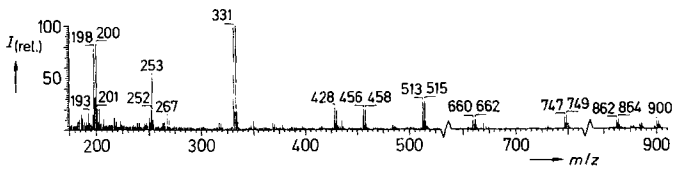
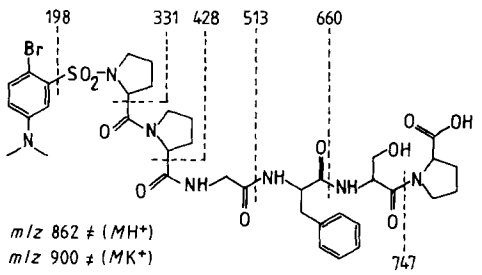


Fig. 10. FAB mass spectrum of the positive ions of the hexapeptide Pro-Pro-Gly-Phe-Ser-Pro derivatized with 2-bromo-5-(*N*,*N*-dimethylamino)benzenesulfonyl chloride.



Scheme 21. Formation of ions observed in the FAB mass spectrum (shown in Figure 10) of the derivatized hexapeptide Pro-Pro-Gly-Phe-Ser-Pro; the masses given are relative to ^{79}Br.

added auxiliary gas. The masses of the secondary fragments of the selected primary ions can now be determined and the fragmentation mechanisms investigated by varying (scanning) the magnetic field; for example, the stepwise formation of fragments can be followed and thus the sequence of a peptide can be determined.

The resolving power of the instrument and the necessary mass determination limit the usefulness of the FAB-MS method for large peptides. A procedure recently developed by *Biemann* et al. seems to be suitable for examining these peptides and combines both the sequencing of nucleic acids and that of peptides. A peptide mixture that has been partially digested with trypsin is investigated by means of FAB-MS. The molecular ions of the peptides in the mixture are easy to obtain and must correspond to molecular weights that can be predicted from DNA sequencing. If no differences are found, the DNA sequence is confirmed. If this is not the case, errors can be identified and corrected. This combined procedure seems to have a promising future.[157]

12. Concluding Remarks

The metabolism of an individual is apparently predetermined from birth. Large differences exist, however, between individuals. These are perhaps a result of undiscovered, harmless genetic defects, but may become significant if a disease has to be treated with drugs and the pharmacologically active agents are also metabolized differently, as has already been shown.[158]

If it were possible to recognize these defects at an early stage in small children and to construct a metabolic chart for each individual, drug treatment of disease could then be designed on an individual basis and preventative measures against nutritional damage could be taken if required.

The great effort involved in the use of GC/MS would probably not be necessary if key compounds typical of certain hidden defects were discovered, since radioimmunoassays could be developed to detect them. This is, however, still a dream of the future.

The question of whether such studies can be at least partially realized mainly depends on whether organic chemists will in the future attach more importance to research into biological materials and metabolic processes than they have done in the past. This is the task that faces young chemists.

The studies of my own group mentioned in this review are the results of the efforts, skill, and ideas of my coworkers. I would like to thank them for their persistence despite setbacks and the courage with which they have followed the course traced out for them. They are S. Bauer, H.-J. Egger, M. Ende, A. Grupe, A. Heindl, C. Hölzel, H. Ludwig-Köhn, M. Neupert, P. Pfeifer, J. Pfordt, O. Rau, J. Reiner, D. Renner, K. Schneider, M. Spiteller, Jr., and B. Zielinska. I am grateful to the Deutsche Forschungsgemeinschaft, the Fonds der Chemischen Industrie, and Schering for their financial support.

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Growth and Dissolution of Organic Crystals with "Tailor-Made" Inhibitors—Implications in Stereochemistry and Materials Science

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In memoriam Gerhard M. J. Schmidt

When crystals of organic compounds are grown in the presence of growth inhibitors, there is a change in crystal morphology. A stereochemical correlation exists between the crystal structure, its modified morphology, and the molecular structure of the inhibitor. This correlation has been successfully exploited for the efficient resolution of conglomerates, the engineering of organic crystals with desired morphologies, the direct and relative assignment of the absolute configurations of chiral molecules and crystals, and for the design of a new model for the spontaneous generation of optical activity. In an analogous way dissolution of organic crystals in the presence of these growth inhibitors induces etch pits at preselected faces. The effect of solvent on crystal growth has been analyzed in some model systems. The experimental results are complemented by atom-atom potential energy calculations.

1. Introduction

The various and beautiful morphologies of crystals have attracted the attention of natural philosophers since ancient times. Crystal formation from the smallest irreducible units had already been conceived as long ago as 1611 by *Kepler*;[1] this concept played an important role in the development of molecular theory.

The relation between the morphology of a crystal and its internal symmetry at a molecular level was first demonstrated by *Louis Pasteur*[2] in 1848. In his now famous experiment he separated, for the first time, the two enantiomers of sodium ammonium tartrate, utilizing the asymmetric habit of their crystals. Over the years, however, it became evident that the morphological characteristics of the crystals of a given compound depend not only on its crystal structure, but also on external parameters of the overall crystallizing system such as solvent, supersaturation, temperature, and specifically impurities present in the system[3].

In 1931 *Miles*[4] demonstrated that crystals of $PbCl_2$, which normally crystallize with centrosymmetric point symmetry ($2/m,2/m,2/m$), assume a chiral morphology of symmetry 222 when grown in the presence of dextrin. With the advent of new and efficient methods of crystal structure determination, most efforts were devoted to such determinations and less interest was focused on correlating crystal structure and morphology. As a result, many important properties of materials which depend on this correlation were not exploited in a systematic way. On the other hand, the use of dopants for inducing a particular crystal morphology is a widespread technological tool, even though the mechanism of the effect is scarcely understood. Thus, for example, small amounts of ions such as Pb^{2+} or SO_4^{2-} have long been routinely used as crystallization moderators in the industrial production of large NaCl single crystals for IR and Raman spectroscopy.[5] Similarly, sugar technologists recognized and studied the critical role played by oligosaccharides in determining the rate of crystallization and habit of sucrose crystals on extraction from molasses.[6]

In the course of investigating the packing and growth of organic molecular crystals, we initiated a study on the systematics of the interactions between a crystallizing substrate and its environment, in general, and the solvent and stereospecific "tailor-made" growth inhibitors in particular. We shall illustrate here some mechanistic aspects of the above interactions as they have emerged during these studies and some applications thereof to the amplification of chirality by crystallization, resolution of conglomerates, the direct and relative assignment of absolute configuration of chiral molecules, the study of molecular interactions in crystals, the engineering of crystals with desired morphologies, and the selective etching of crystal surfaces upon dissolution.

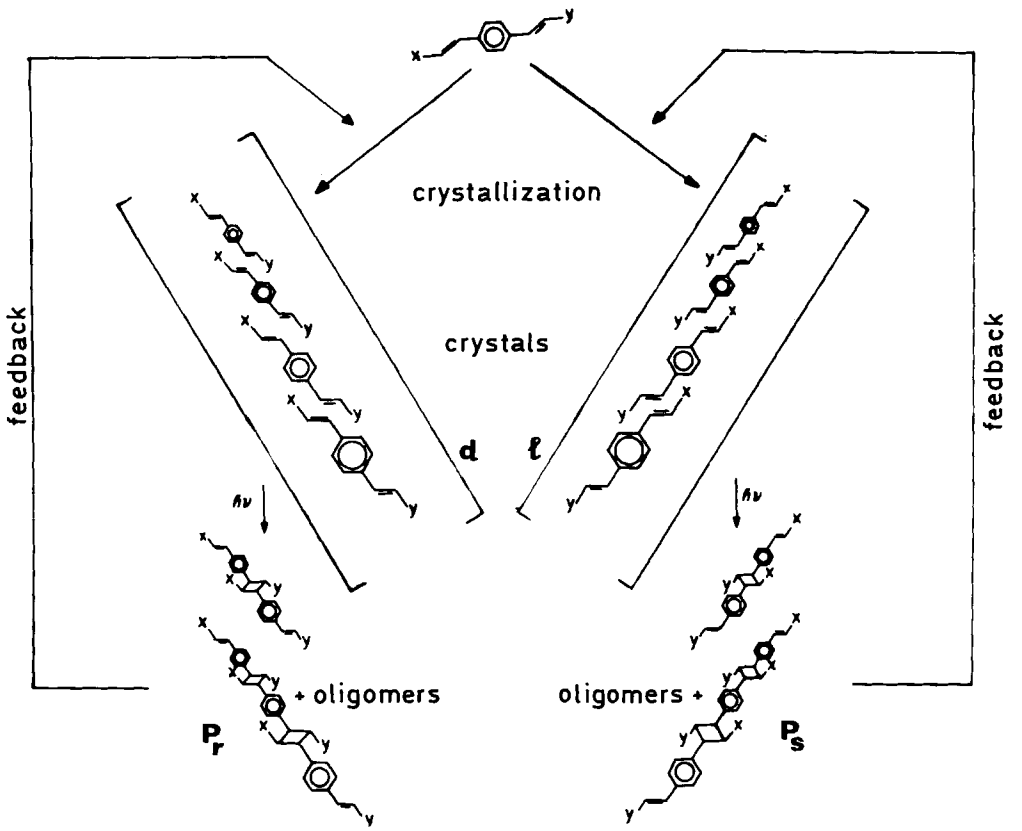
2. Amplification of Chirality by Crystallization with Chiral Additives; a New Method for the Resolution of Conglomerates of Enantiomers

The synthesis of chiral enantiomerically pure materials from nonchiral reagents has been accomplished by crystallization of the (in solution) nonchiral substrate in appropriately packed chiral single crystals, followed by a lattice controlled reaction.[7] This concept is illustrated in Scheme 1 for the generation of chiral cyclobutane polymers from nonchiral dienes packing in "engineered" chiral crystals.[8]

The molecules in each chiral crystal, (denoted by $[\,]_d$ or $[\,]_l$ in Scheme 1), are related by translation such that the neighboring C=C bonds are in appropriate proximity for photodimerization. UV irradiation of a single crystal yields dimers, trimers, and oligomers of a single chirality P_r or P_s.

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Scheme 1. Lattice-controlled generation of chiral cyclobutane derivatives (enantiomers P_r and P_s) from non-chiral dienes packing in "engineered" chiral crystals (d and l symbolize the respective enantiomeric packings). For examples of the dienes, see Table 1. The feedback leads to an inhibition of crystallization.

In a nonchiral solvent the d and l crystals are formed in equal amounts, so that no net asymmetric induction of the reaction products P_r and P_s is observed. On the other hand, a net asymmetric induction of one of the crystalline phases is achieved when chiral dimers, trimers or oligomers of a *single* chirality (i.e. P_r *or* P_s) are present during the process of crystallization. In all experiments it was observed that a large excess of that phase was formed which was enantiomorphic to the one in which the additive itself had been generated; namely, d crystals were obtained from a solution containing additives P_s and l crystals from solutions containing additives P_r (Fig. 1).

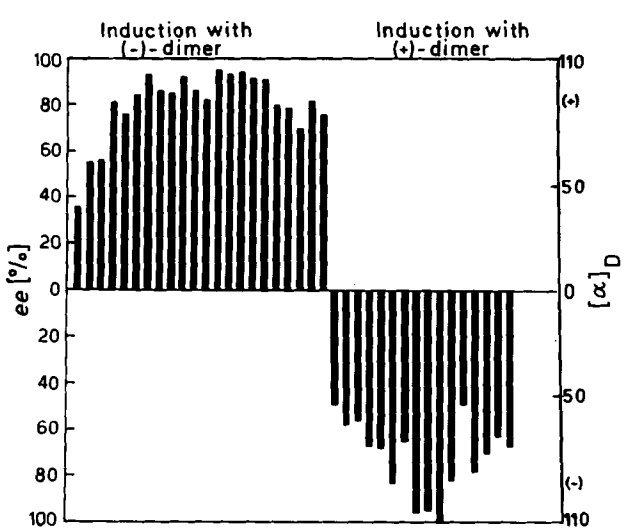
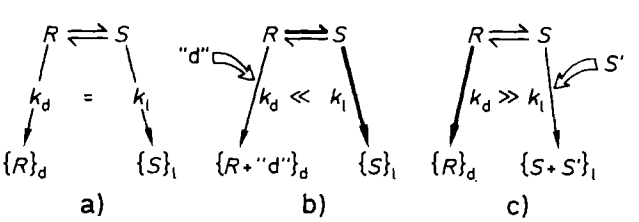


Fig. 1. Enantiomeric excess (*ee*) of the dimers obtained by lattice controlled reaction after crystallization of the monomer in the presence of chiral dimers as additives under various experimental conditions (see Scheme 1 and Table 1).

The stereochemical similarity between the additive and the respective enantiomorphous crystal of the monomer was found to be of paramount importance,[9,10] while parameters like temperature, concentration, or nature of the medium had only a quantitative effect on the observed asymmetric induction.

We suggested that, by virtue of this stereochemical similarity, a chiral dimer, trimer, or oligomer may substitute two, three, or n monomer units at a growing site of that crystal with the same absolute configuration as the parent crystal of the photoproducts. The adsorption should cause a drastic decrease in the rate of growth of this same crystal, shifting the crystallization equilibrium towards the unaffected phase. This process of crystal growth and inhibition is illustrated in Scheme 2, where the achiral monomer is



Scheme 2. (a) Spontaneous crystallization of a racemate (*RS*) to give a $\{R\}_d/\{S\}_l$ conglomerate; (b) crystallization in presence of the additive "d" (lattice-controlled product of the $\{R\}_d$ phase); preferred crystallization of $\{S\}_l$; (c) crystallization in presence of a chiral additive *S'* (with stereochemical similarity to *S*); delayed crystallization of $\{S\}_l$.

represented as a fast racemizing mixture of chiral conformations R and S in solution, and $\{R\}_d$ and $\{S\}_l$ represent the chiralities of the crystalline phases.

A natural extension of this scheme to any racemic mixture, fast racemizing or not, crystallizing in the form of a conglomerate of $\{R\}_d$ and $\{S\}_l$ crystals, led to the suggestion of a new method for kinetic resolution of such systems. It is based on selective retardation of the growth of the crystals of one enantiomorph, say S, induced by small amounts of chiral additives, say S', with related stereochemistry (Scheme 2c).[10]

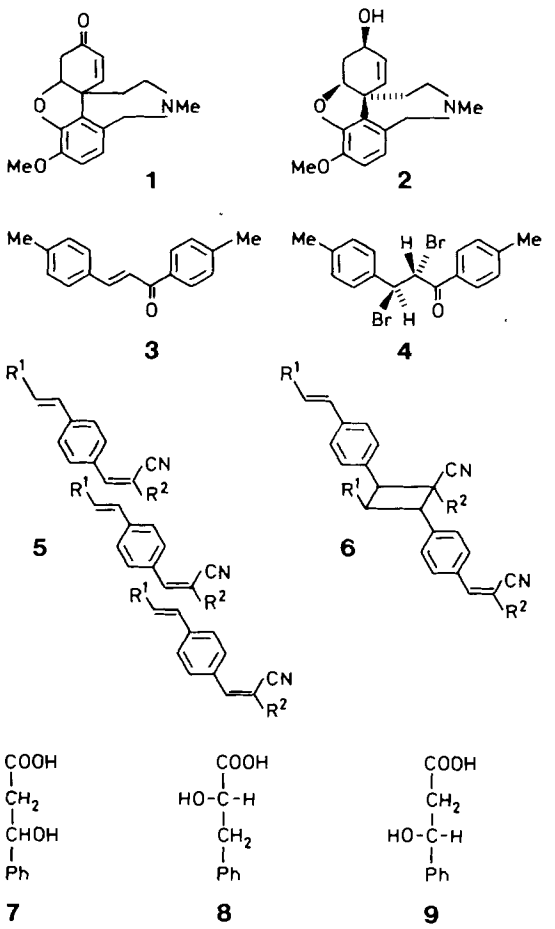
In the light of this proposed mechanism we could rationalize various experimental results, describing kinetic resolutions accidentally observed in the presence of chiral additives, and where the fast crystallizing enantiomer had absolute configuration opposite to that of the additive (Table 1).[10] The predictive power of the hypothesis was further tested on other conglomerate systems including threonine, glutamic acid · HCl, and asparagine · H_2O. These were resolved with the assistance of a variety of other amino acids used as growth retarders (Table 1).[10]

The efficiency of the resolution was found to vary from one system to another, and to depend upon the nature and

Table 1. Resolution of conglomerates of enantiomeric compounds or crystals. Top: previously described resolutions with chiral additives which are in accord with our "rule of reversal". Bottom: resolutions of conglomerates accomplished in our laboratory and designed on the basis of the same rule.

Conglomerate	Chiral Additive [a]	Enantiomer first precipitating in excess	Ref.
Glu	(*S*)-Asp, (*S*)-Leu	(*R*)-Glu	[11]
Glu	(*S*)-Glu-γ-Me ester	(*R*)-Glu	[12]
$Cu(Asp)_2$	(*S*)-Glu, (*S*)-Ala	(*R*)-$Cu(Asp)_2$	[13]
Sodium ammonium tartrate	D-(+)-Malic acid	D-(−)-Sodium ammonium tartrate	[14]
Narwedine **1**	(−)-Galanthamine **2**	(+)-Narwedine	[15]
p,p'-Dimethylchalcone **3**	(2*R*,3*S*)-2,3-Dibromo-1,3-bis(*p*-tolyl)-1-propanone **4** from d-crystals [b]	*p,p'*-Dimethylchalcone, l-crystals [b]	[16]
3,3'-(*p*-Phenylene) diacrylates **5** [c]	Dimeric 3,3'-(*p*-phenylene) diacrylates **6** from d-crystals [b]	3,3'-(*p*-Phenylene) diacrylates, l-crystals [b]	[9]
Thr	(*S*)-Glu, (*S*)-Gln, (*S*)-Asn, (*R*)-Cys, (*S*)-Phe, (*S*)-His, (*S*)-Lys, (*S*)-Asp	(*R*)-Thr	[10]
Glu · HCl	(*S*)-Lys, (*S*)-Orn, (*S*)-His, (*S*)-Ser, (*S*)-Thr, (*S*)-Cys, (*S*)-Tyr, (*S*)-Leu	(*R*)-Glu	[10]
Asn · H_2O	(*S*)-Glu, (*S*)-Asp, (*S*)-Ser, (*S*)-Gln, (*S*)-Lys, (*S*)-Orn, (*S*)-His	(*R*)-Asn	[10]
p-Hydroxyphenylglycine-*p*-toluenesulfonate	(*S*)-Phenylglycine, (*S*)-Tyr, (*S*)-*p*-Methoxyphenylglycine, (*S*)-Phe, (*S*)-Dopa, (*S*)-Methyldopa	(*R*)-*p*-Hydroxyphenylglycine	[10]
His · HCl	(*S*)-Trp, (*S*)-Phe	(*R*)-His	[10]
3-Phenylhydracrylic acid **7**	(*S*)-Phenyllactic acid **8**	(*R*)-3-Phenylhydracrylic acid **9**	[10]

[a] All amino acids that have been used as chiral additives belong to the L-series, i.e. with the exception of Cys they are (*S*)-configurated. [b] d und l arbitrarily denote the different chirality of the crystals (without reference to the absolute configuration). [c] Examples: R^1 = COOCHEt$_2$, R^2 = COOMe, COOEt, COO*n*Pr; R^1 = (*RS*)-COO*s*Bu, R^2 = COOEt, COO*n*Pr.



concentration of the additive. In the best cases, [(*RS*)-glutamic acid · HCl + (*S*)-lysine; (*RS*)-threonine + (*S*)-glutamic acid; (*RS*)-asparagine + (*S*)-aspartic acid] complete resolution (100% *ee*) was achieved. The growth of the affected crystals in these instances was delayed up to several days with respect to that of the unaffected ones. In all the systems investigated we could demonstrate that the additive is occluded throughout the bulk of the affected crystals in amounts ranging typically from 0.05 to 1.5% w/w of substrate; it is found in much smaller amounts, if any, in the crystals of the enantiomorph.

The inhibiting effect of the additive on the growth of the affected enantiomorph has also been proven by direct comparison of the size of $\{R\}_d$ and $\{S\}_l$ single crystals grown in parallel from seeds under conditions close to equilibrium (Fig. 2). Although there are indications that the same kind of inhibition may also influence the crystal nucleation rate, such an effect is more difficult to isolate and quantify.

The most convincing demonstration of the adsorption-growth inhibition mechanism is provided by the changes in the morphology of the affected crystals. The morphology of a crystal is determined by the relative rates of growth of its various faces. Since the growth rates of only those crystal faces where adsorption of inhibitor takes place are affected, crystals growing in the presence and in the absence of additives are expected to display different habits. Indeed, in the resolution experiments it was consistently observed that the appearance of crystals of normal habit was

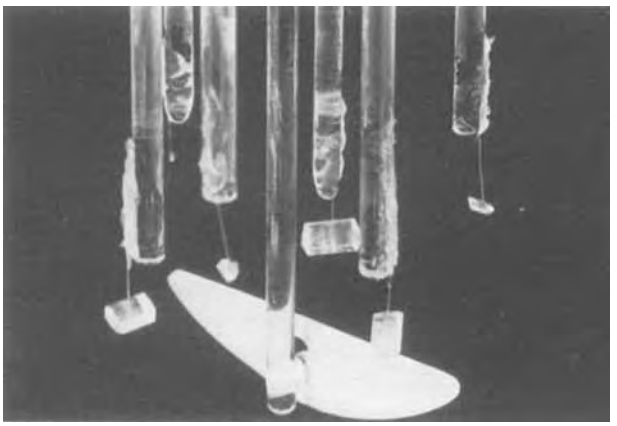


Fig. 2. Three (*R*)- and three (*S*)-crystals of asparagine·H_2O grown together for 45 days under conditions near to equilibrium in the presence of (*S*)-serine. The large crystals are (*R*)- asparagine·H_2O and the small ones are (*S*)-asparagine·H_2O.

followed (after variable time depending on the system) by that of crystals of distinctly different morphology: when the two types were separated by visual sorting, they were found to consist of the unaffected and the affected enantiomers respectively. As expected, the crystallization of asparagine in the presence of different additives consistently yielded crystals with different morphologies (Fig. 3). In the case of (*RS*)-threonine, grown in the presence of say (*S*)-glutamic acid, and (*RS*)-glutamic acid·HCl, grown in the presence of (*S*)-lysine·HCl, the inhibition of growth is so strong that the affected (*S*)-enantiomer appeared as a fine powder coating the well-formed crystals of the (*R*)-enantiomorph (Fig. 4).[17]

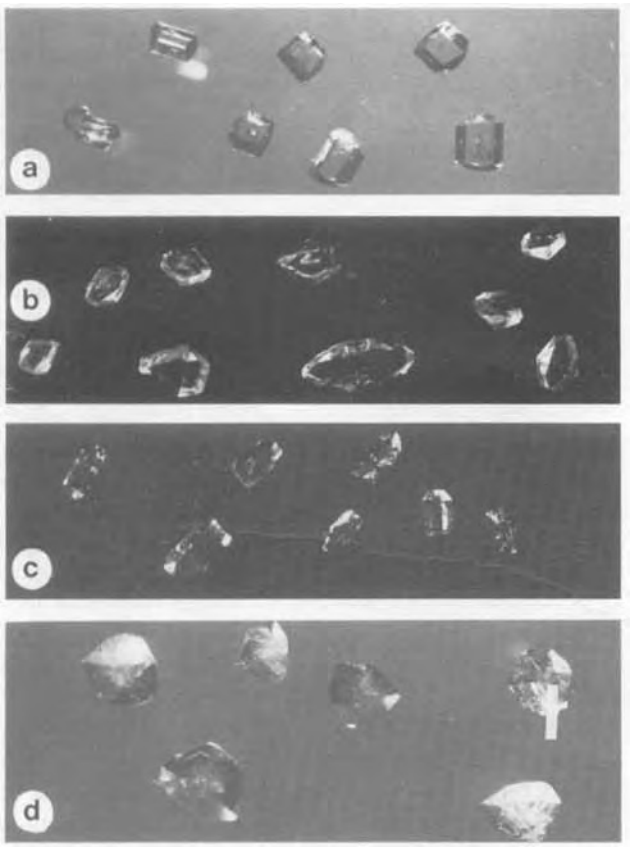


Fig. 3. Crystals of (*S*)-asparagine·H_2O grown in the presence of additives: (a) none, or (*R*)-additives; (b) (*S*)-glutamine as additive; (c) (*S*)-serine as additive; (d) (*S*)-ornithine as additive. In each case the crystals were obtained from (*RS*)-asparagine as a mixture of (*R*)-asparagine crystals displaying a morphology as in (a), and (*S*)-asparagine crystals displaying a morphology as in (b)–(d) or others, depending on the additive.

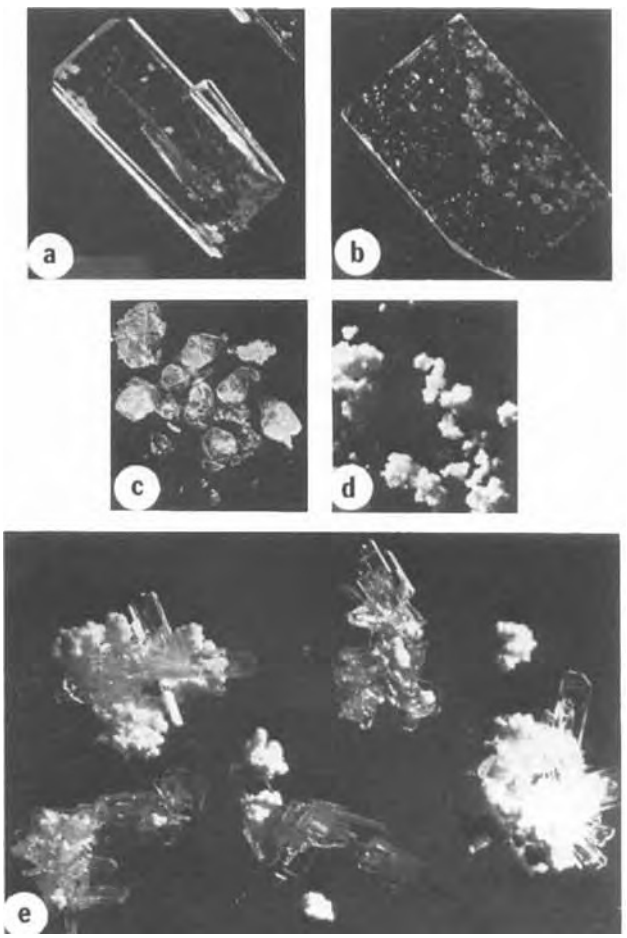


Fig. 4. Crystals of (*S*)-glutamic acid·HCl grown in the presence of increasing amounts of additive lysine: (a) no additive or (*R*)-lysine; (b) +2 mg/mL (*S*)-lysine; (c) +5 mg/mL (*S*)-lysine; (d) +50 mg/mL (*S*)-lysine; (e) crystals of (*R*)- and (*S*)-glutamic acid·HCl grown in the presence of (*S*)-lysine: the plates are the (*R*)-enantiomer while the powder is the (*S*)-enantiomer.

This phenomenon offers the possibility of modifying *Pasteur*'s classical experiment and of extending it to systems which undergo spontaneous resolution but do not display hemihedrism so that one cannot distinguish the enantiomorphous crystals by their morphologies.[18] Another kind of visual differentiation of the enantiomorphs was obtained by crystallizing a conglomerate of colorless crystals in the presence of a resolved and colored "tailor-made" inhibitor. When the plate-like crystals of (*R*)- and (*S*)-glutamic acid·HCl are grown in the presence of yellow N^{ε}-(2,4-dinitrophenyl)-(*S*)-lysine as additive, colorless crystals of (*R*)-glutamic acid·HCl precipitate first, and then yellow ones of the (*S*)-enantiomer (Fig. 5a–c).

The stereochemical correlations between the enantiomorphous crystals and their chiral inhibitors, namely that the additive only affects the enantiomer of the same absolute configuration, provides us with a new method for the determination of absolute configuration on a relative scale.

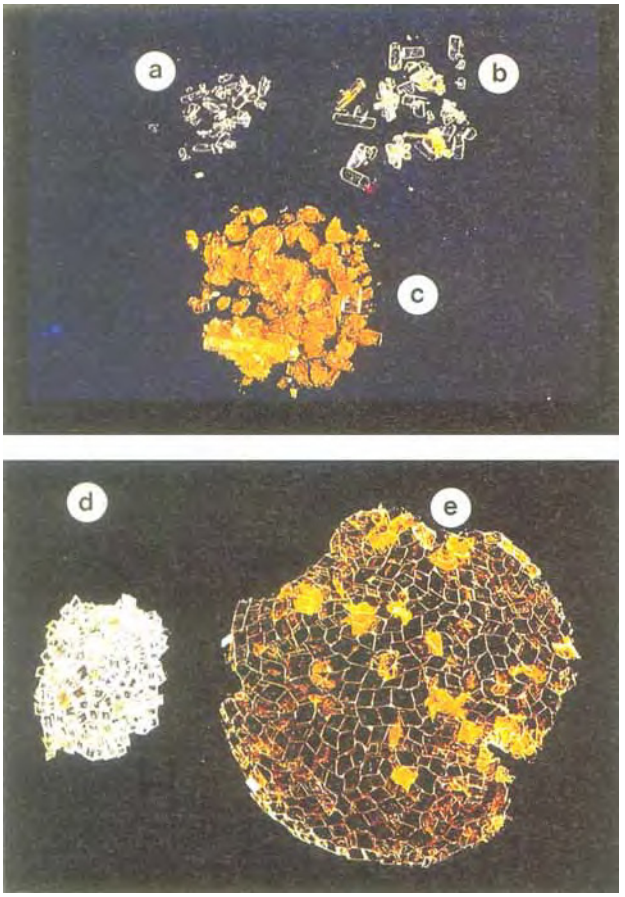


Fig. 5. Top: Crystallization of (*R*)- and (*S*)-glutamic acid·HCl in the presence of N^{ε}-(2,4-dinitrophenyl)-(*S*)-lysine. (a) First crop: colorless crystals of (*R*)-glutamic acid·HCl; (b) second crop: mixture of colorless (*R*)-glutamic acid·HCl and yellow (*S*)-glutamic acid·HCl; (c) third crop primarily contains small, yellow crystals of (*S*)-glutamic acid·HCl.—Bottom: Crystals of glycine grown at an air/water interface from aqueous solutions (concentration: 0.3 g/mL) in the presence of (d) (*S*)-leucine + N^{ε}-(2,4-dinitrophenyl)-(*S*)-lysine and (e) (*R*)-leucine + N^{ε}-(2,4-dinitrophenyl)-(*S*)-lysine (see Section 5).

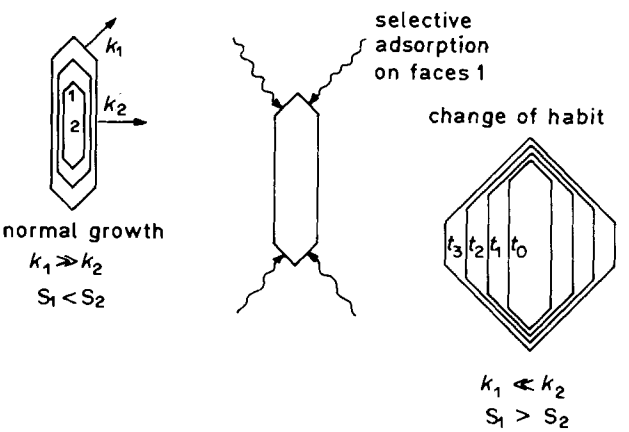
This is revealed independently by morphological changes and enantioselective occlusion of additives. The method is related to the quasi-racemate technique of *Fredga*,[19] but has the advantage of a wider applicability.

3. Morphological Crystal Engineering

The dramatic morphological changes associated with the growth of organic crystals in the presence of additives reveal the high degree of specificity in the interaction of the foreign material with the different structured surfaces of the crystalline matrix. The morphological changes have therefore a direct bearing on the mechanism of the adsorption-inhibition process on a molecular level.

In general, when growth is inhibited in a direction perpendicular to a given face, the area of this face is expected to increase relative to those of other faces of the same crystal (Scheme 3). Differences in the relative surface areas of the various faces of pure and affected crystals allow, therefore, identification of the affected faces and consequently of the crystallographic directions involved. This type of morphological analysis was carried out on a variety of organic compounds crystallized in the presence of additives of molecular structure similar to those of the corresponding substrate molecules.[17] A stereochemical correlation between the structures of the affected crystal surfaces and the molecular structure of the inhibitor could be deduced in each system. We could infer that the additive may be adsorbed only at those faces in which the part of the adsorbate that differs from that of the substrate points away from the crystal interior. Once adsorbed, the additive inhibits the regular deposition of oncoming layers of substrate molecules, slowing down the growth perpendicular to that face and leading to a concomitant relative increase in its surface area. A similar mechanism had been invoked by *Smythe*[6] in his elegant studies on the changes in habit of the crystals of sucrose grown in the presence of oligosaccharides as additives.

Once this mechanism was established, it became possible to exploit it in order to systematically modify the morphology of crystals by tailoring additives which bind at a preselected face and thus inhibit growth in a predictable manner.



Scheme 3. Formation of crystal faces f with surface area S as a function of their selative growth rates *k*. The change in habit results from selective adsorption of inhibitor on faces of type 1. Left: Habit during normal growth. Right: Change of habit by inhibition of growth of faces 1.

This approach is illustrated here for benzamide, which crystallizes from ethanol in the form of {001} plate-like crystals elongated along the *b* axis (Fig. 6a). The main packing feature of the structure (Fig. 7) consists of the typical ribbon motif[20] of hydrogen bonded cyclic dimers interlinked by NH···O bonds along the *b* axis. Retardation of growth of the {011} faces along *b* was achieved with benzoic acid as additive. The substitution of a molecule of benzamide at the end of the ribbon motif by benzoic acid results in replacement in the *b* direction of an NH···O bond by a repulsive O···O interaction, thus retarding growth in this direction and inducing the growth of bar-shaped crystals elongated in *a* (Fig. 6b). Inhibition of growth along *a* was accomplished by adding *o*-toluamide to the crystallization solution. The crystals consistently grew as bars elongated in *b* (Fig. 6c). The additive *o*-toluamide can be easily adsorbed in the hydrogen-bonding chain without interfering with growth in the *b*-direction. The *o*-CH_3 group emerges, from the $(10\bar{4})$ side face, and

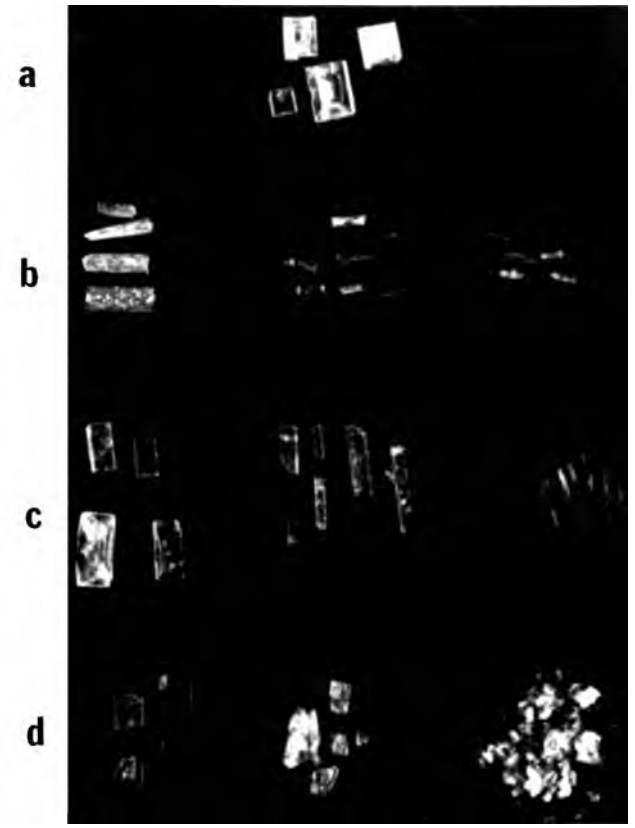


Fig. 6. Crystals of benzamide: (a) Crystallization with no additive. (b) – (d) Crystallization in the presence of increasing amounts (from left to right) of (b) benzoic acid; (c) *o*-toluamide; (d) *p*-toluamide.

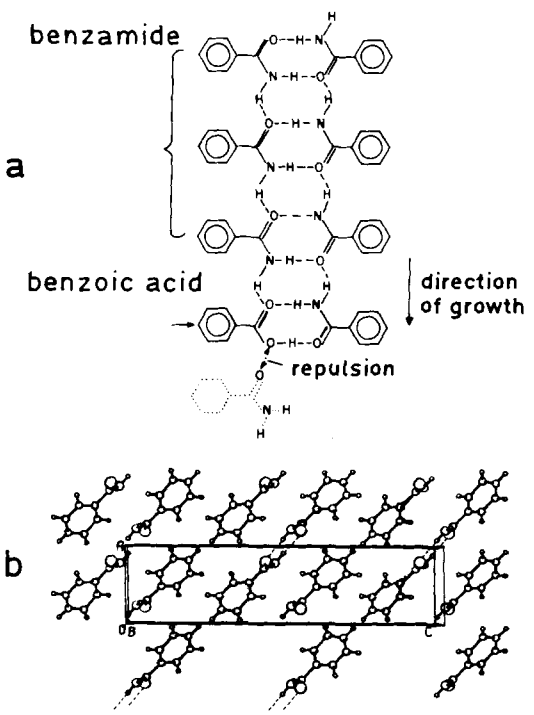
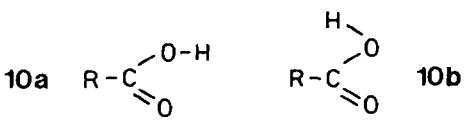


Fig. 7. (a) Schematic representation of part of the benzamide structure showing a benzoic acid molecule inserted at the end of the ribbon motif of hydrogen bonded dimers along the *b* axis. (b) Packing arrangement of benzamide viewed along the *b* axis (*b* axis perpendicular to plane of paper).

thus interferes with growth along the *a* direction, in which the dimers are stacked (Fig. 7b). Finally, thinner and thinner plates are obtained by adding increasing amounts of *p*-toluamide, whose methyl substituent perturbs the already weak van der waals interactions between the phenyl layers in the *c* direction (Fig. 6d, 7b).[21]

Similar morphological changes were induced in crystals of other primary amides and of other organic molecules, including carboxylic acids, amino acids, dipeptides and steroids.

In accounting for the effect of a carboxylic acid additive on the crystal habit of the corresponding primary amide we assumed that the carboxyl group adopts the commonly observed synplanar conformation **10a**, as against the rarely observed antiplanar conformation **10b**.[22]



This postulate was eventually demonstrated by a diffraction experiment on the host-additive system asparagine-aspartic acid[23] and confirmed by potential energy calculations on benzamide-benzoic acid.[24]

Crystals of asparagine·H_2O undergo a change in habit when grown in the presence of aspartic acid[17] (Fig. 8a). We explain this change using arguments akin to those given above for benzamide-benzoic acid. The affected crystals are {010} platelets, whose formation can be rationalized in terms of adsorption of aspartic acid on an (010) face with the condition that its hydroxyl oxygen atom emerges from the face. Further growth at such a surface site is inhibited by the replacement of an amide N–H···$O_{carboxy}$ hydrogen bond between asparagine molecules by an $O_{hydroxy}$···$O_{carboxy}$ repulsion (Fig. 8b). The adsorption-inhibition is compatible only with a synplanar O=C–O–H conformation (see **10a**) in the host crystal. The concentration of occluded aspartic acid (15%) was sufficient to allow us to establish the conformation of the acid by low-temperature X-ray diffraction (Fig. 8c).

Energy calculations were carried out on the benzamide-benzoic acid system in order to quantify the substrate-additive interactions on the basis of the established mechanism of adsorption and inhibition. To ascertain on which face the additive may be adsorbed with the least loss in energy, relative to the pure substrate molecule, we calculated the binding energies of the additive and substrate molecules at the different symmetry-related sites on the various crystal faces (Fig. 6a). It was found that benzoic acid with a synplanar O=C–O–H conformation is most easily adsorbed on the (011) face, with an energy loss of 7 kcal/mol. This loss of energy relative to benzamide originates primarily from the fact that the amide oxygen atom is a much stronger proton acceptor than the corresponding carboxy oxygen.[22] Once bound, such a benzoic acid molecule interacts with an oncoming benzamide layer with an energy loss as high as 10 kcal/mol relative to a corresponding benzamide molecule adsorbed at the site of the additive. An analogous calculation for the antiplanar conformer of

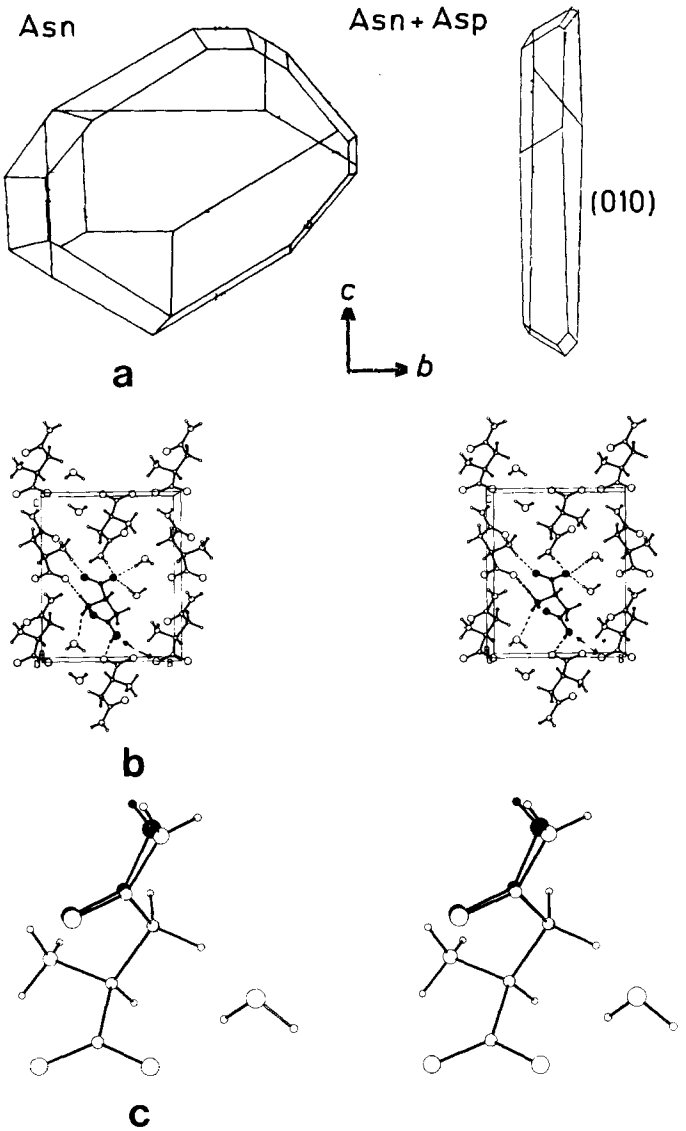


Fig. 8. (a) Crystal morphologies of pure (*S*)-asparagine·H_2O (left) and of (*S*)-asparagine·H_2O grown in the presence of (*S*)-aspartic acid (right); (b) crystal structure (stereoview) of (*S*)-asparagine·H_2O with occluded (*S*)-aspartic acid (full circles); (c) molecular structures (stereoviews) of asparagine and aspartic acid in the crystal structure of asparagine (OH group full circle).

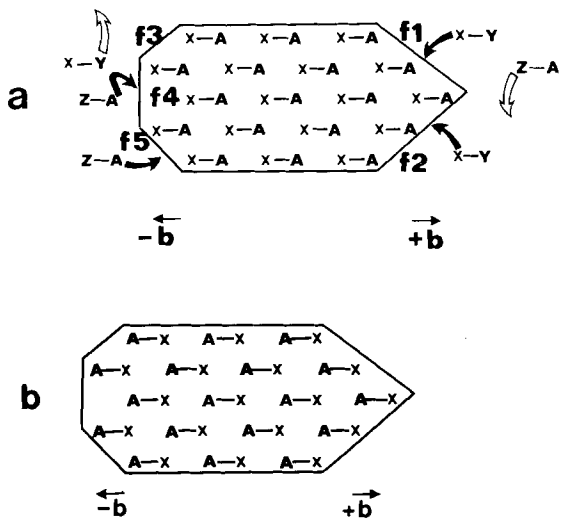
benzoic acid shows that it may be adsorbed and hinder growth only at faces which are experimentally found to be unaffected. This provides further support for the assignment of a synplanar conformation.

These theoretical and empirical considerations allow us both to understand and to predict the induced changes in crystal habit. We shall now show how this knowledge was applied to the solution of certain fundamental problems in stereochemistry.

4. Direct Determination of the Absolute Configuration of Chiral Molecules

Ever since the recognition of chirality in molecules, the direct assignment of the absolute configuration of a chiral molecule in a chiral crystal which develops hemihedral faces has challenged the chemical crystallographer.

The essence of the problem is that conventional X-ray diffraction analysis of chiral crystals (i.e. assumption of Friedel's law) does not allow assignment of the absolute orientation of the chiral molecule with respect to the crystal axes or crystal faces.[25] In other words, it is not possible to distinguish between the polar structure of Scheme 4a



Scheme 4. Schematic representation of the two possible enantiomeric crystal structures (*a*) and (*b*) of the compound X–A with respect to the polar axis *b* (space group $P2_1$); interaction of the polar faces with the additives X–Y and Z–A. a, b see text.

(where the chiral molecule is represented by X-A) and the enantiomeric structure of Scheme 4b (in which the orientation of X-A with respect to the polar *b* axis is reversed). A pictorial representation of a polar motif from a drawing by *Escher* is given in Figure 9.

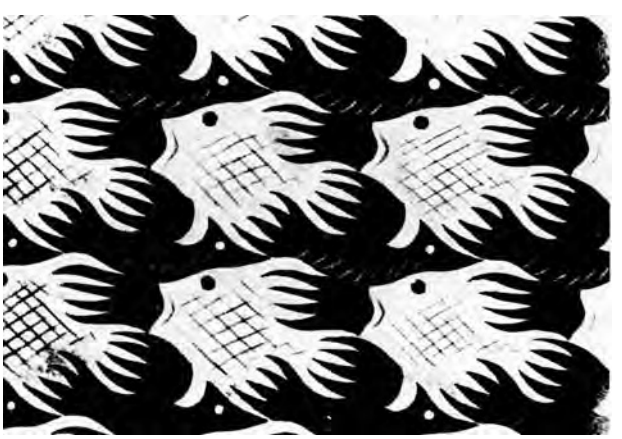


Fig. 9. Drawing by *M. C. Escher* displaying polar symmetry: the fish swim in one direction while the birds fly in the opposite one. (Copyright M. C. Escher heirs, c/o Cordon Art–Baarn–Holland.)

In 1949, *Waser*[26] tried to establish the absolute configuration of (D)-tartaric acid by correlating the relative rates of growth of the hemihedral (*hkl*) and ($\overline{hkl}$) faces with the ease of attachment of the "free" molecule at either face in terms of intermolecular distances between the crystal and the molecule to be attached. In fact, as *Turner* and *Lonsdale* pointed out,[27] given an asymmetric molecule X–A in

a polar crystal, as in Scheme 4, there is no *a priori* reason why, on the basis of intermolecular distances only, the attachment of an X to an "A face" should take place more readily than that of an A to an "X face". The observed differences in development of hemihedral faces may be explained primarily in terms of surface-solvent interactions or polarizability effects.

We developed a new method, based on controlled morphological modifications through adsorption of tailor-made additives, for the direct assignment of the absolute configurations of chiral molecules. First, we shall discuss the case of polar crystals.[28]

4.1. Polar Crystals

Scheme 4 describes an appropriate polar crystal belonging to space group $P2_1$. The unique axis of the crystal is parallel to the X–A direction. Faces f1 and f2 delineate the crystal in the polar $+b$ direction and f3, f4, f5 in the $-b$ direction. The faces within each pair f1, f2, and f3, f5, are homotopic since they are related by 2-fold symmetry. Since the crystal is polar, the structures of the faces at the $+b$ and $-b$ ends are different. By application of the two-step mechanism of adsorption-inhibition, in the crystal of Scheme 4a an inhibitor X–Y will bind selectively at faces f1 and f2, and once bound, will retard growth along $+b$ and possibly other directions but not along $-b$. In an analogous way an inhibitor Z–A will hinder the growth of faces f3, f4 and f5 but not of f1 and f2 (the opposite would happen in the structure of Scheme 4b). Such retardation will be associated either with an increase in the areas of the inhibited faces with respect to the unaffected ones or with the appearance of new faces on the affected side of the crystal. The observed morphological differences between crystals grown in the presence and in the absence of the additive thus establish the direction of the substrate molecule X–A with respect to the polar axis. Consequently, the absolute configuration of the crystal and that of its chiral molecular constituents can be derived.

We shall briefly illustrate here the case of lysine·HCl and cinnamoyl alanine.[28] (*S*)- and (*R*)-lysine·HCl crystallizes from water as a dihydrate in a monoclinic structure of space group $P2_1$. The packing arrangement delineated by the crystal faces of the unaffected crystal is shown in Figure 10 (cf. Fig. 11a). In the crystal the lysine molecules are aligned parallel to the *b* axis with the $^{\oplus}H_3N{-}CH{-}COO^{\ominus}$ moiety emerging from the $+b$ end of the crystal and the ε-$NH_3^{\oplus}$ pointing towards $-b$. In agreement with the analysis presented above, additives with a modified carboxyl or α-amino group, like lysine methyl ester, indeed inhibited growth in the $+b$ direction, inducing development of the (010) face (Fig. 11b). Conversely, additives which bear a modified ε-amino group, like norleucine or norvaline, inhibited growth along the $-b$ direction, with a concomitant pronounced increase in the areas of the $(1\bar{1}0)$ and $(\bar{1}\bar{1}0)$ faces (Fig. 11c).

The observed changes in morphology implied that the occluded inhibitor would be distributed anisotropically along the polar *b* axis of the crystal. This expectation was experimentally confirmed for the crystals of (*S*)-lysine·HCl grown in the presence of (*S*)-norleucine. According to a chromatographic analysis of the material taken from the $+b$ and $-b$ ends of the crystal, the additive was occluded preferentially at the $-b$ end (Fig. 12).

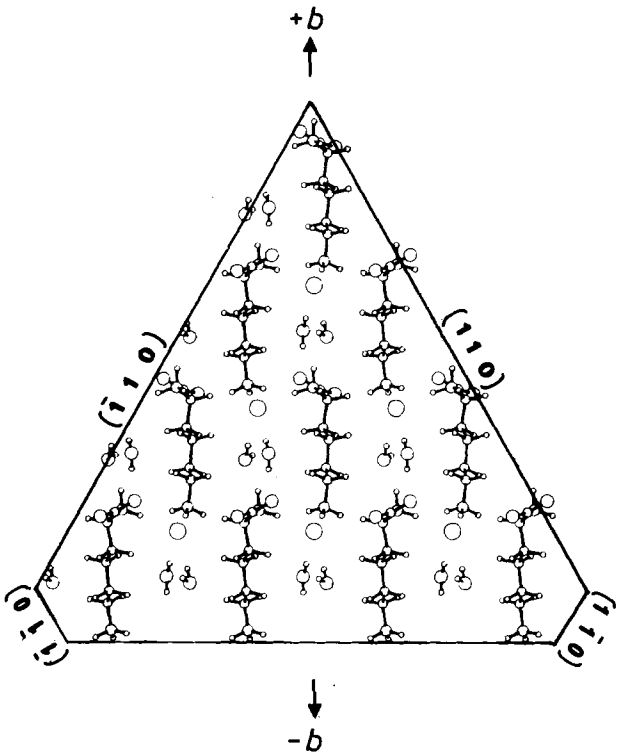


Fig. 10. Packing arrangement of the crystals of (*S*)-lysine·HCl·2 H_2O viewed along the *c* axis, as delineated by the observed {*hk*0} crystal faces.

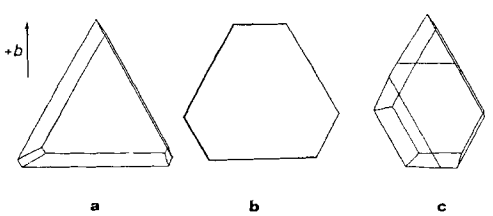


Fig. 11. Computer-drawn pictures of typical crystals of (*S*)-lysine·HCl·2 H_2O viewed along the *c* axis, grown in the presence of: (a) no additives; (b) (*S*)-lysine methyl ester; and (c) (*S*)-norleucine.

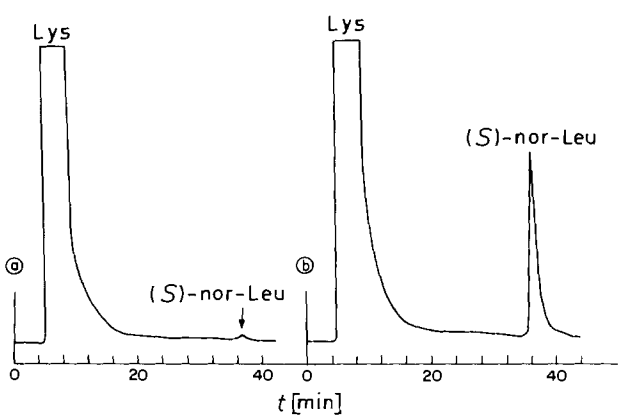


Fig. 12. HPLC analysis of (*S*)-norleucine occluded at the two opposite sides of the polar *b* axis of crystals of (*S*)-lysine·HCl·2 H_2O. In experiments ⓐ and ⓑ the analyses were performed on equal amounts of (*S*)-lysine·HCl·2 H_2O.

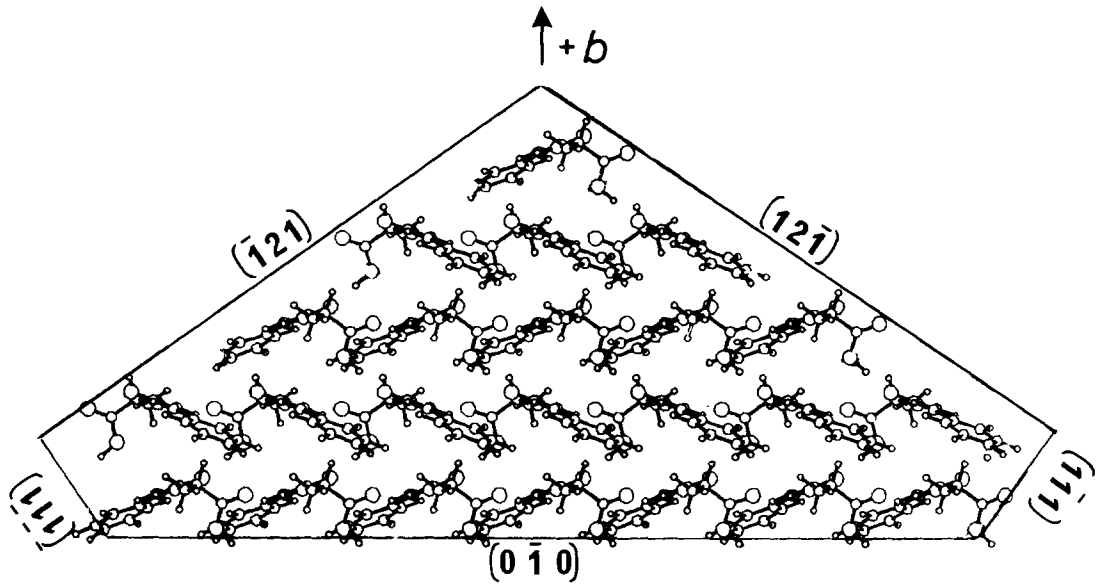


Fig. 13. Packing arrangement of the crystals of cinnamoyl-(*S*)-alanine as delineated by the observed {*hkl*} crystal faces.

Cinnamoyl alanine crystallizes in space group $P2_1$ (cinnamoyl = *trans*-3-phenylpropenoyl). In the crystal structure of the (*S*)-enantiomer all the OH groups form hydrogen bonds with a major component along $-b$, while the C(chiral)–H bond is directed along $+b$. Figure 13 shows the orientations of the molecules with respect to the crystal faces. The pure crystals are depicted in Figure 14a.

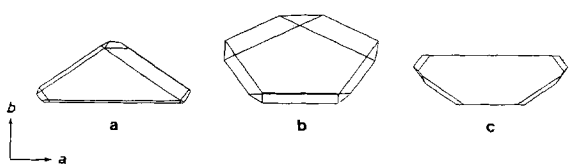


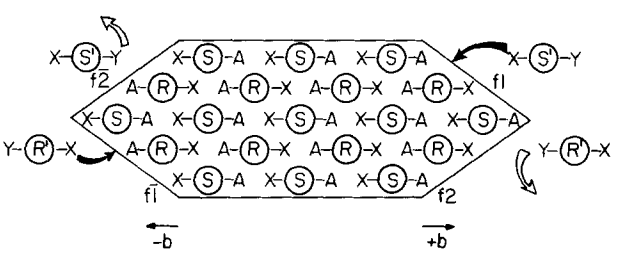
Fig. 14. Computer-drawn pictures of typical crystals of cinnamoyl-(*S*)-alanine (viewed along the *c* axis) grown in the presence of: (a) no additive; (b) methyl cinnamoyl-(*S*)-alaninate; and (c) cinnamoyl-(*R*)-alanine.

We found, as expected, that the methyl ester of the substrate with the same absolute configuration induced large ($1\bar{1}1$) and ($\bar{1}\bar{1}\bar{1}$) faces (Fig. 14b), thus fixing the absolute direction of the O–H bond with respect to the polar axis and hence also the absolute configuration of the substrate molecule. On the other hand cinnamoyl (*R*)-alanine, of configuration opposite to that of the host, induced, as expected, formation of an (010) face (Fig. 14c), because adsorption of this molecule can take place only from the $+b$ side of the crystal since the $C-CH_3$ group of the inhibitor points away from the surface along the $+b$ direction.

Application of the present analysis to the morphological differences observed by *Smythe*[6] in polar crystals of sucrose grown in the presence and in absence of raffinose (and other di- and tri-saccharides), enabled us to assign the absolute configurations of these sugars.

4.2. Enantiopolar Crystals

The above method of determining absolute configuration is not limited to the molecules in polar crystals, but is also applicable to chiral molecules which induce morphological changes in centrosymmetric crystals composed of racemic mixtures or meso compounds.[29,30] The method is based on the fact that, unlike chiral crystals, in centrosymmetric ones the orientations of the constituent molecules with respect to the crystal axes are unambiguously assigned by conventional X-ray analysis. The known orientation of the enantiomers in such crystals can be exploited for the direct assignment of the absolute configuration of chiral resolved additive molecules, provided this structural information can be transferred to such molecules. The absolute configuration of the resolved additives is determined through the morphological changes they selectively induce on the enantiotopic faces of appropriately selected crystals.



Scheme 5. Structure of an enantiopolar crystal and interaction of the enantiotopic faces with enantiomeric additive molecules, schematic.

A prerequisite for application of this method is that within the centrosymmetric racemic crystal a specific functional group (A) attached to an (*R*)-molecule will point towards the face f$\bar{1}$ but not towards f1 (Scheme 5). Correspondingly, the same functional group attached to an (*S*)-molecule will emerge at the enantiotopic face f1, but not at f$\bar{1}$. It is useful here to regard centrosymmetric crystals containing chiral molecules as enantiopolar. We define an enantiopolar crystal as comprising two enantiomeric sets of intermeshed polar crystal structures related to each other by symmetry elements of the second kind, e.g. a center of

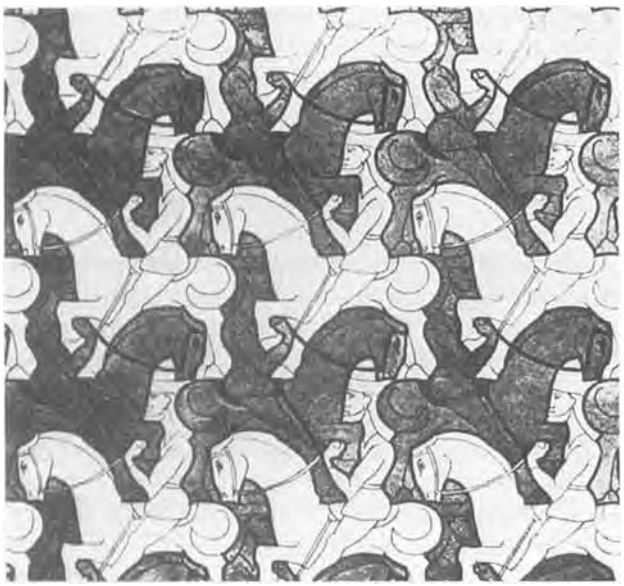
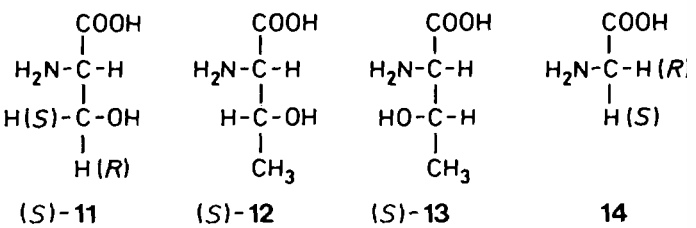


Fig. 15. Drawing by *M. C. Escher* displaying enantiopolar symmetry: treating the white and the black horses as chiral objects of opposite handedness, the two enantiomeric ensembles of the white and the black horses are enantiopolar, pointing in opposite directions along the horizontal axis. (Copyright M. C. Escher heirs, c/o Cordon Art—Baarn—Holland.)

inversion or a glide plane. This is also neatly illustrated in a drawing by *Escher* (Fig. 15). Crystallization of such compounds in the presence of a chiral additive R', appropriately designed so that it will fit in the site of an (R)-molecule on the growing crystal faces f$\bar{1}$ or f$\bar{2}$, but not on the enantiotopic faces f1 or f2, will hinder growth along the $-b$ direction but not along $+b$. By virtue of symmetry, the enantiomeric additive (S') will inhibit growth of faces f1 and f2, while the racemic additive ($R'S'$) will inhibit growth along both directions, $+b$ and $-b$.

These principles were applied to the monoclinic crystals of (RS)-serine[29] and glycine.[30] Racemic serine crystallizes in a molecular packing appropriate for this analysis, space group $P2_1/a$ (Fig. 16). Within the structure, the C–H(Si)-bond vector[*] of the rigid methylene group of (R)-serine has a major component along $+b$ and, by symmetry, the C–H(Re)-bond vector of the (S)-serine (S)-**11** along $-b$.



Thus, their replacement by a methyl, as in threonine, will inhibit growth along the b direction. Namely an (R)-threonine molecule with the side-chain β-carbon of chirality (S), will inhibit growth along $+b$, while the $-CH_3$ group of (S)-threonine will replace the pro-(Re) hydrogen of (S)-serine and hence inhibit growth along $-b$; (R)- and (S)-threonine are (2R,3S)- and (2S,3R)-configurated, respectively.

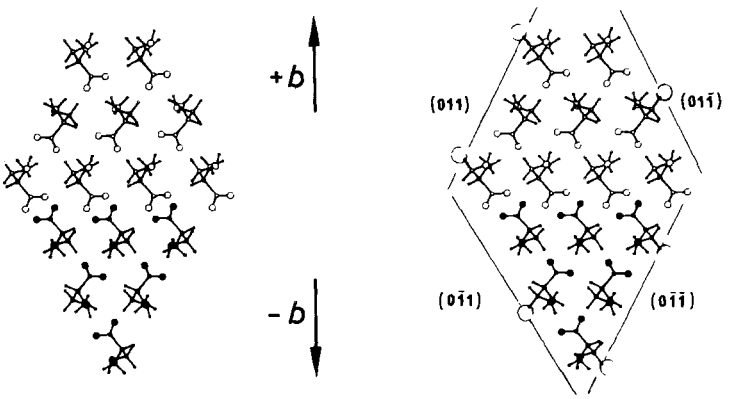


Fig. 16. Packing of (*RS*)-serine viewed along the *a* axis (stereoview). The enantiomers are packed in homochiral *bc* layers: for clarity only half of each *R* (open circles) or *S* (full circles) molecular layer is shown, delineated by the four {011} crystal faces.

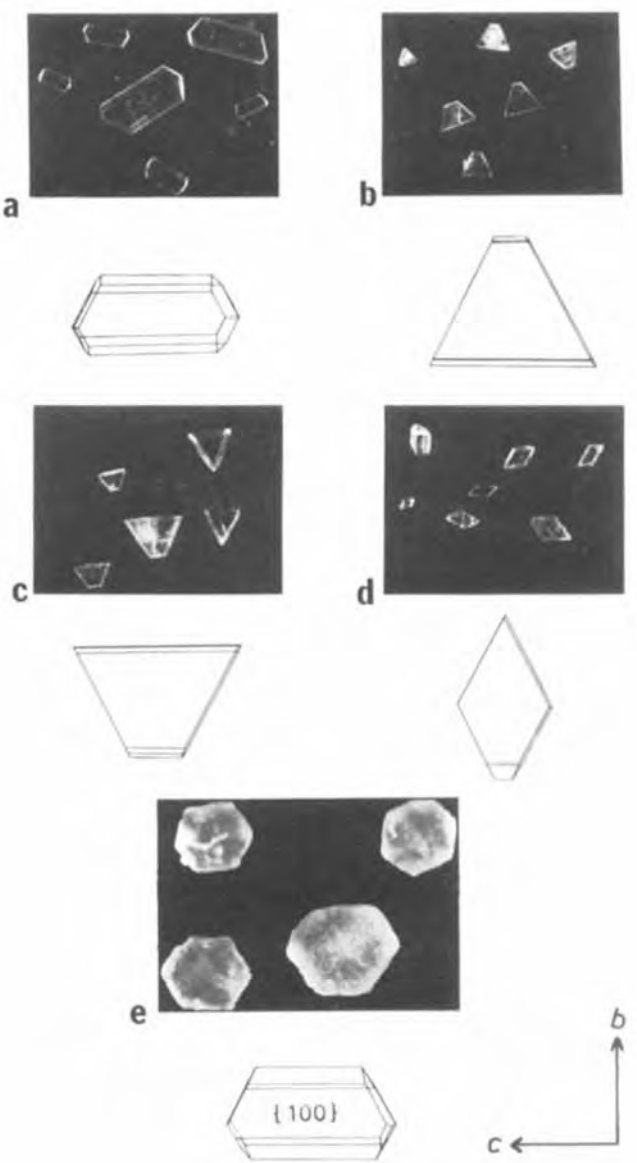


Fig. 17. Photographs and computer-drawn pictures of crystals of (*RS*)-serine grown in the presence of: (a) no additives; (b) (*R*)-threonine; (c) (*S*)-threonine; (d) (*RS*)-threonine; and (e) (*R*)- or (*S*)-allothreonine ((2*R*,3*R*)- and (2*S*,3*S*)-configurated, respectively).

[*] H(Si) denotes the *pro-S* H-atom and H(Re) the *pro-R* H-atom.

(*RS*)-serine forms tabular crystals, with point symmetry $2/m$ (Fig. 17a); the crystals affected by either (*R*)- or (*S*)-threonine exhibit reduced morphological symmetry 2 (the mirror plane is lost) and are enantiomorphous (Fig. 17b and 17c, resp.). When (*RS*)-threonine is used as additive, the morphological symmetry $2/m$ is left unchanged as a result of a combination of the effects induced by each additive separately. The crystals turn into rhombs (Fig. 17d).

The morphological changes, and our interpretation thereof, imply that in this last experiment (*RS*)-threonine must segregate along the *b*-axis during crystal growth; occluded (*R*)-threonine will prevail in the $+b$ half of the crystal, whereas (*S*)-threonine will prevail in the $-b$ half. This expectation was confirmed experimentally by HPLC analyses (Fig. 18a, b, c) through work done in collaboration with *S. Weinstein* using the chiral mobile phase of *N,N*-dimethyl-(*S*)-valine and cupric acetate.[31]

The discriminative power of the various faces of a crystal of (*RS*)-serine is further manifested by the differences

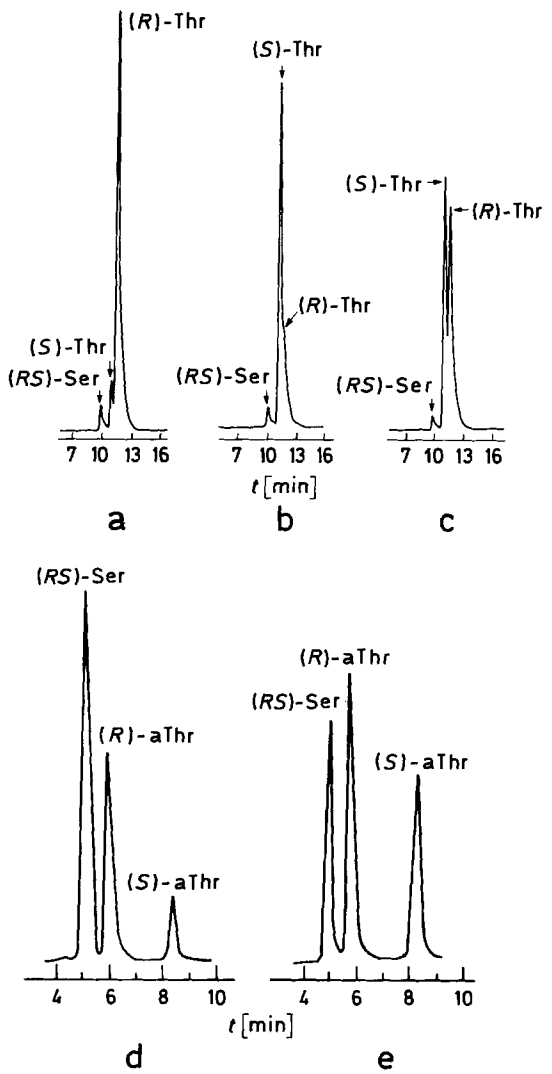


Fig. 18. Enantiomeric analysis of threonine occluded in the rhomb-like crystals of (*RS*)-serine (Fig. 17d) after separation of serine by cation exchange: Material taken from: (a) tip of the crystal at the $+b$ end; (b) tip of the same crystal at the $-b$ end; (c) whole crystal. Enantiomeric analysis of allothreonine (Fig. 17e) occluded in (*RS*)-serine crystals: (d) from the $+b$ end; (e) from the $-b$ end.

in morphology induced by the additives threonine as against allothreonine (cf. (*S*)-**13**, and Fig. 17d and 17e, resp.). The established mechanism of adsorption-inhibition allows a rationalization of this difference. The relative orientation of molecular serine *vis-à-vis* its various crystal faces, suggests that allothreonine can be adsorbed on the homotopic {100} faces as well as on the enantiotopic {011} faces[*] (Fig. 17e).

This would imply that no distinct morphological differences can be expected between (*RS*)-serine crystals grown in the presence of resolved or racemic allothreonine, as was indeed observed (Fig. 17e). Furthermore, (*R,S*)-allothreonine, in contrast to (*RS*)-threonine, should not segregate enantiomerically along the *b* axis; this was confirmed by HPLC analysis of tips of the crystal which were taken from the opposite ends of the *b* axis (Fig. 18d, e). The effect of threonine and allothreonine on the crystals of (*RS*)-serine is further independently explained by dissolution experiments (see Section 6) and by atom-atom potential energy calculations.[32]

According to the surface binding energies of the additives threonine and allothreonine relative to pure serine at several crystal faces, (*R*)-threonine may be easily adsorbed only on faces (011) and (01$\bar{1}$) and, by symmetry, (*S*)-threonine should preferably adsorb on (0$\bar{1}\bar{1}$) and (0$\bar{1}$1); in fact threonine is better bound than substrate serine by 3 kcal/mol. (*S*)-allothreonine may be easily adsorbed on {100}, (011) and (01$\bar{1}$), and, by symmetry, (*R*)-allothreonine on faces {100}, (0$\bar{1}\bar{1}$) and (0$\bar{1}$1). The binding energies of allothreonine relative to serine are -2.1 kcal/mol at {100} and -0.7 kcal/mol at {011}. These results are completely compatible with experiment. In particular, we account for the observation that the resolved and racemic allothreonine do not induce obvious changes in habit because they can each be adsorbed on two principal faces. Moreover, the possibility of occluding (*R*)- and (*S*)-allothreonine through the large {100} faces masks any enantioselective segregation along the *b* axis in accordance with the HPLC results (Fig. 18d, e).

The ability of the serine crystals to recognize the subtle differences between diastereotopic hydrogens suggested that the crystal of prochiral glycine may serve as a matrix for the assignment of absolute configuration of all the chiral α-amino acids.[30] The glycine molecule, although nonchiral, has two prochiral hydrogen atoms, H(*R*) and H(*S*). In the α-modification of the crystal with space group $P2_1/n$ (Fig. 19), the glycine molecules form two enantiopolar sets, which are represented in Figure 19 by shaded and nonshaded atoms, respectively. All the molecules in the nonshaded set have the C–H(*R*) bond aligned with the *b* axis and pointing towards $+b$, so that C–H(*R*) emerges from the (010) face, while C–H(*S*) lies almost perpendicular to it in the *ac* molecular layer. Only an (*R*)-amino acid additive, whose side chain will be parallel to the C–H(*R*) bond, can be adsorbed at the (010) face and would subsequently hinder the crystal growth perpendicular to it. By virtue of symmetry, an (*S*)-amino acid can be adsorbed only at the (0$\bar{1}$0) face.

[*] The symbol {*hkl*} represents all the symmetry related faces, e.g. in serine, {011} denotes (011), (0$\bar{1}$1), (01$\bar{1}$) and (0$\bar{1}\bar{1}$) faces. The symbol (*hkl*) represents only the specified (*hkl*) face.

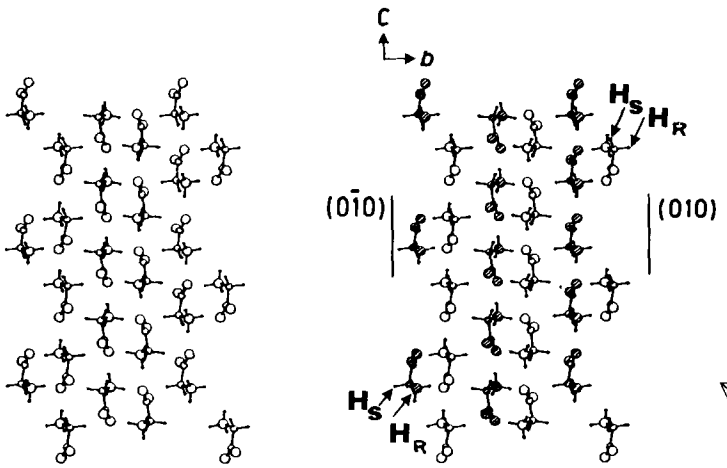


Fig. 19. Packing of glycine crystals with layers of glycine molecules parallel to the *ac* plane (stereoview along the *a* axis). The two enantiopolar sets are represented by shaded and nonshaded molecules.

Pure glycine crystallizes from water in the form of bipyramids, with the *b* axis perpendicular to the base of the pyramid (Fig. 20a). It was observed that all natural (*S*)-amino acids, apart from proline, induce a dramatic morphological change at the $-b$ side of the crystals, with the appearance of pyramids exhibiting a predominant (0$\bar{1}$0) face (Fig. 20b). All (*R*)-amino acids induce the development of a large (010) face (Fig. 20c), while a racemic additive causes crystallization of {010} platelets (Fig. 20d).

Amounts in the range 0.02 to 0.2% of the additives were found in the bulk of the glycine crystals. HPLC analysis (Fig. 21) of these occluded α-amino acids inside single

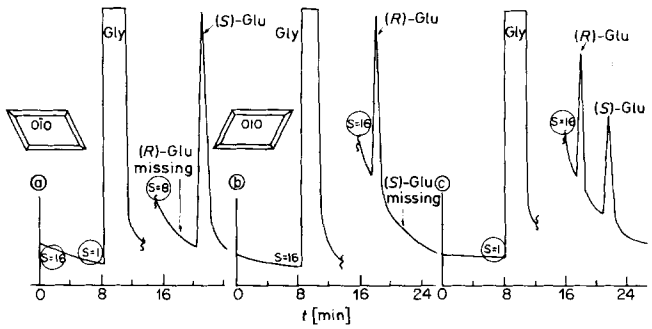


Fig. 21. Enantiomeric distribution of occluded (*RS*)-glutamic acid in the {010} plate-like crystals of glycine by HPLC: (a) Only additive (*S*)-glutamic acid is present in material shaved from the (0$\bar{1}$0) face of the crystal; (b) only additive (*R*)-glutamic acid is present in material shaved from the (010) face; (c) relative distribution of (*RS*)-glutamic acid in the remaining whole crystal. S = sensitivity in arbitrary units.

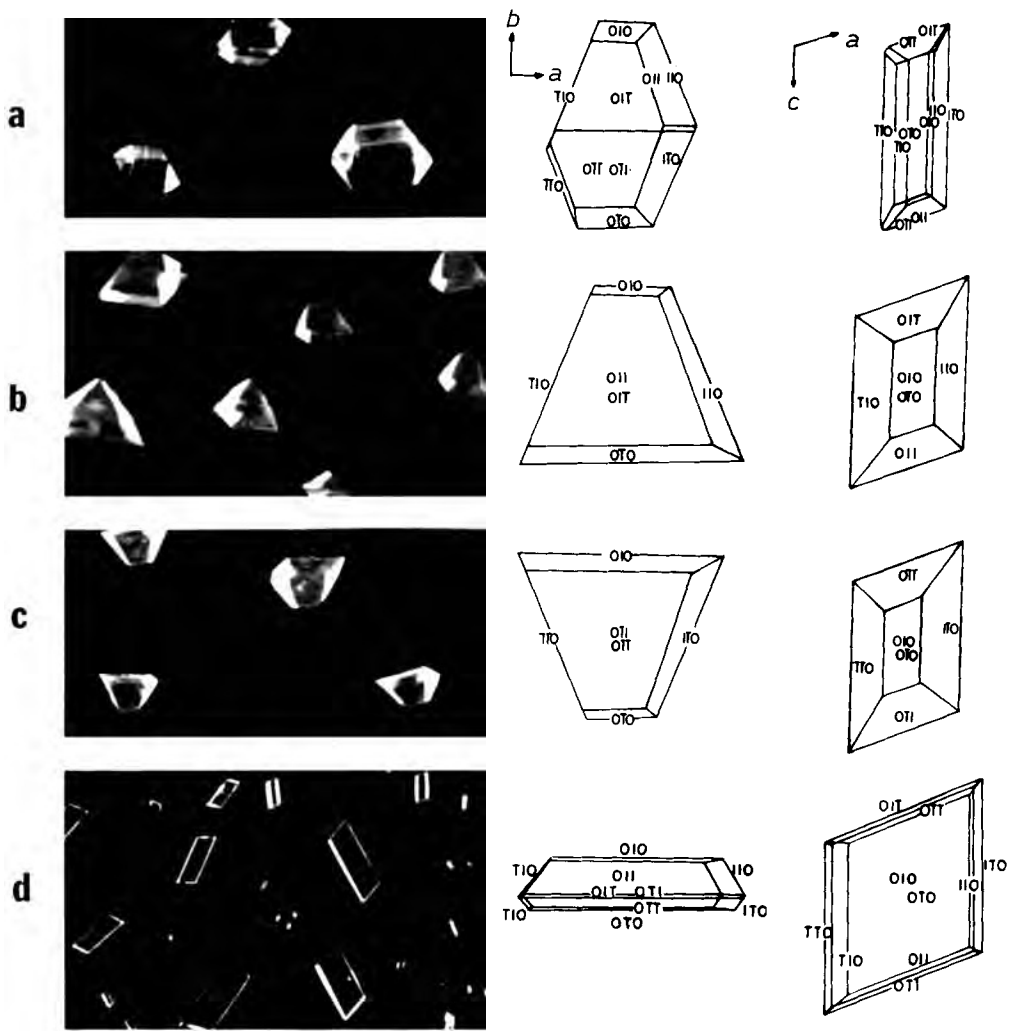


Fig. 20. Comparison between crystals of α-glycine grown in the presence of: (a) no additives; (b) (*S*)-α-amino acids; (c) (*R*)-α-amino acids; (d) racemic α-amino acids.

plate-like crystals of glycine demonstrated a total enantioselective segregation along the b axis; as expected, the (R)-amino acids predominate in the $+b$ half of the crystal and the (S)-amino acids in the $-b$ half. This segregation suggests that the overall symmetry of the crystal has been lowered from $P2_1/n$ to $P2_1$.

The changes in crystal habit of glycine as studied by potential energy calculations[30] were completely consistent with the above-mentioned observations.

5. A New Model for Spontaneous Generation of Optical Activity

The results reported on the glycine system acquire further interest as the {010} plate-like crystals of glycine, grown in the presence of other (*RS*)-α-amino acids, have a tendency to float at the air/water interface with the b-axis perpendicular to the interface.[33] Each such floating crystal will grow either along its $+b$ or $-b$ direction, depending upon whether face (010) or ($0\bar{1}0$) is pointing towards the water solution. Thus, if a single crystal of glycine exposes its (010) face to a solution of glycine containing a mixture of (*RS*)-amino acids, only the (*R*)-acids will be occluded, if the ($0\bar{1}0$) face is exposed to the solution, the (*S*)-acids will be occluded. HPLC analysis of the enantiomeric content of the occluded amino acids indeed confirmed these expectations. Such resolutions of (*RS*)-leucine and (*RS*)-valine are shown in Fig. 22a, b, c.

It is clear that in a racemic mixture there is equal probability for a given crystal to float on its (010) or ($0\bar{1}0$) face. We have observed, however, that if glycine is crystallized in the presence of small amounts of resolved amino acids bearing hydrophobic side chains, like (*S*)-leucine, (*S*)-phenylalanine, or (*S*)-α-aminooctanoic acid, the floating crystals of pyramidal shape always expose their ($0\bar{1}0$) face to the air. In fact, when crystals were grown in the presence of equal amounts of two amino acids with side chains of different character and opposite absolute configuration, for example (*S*)-leucine with (*R*)-glutamic acid or (*R*)-alanine, or (*R*)-serine, all the resulting platelets had their ($0\bar{1}0$) faces directed to the air. This indicates that stereospecifically adsorbed leucine molecules are capable, even in tiny amounts, of orienting the glycine crystals by virtue of the hydrophobic character of their side chains.

The tendency of leucine molecules to orient floating glycine crystals and the enantioselective adsorption at the face exposed to the solution were exploited to induce resolution of racemic amino acids by crystallization of glycine at interfaces in the presence of resolved leucine; for example glycine, grown in the presence of racemic hydrophilic amino acids plus small amounts of (*S*)-leucine, yielded platelets all floating with their ($0\bar{1}0$) faces pointing upwards, thus selectively occluding the (*R*)-enantiomers (Fig. 23a, b). Furthermore, even under conditions where polycrystalline crusts of glycine were formed (Fig. 23c, d) resolution occurred with an enantiomeric excess higher than 70% (Fig. 23d) in the examples studied. This effect was also demonstrated visually by the formation of polycrystalline crusts of glycine grown in the presence of (*S*)-leucine + N^{ε}-(2,4-dinitrophenyl)-(*S*)-lysine and (*R*)-leucine + N^{ε}-(2,4-dinitrophenyl)-(*S*)-lysine. We obtained respectively colorless and colored crusts of glycine (Fig. 5d, e in Section 2).

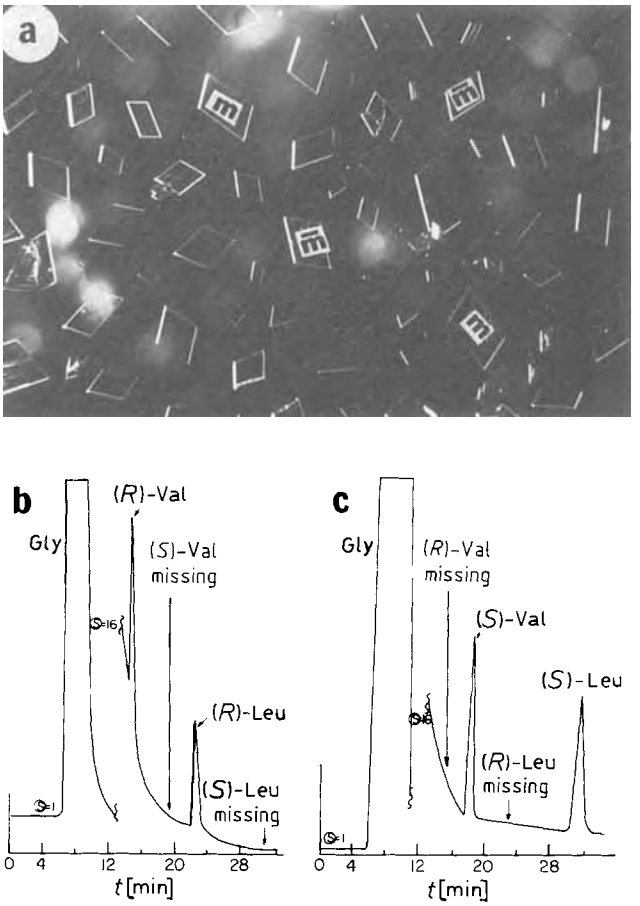


Fig. 22. (a) Floating plate-like crystals of glycine grown from a water solution (4.4 M) containing racemic 1%-w/w (*RS*) leucine and 1%-w/w (*RS*)-valine. The crystals display both enantiomorphous morphologies, labelled m and $\bar{m}$; (b) HPLC analysis of crystals m with the (010) face exposed to solution, after washing with water; (c) HPLC analysis of glycine crystals $\bar{m}$ with the ($0\bar{1}0$) face exposed to the solution after washing with water.

The experiments described above provide us with a possible model for the generation and amplification of optical activity in an initially symmetrical world. Let's assume that the first plate-like crystal of glycine formed from the 'prebiotic soup' floats with its (010) face upward. During growth the crystal will occlude exclusively the (*S*)-amino acids present in the "soup", thus leaving the solution enriched in the (*R*)-enantiomers. The excess of hydrophobic (*R*)-amino acids so generated will in turn direct the floating of later-formed crystals with their (010) faces again upward, thus ever further enriching the solution with (*R*)-enantiomers.

6. "Tailor-Made" Etchants for Organic Crystals

Growth and dissolution of crystals are considered reciprocal processes that can be interchanged by altering the degree of saturation of the solution. This implies that an inhibitor of growth of a given crystal face must in principle affect the rate of dissolution of that same face.[5] In order to

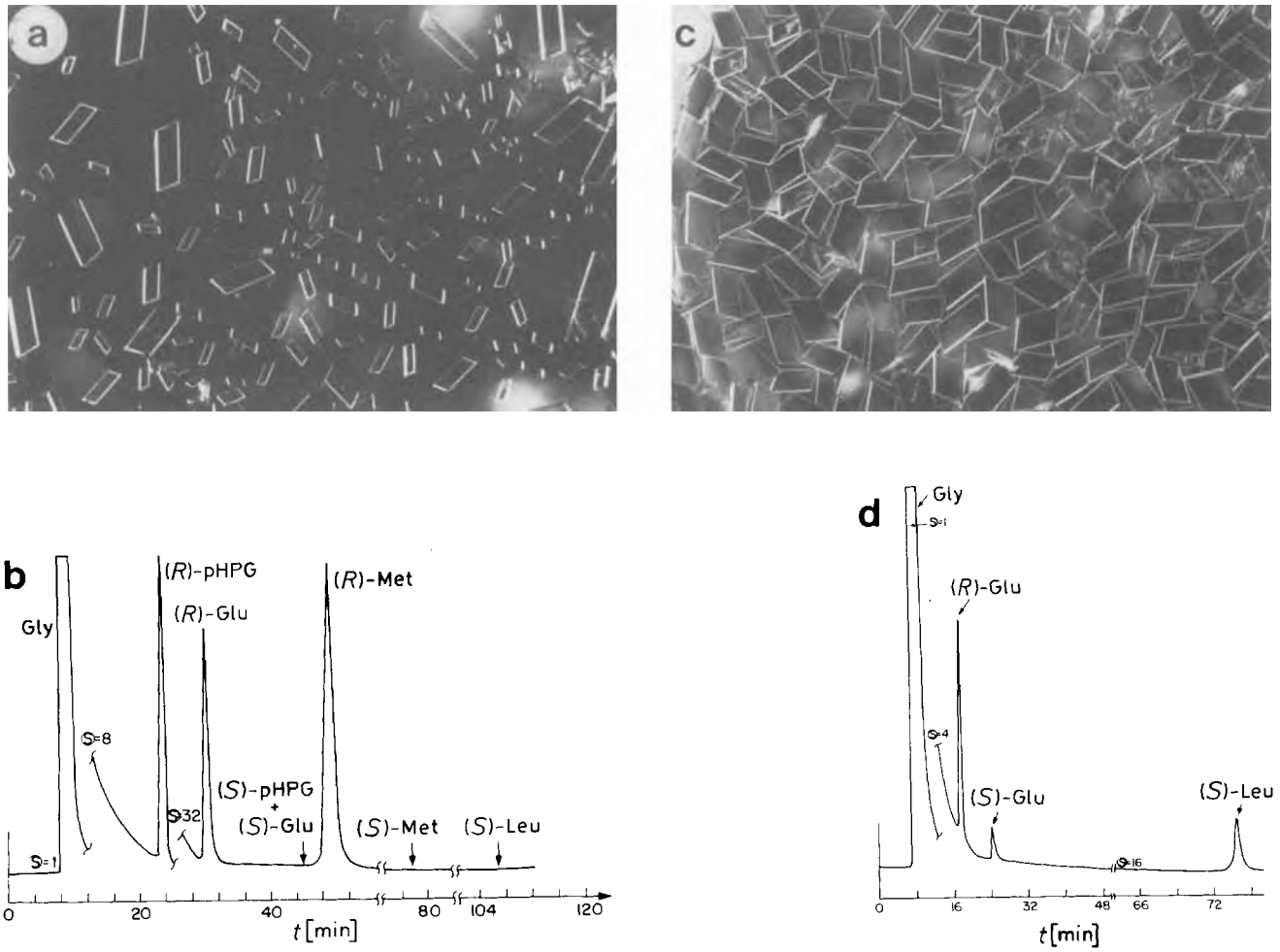


Fig. 23. (a) Floating plate-like crystals of glycine grown in the presence of 1%-w/w (*S*)-leucine and racemic *p*-hydroxyphenylglycine (0.5% w/w), racemic glutamic acid (1%) and racemic methionine (0.5%). All the crystals float with their $(0\bar{1}0)$ faces exposed to air and exhibit the same enantiomorphous morphology; (b) HPLC analysis of the enantiomers of *p*-hydroxyphenylglycine (pHPG), glutamic acid, methionine and leucine occluded inside the crystals; only the (*R*)-enantiomers of pHPG, glutamic acid and methionine are found; (c) crystalline crust of glycine grown at the air/water interface. The aqueous solution (4.4 M) contains 1%-w/w (*S*)-leucine and 3%-w/w racemic glutamic acid; (d) HPLC analysis of the same crust, indicating an *ee* of 70% of occluded (*R*)-glutamic acid.

test this reciprocity, a systematic study was undertaken on crystal dissolution in the presence of "tailor-made" growth inhibitors. As models, we investigated some of the systems we described above for crystal growth.[34]

Plate-like crystals of glycine (see Sections 4 and 5) with well-developed {010} faces were submitted to partial dissolution in an undersaturated solution of glycine containing variable amounts of other α-amino acids. When resolved (*R*)-alanine was present in the solution, well-developed etch-pits were formed only on the (010) face. These pits exhibit twofold morphological symmetry with surface edges parallel to the *a* and *c* axes of the crystal (Fig. 24a). The enantiotopic $(0\bar{1}0)$ face dissolved smoothly (Fig. 24b), exactly as it does when the crystal is dissolved in an undersatu-

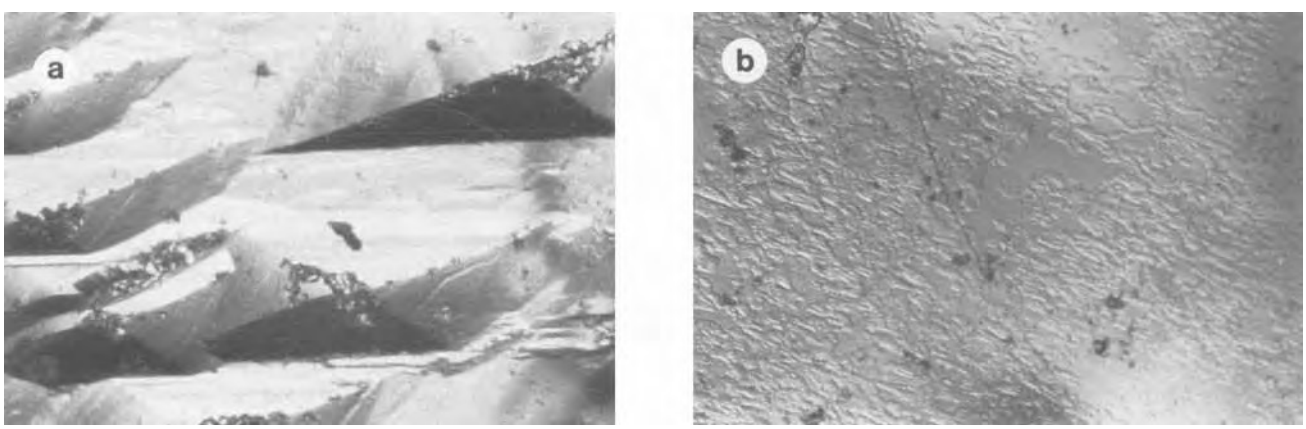


Fig. 24. Optical microscope pictures (×50) of the {010} faces of a glycine crystal after partial dissolution in the presence of (*P*)-alanine: (a) the (010) face; (b) $(0\bar{1}0)$ face.

rated solution of pure glycine. As expected, (*S*)-alanine induced etch-pits on the (0$\bar{1}$0) face. Racemic (*RS*)-alanine etches both {010} faces.

An explanation of these, and other similar results, takes into consideration that dissolution from a given surface is considered to begin at sites of emerging dislocations.[35] At these sites, more than one type of facial surface is exposed to the solvent (Scheme 6). The dissolution front propagates



Scheme 6. Formation of etch pits at the sites of emerging dislocations as a result of selective binding of additive to the horizontal faces.

from these centers in various directions, at the same relative rates as for their growth. Under such circumstances the overall shape of the crystal is preserved. On the other hand, when an additive which binds selectively to a given face of the crystal is present in the solution, the crystal will dissolve in different directions with rates which differ from those in pure solvent. As a result, the rate of dissolution in a direction perpendicular to the affected face will decrease relative to that perpendicular to the unaffected ones, and etch pits will be formed at the dislocation centers on the former faces.

The generality of the above stereochemical correlation was tested for all the systems described above, including serine/threonine and serine/allothreonine (see Section 4) and for the enantiomorphous pairs of glutamic acid·HCl and of asparagine·H_2O. When rhomb-like crystals of (*RS*)-serine are partially dissolved in the presence of (*R*)-threonine, well formed etch-pits develop at the (011) and (01$\bar{1}$) faces (see Figs. 16, 17). By virtue of symmetry, similar etch-pits form at the (0$\bar{1}$1) and (0$\bar{1}\bar{1}$) faces when (*S*)-threonine is present in the solution. In neither experiment were etch-pits formed at the {100} faces. On the other hand, both resolved and racemic allothreonine etch primarily the {100} faces, in keeping with the results of the morphological and segregation studies and with theoretical calculations.

The present method was also exploited for the manual separation of a pair of enantiomorphous crystals. For example, when a crystalline conglomerate of asparagine·H_2O was partially dissolved in a solution of (*S*)-aspartic acid, well formed etch-pits were formed only on the {010} faces of the (*S*)-crystals, but not on the (*R*)-enantiomorph (Fig. 25). The treated enantiomorphous crystals are thus visually distinguishable and, therefore, separable.

In several ways the etching experiments yield results complementary to those obtained from the studies on morphological changes and enantiomeric segregation. On the other hand, etching provides a unique probe for differentiating between the two steps of binding of inhibitor and retardation of growth. Furthermore, the etching experiments should provide a decisive insight into those systems where the inhibitors appear to bind at one face but retard growth at another. In addition, increase of the surface area upon etching by the additives should influence the overall rate of the crystal dissolution. This approach is currently

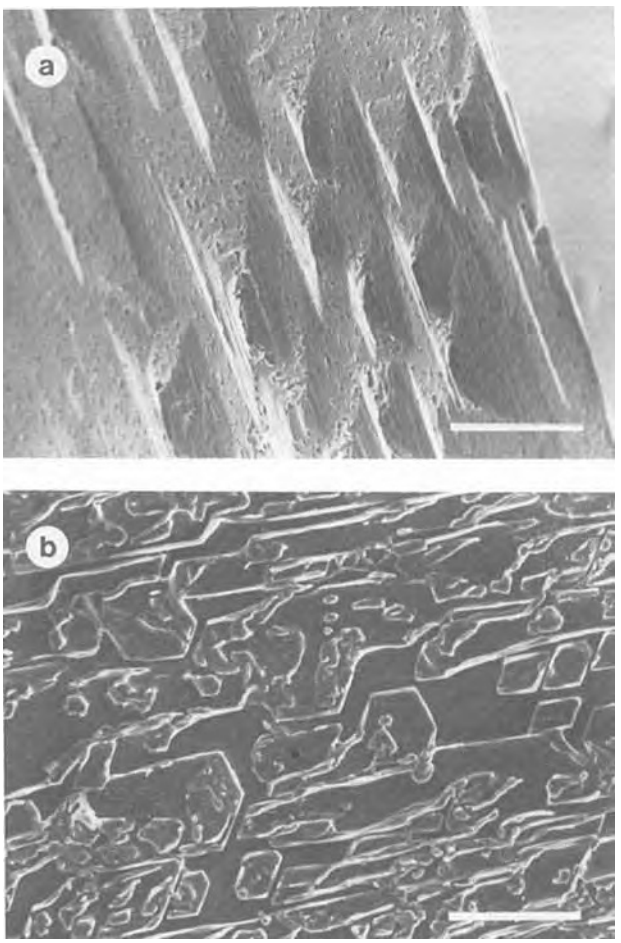


Fig. 25. Scanning electron micrograph of the (010) face of crystals of asparagine partially dissolved in the presence of (*S*)-aspartic acid; (a) (*S*)-asparagine crystal; (b) (*R*)-asparagine crystal. White line: 100 μm.

being resorted to for increasing the rate of dissolution of organic crystals in general, and of sparingly soluble drugs in particular.

7. Simulation of Crystal Morphology by Energy Calculations

Atom-atom potential energy calculations were undertaken in order to gain an understanding of crystal morphology in terms of the intermolecular interactions between substrate molecules in the crystal bulk, and between substrate and solvent or substrate and additive at the crystal solvent interface.

A controlling factor in crystal growth is the energy of the interactions between neighboring molecules. According to *Hartman* and *Perdok*,[36] the crucial relationship is between the attachment energy E_{att}, the energy per molecule released when a new layer is attached to the crystal face, and the layer energy E_l which is defined as the energy per molecule released when a new layer is formed. E_l measures the stability of a layer and E_{att} controls the growth rate perpendicular to this layer. Studies on the relationship between the internal structure of the crystal and its morphology led to the working hypothesis that the morphological importance of a crystal face decreases with increasing at-

tachment energy. From the known crystal structure it is possible to calculate the corresponding values of E_{att} for various low-index faces. This information is used to derive the theoretical form, i.e., the calculated morphology of the crystal which best represents the crystal habit obtained by sublimation.[37,38] To derive the habit of the crystal grown from solution in the presence or absence of additives, substrate-solvent and substrate-additive interactions at the crystal-solution interface must be taken into account.

7.1. The Theoretical Form of Glycine and the Solvent Effect

The theoretical crystal form of glycine, depicted in Figure 26 (left), is in nice agreement with the morphology of glycine crystals obtained by sublimation (Fig. 26, right). Its habit is distinctly different from that of glycine grown from aqueous solution. The most striking differences between the two forms (Fig. 26 and Fig. 20, resp.), are the complete disappearance in the latter of the {001} and {10$\bar{1}$} faces, the formation of {011}, and the drastic reduction in relative area of {010}. We account for these differences in terms of the higher affinity of the water solvent for the crystal faces {110} and {011} than for {010} and {001}.

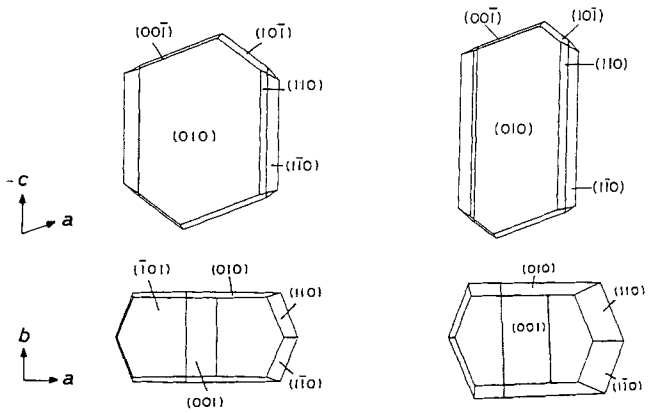


Fig. 26. left: Theoretical crystal form of glycine; right: morphology of glycine crystals obtained by sublimation.

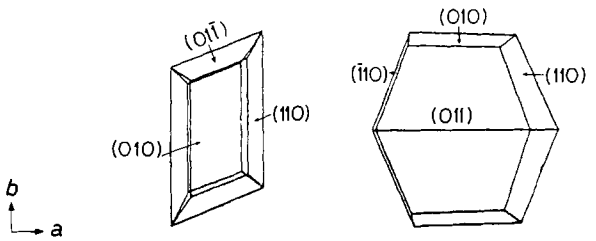


Fig. 28. Calculated crystal form of glycine incorporating the solvent effect.

To establish the relative hydrophilic affinities of these faces the Coulomb potential energy was calculated at closest approach distances from the surface of each of the four faces (Fig. 27). From these maps we may conclude that the {010} face is the least polar and (011) the most polar face. Thus, preferential adsorption of water molecules on the polar faces, primarily on {011}, causes a reduction in the growth rate normal to these faces relative to that of {010}, with a concomitant increase in their surface areas. When this solvent effect was simulated in the calculation of the theoretical form[37,38] we obtained the habit shown in Figure 28, which is in agreement with the observed morphology (Fig. 20a). Several other systems were studied, in-

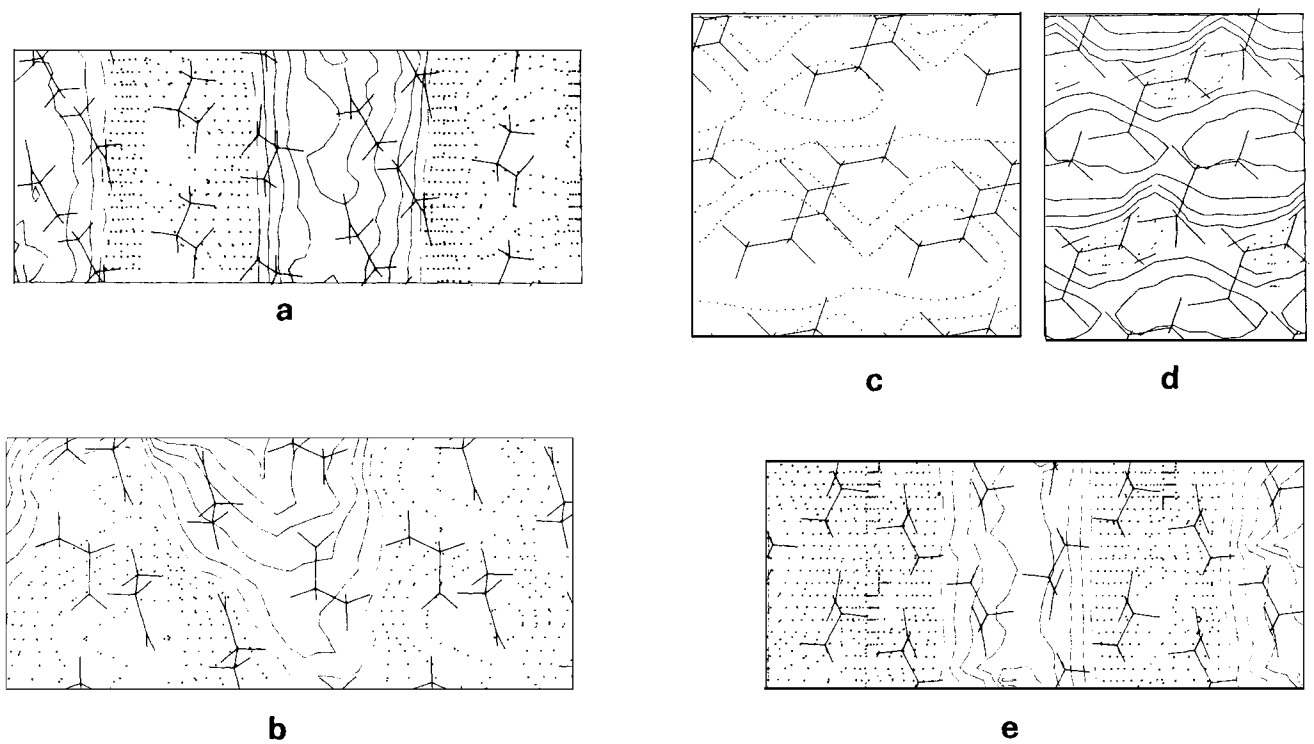


Fig. 27. Electrostatic potential energy maps at closest approach distances of a unit positive charge from the surfaces of various glycine crystal faces. Solid contour lines represent repulsive energies, and broken lines attractive energies. (a) {011} faces; (b) {110} faces; (c) {010} faces at the layer exposing the C–H bonds (i.e. unshaded molecules at the (010) surface in Fig. 19). (d) {010} faces at the layer exposing the NH bonds (i.e. the shaded molecules at the (010) surface in Fig. 19). (e) {001} faces.

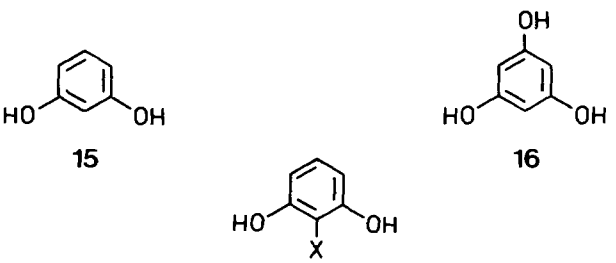
cluding benzamide, cinnamide[24,38], and serine[29,32], and yielded theoretical forms consistent with the observed habits.

7.2. The Riddle of Resorcinol

Polar crystals are ideal for elucidating the effect of solvent on crystal growth, because the difference in growth rates of opposite faces (*hkl*) and ($\bar{h}\bar{k}\bar{l}$) along a polar direction originate primarily from the differences in their solvent-surface interactions. However, due to the practical difficulty in determining the absolute polarity of crystals, in particular for crystals composed of nonchiral molecules and containing light atoms only, this approach has been somewhat neglected to date. Our technique of "tailor-made" additives for the determination of the absolute configuration of crystals, allowed us to tackle such a problem and clarify the influence of solvent on growth of the polar crystal of α-resorcinol, **15**.

In 1949, *Wells*[39] found that in an aqueous solution the α-form of resorcinol (space group $Pna2_1$) grows unidirectionally along the polar *c* axis. The crystal (Fig. 29, left) exhibits "phenyl-rich" (011) and ($0\bar{1}1$) faces at one end of the *c* axis and "hydroxy-rich" ($01\bar{1}$) and ($0\bar{1}\bar{1}$) faces at the other end (Fig. 29, right). The absolute direction of growth along the polar axis with respect to the crystal structure could not be fixed at that time, however, so that *Wells* did not know which end of a given crystal was phenyl-rich and which end hydroxy-rich. *Wells* interpreted this unidirectional growth along *c* to take place at the phenyl-rich faces as a result of stronger adsorption of water to the hydroxy-rich {$0\bar{1}\bar{1}$} faces, so inhibiting their growth relative to the phenyl-rich {011} faces.

Recently, *Davey*[40] has proposed that strong surface-water interactions should enhance crystal growth. By use of oriented growth on silica surfaces, *Davey, Bourne,* and *Milisavljevic*[41] deduced that indeed the OH-rich {011} faces are those that grow quicker in aqueous solution. The assignment by this technique is, however, not unambiguous. In order to resolve the controversy between the two hypotheses we assigned the absolute direction of growth of the resorcinol crystal in aqueous solution by employing the additives **16** to **19**, and independently by the Bijvoet method.[42]



We found that the unidirectional growth in water takes place primarily at the oxygen-rich faces in accordance with the findings of *Davey, Bourne,* and *Milisavljevic*.[41] We tend to the paradoxical view that the unidirectional growth at the hydroxy-rich {$0\bar{1}\bar{1}$} faces is due to inhibition of growth at the phenyl-rich {011} faces because of a higher affinity of water for the latter face. We base our arguments on the relative structures and on the van der Waals and Coulomb energy potentials of these surfaces.

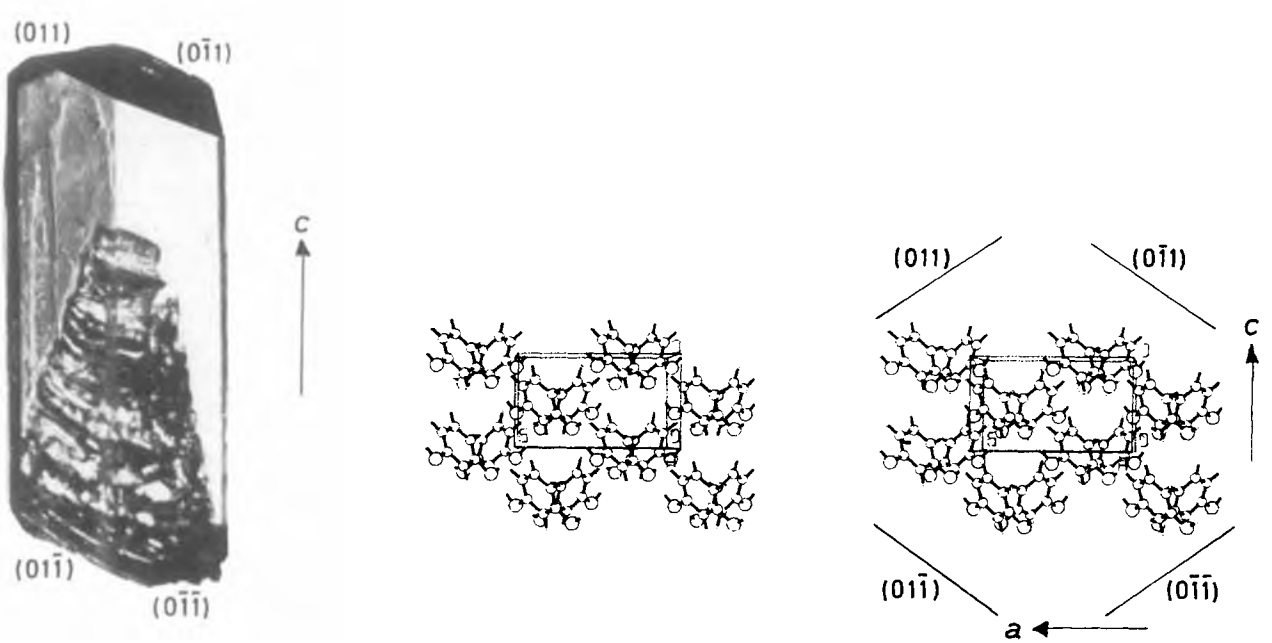


Fig. 29. Left: Typical crystal of α-resorcinol grown from water. The end faces {011}, i.e. (011) and ($0\bar{1}1$), and {$01\bar{1}$}, i.e. ($01\bar{1}$) and ($0\bar{1}\bar{1}$), are marked; right: packing arrangement of α-resorcinol, stereoview along the *a* axis. The planes parallel to the phenyl-rich {011}- and hydroxy-rich {$01\bar{1}$}-faces are denoted.

The {011} face is criss-crossed with grooves forming pockets at their intersections, whereas the hydroxy-rich $\{0\bar{1}\bar{1}\}$ face is relatively flat (Fig. 30). In order to obtain a

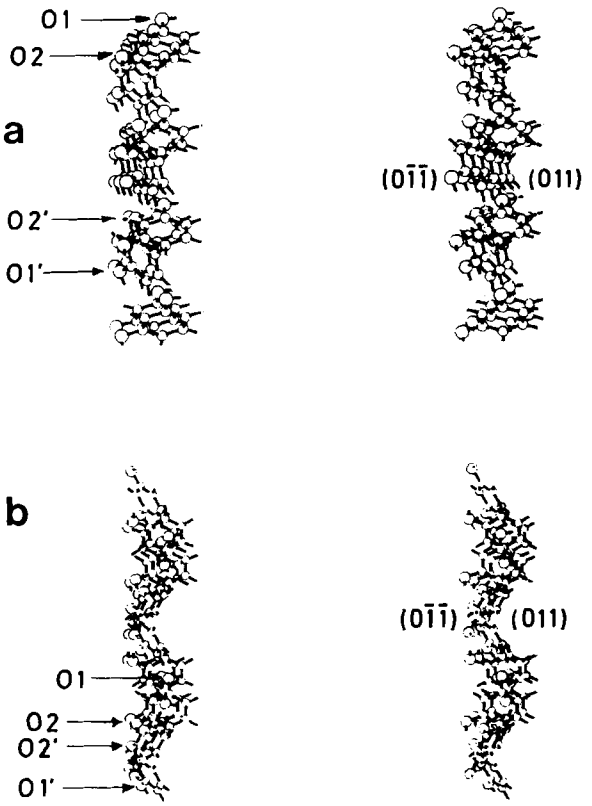


Fig. 30. Resorcinol. Two different stereoviews of an 011 molecular layer showing the surface structures at the (011) and $(0\bar{1}\bar{1})$ faces: (a) along the a axis; (b) along the direction $-b+c$.

measure of the relative affinity of these two faces for water in terms of van der Waals forces, their surface energy potentials were calculated as sensed by a pseudo van der Waals' water atom' brought into best attractive contact along each surface. The result indicates a higher (14%) affinity of the solvent for the {011} face than for $\{0\bar{1}\bar{1}\}$ in accordance with their relative 'roughness'. The relative polarity of these two faces in terms of their Coulomb potential energy surfaces is shown in Figure 31.

The positive potential values at the {011} face indicate that this face best interacts with negative ions or the oxygen of water, whereas $\{0\bar{1}\bar{1}\}$, which is characterized by negative potential values, interacts best with positive ions or with the hydrogen of water. Thus, for solvent water, it is preferable to consider the {011} and $\{0\bar{1}\bar{1}\}$ faces as acidic and basic faces, respectively, rather than as 'phenyl-rich' and hydroxy-rich'. The acidic nature of the {011} face is also evident in so far as it exposes the O1–H bond as well as aromatic C–H bonds (see Fig. 30) which may participate in attractive C–H···O interactions.[43] The proton-acceptor properties of the opposite $\{0\bar{1}\bar{1}\}$ face arise from the fact that three out of four resorcinol oxygen atoms O1, O2, O1′, O2′ are accessible to water (see Fig. 30). The contour values of the two energy maps indicate that the basic face has a deeper potential than the acidic face. Thus, the van der Waals and Coulomb forces appear to balance out in

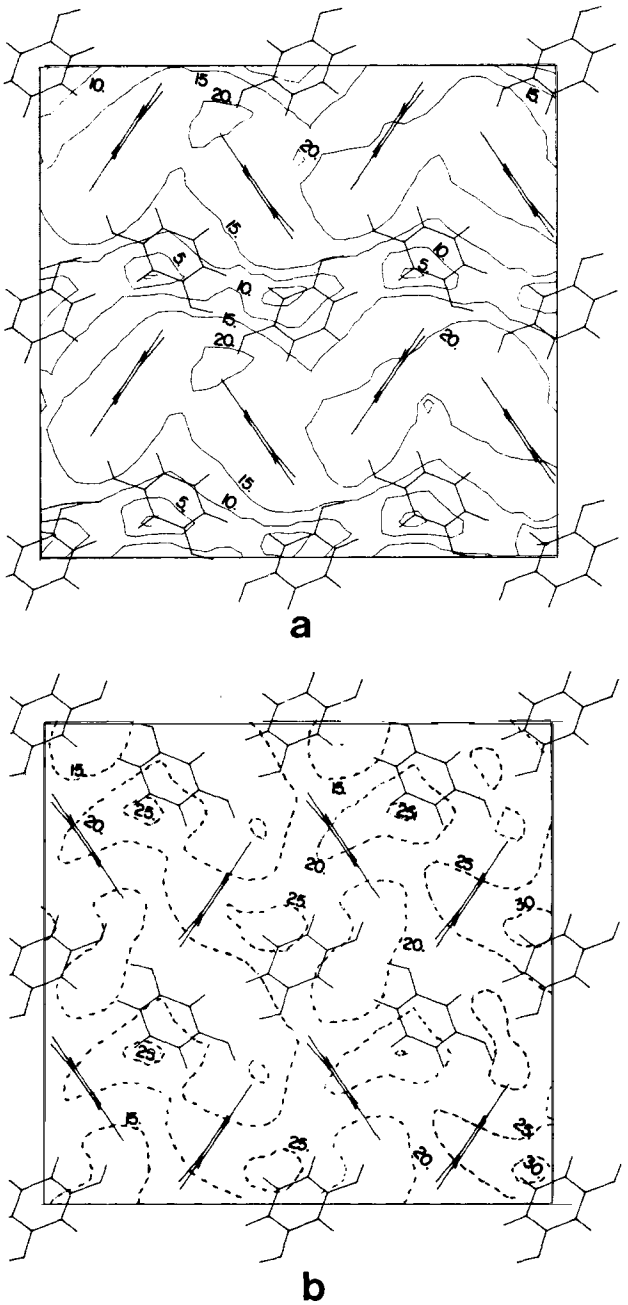


Fig. 31. Electrostatic potential energy maps at closest approach distances of a unit positive charge from the surfaces of: (a) a {011} face; (b) a $\{0\bar{1}\bar{1}\}$ face. Solid contour lines represent repulsive energies and broken lines attractive energies. Contour interval 5 kcal/mol.

terms of preferential binding of water; on the other hand, it is clear that water can bind to both sides. In the light of the experimental data we tend to believe that van der Waals forces play the determining role. Thus, we maintain that *Well*'s interpretation, that growth of a crystal face is inhibited by strong adsorption of solvent, is essentially correct, although in the case of resorcinol he drew the incorrect conclusion about the growth direction, by assuming that water is adsorbed preferentially on the hydroxy-rich face.

This approach in studying solvent-surface interactions is encouraging. Indeed, it may eventually lead to a quantitative unraveling of the relative roles played by internal crys-

tal structure and solvent-surface interactions in determining crystal morphology.[38]

8. Outlook

In the present article, we have attempted to show that it is possible with the assistance of tailor-made additives to control both growth and dissolution of organic crystals. A remarkable aspect of this process is that it provides us with the ability to navigate a given additive through a given face into a selected subset of the symmetry-related sites of the crystal. Thus, for example, in the case of benzamide, benzoic acid may be occluded at only one of the two centrosymmetrically related sites at the end of the ribbon motif (Fig. 7a); the overall symmetry of the crystal is thus reduced from the centrosymmetric space group $P2_1/c$ to the chiral space group $P2_1$. Such "induced chirality" is currently being exploited for the performance of spontaneous asymmetric syntheses. Furthermore, this type of chiral discrimination in centrosymmetric crystals is presumably manifested also in inorganic crystals, including minerals, which might have a bearing on the spontaneous separation of enantiomers in Nature.

The present approach might further provide an effective method for pinpointing fine intermolecular interactions in crystals, (e.g. O···O repulsion in the benzamide-benzoic acid system, (see Section 3) as revealed by the morphological changes they induce.

The role of the tailor-made additives is probably not limited to the growth stage, but includes prenucleation aggregates which are expected to structurally resemble the mature crystal. An extension in this direction might be of importance in the resolution of enantiomers by crystallization.

So far we have confined ourselves to additives which resemble the host molecule. This was done in order to facilitate the extraction of detailed mechanistic information. We can now reduce systematically this similarity, provided strong specific interactions are preserved at interfaces between substrate and additive. This approach provides a unique entry to the study of solvent effects on crystal morphology. It is of particular relevance for the better understanding of crystallizations taking place at structured biological interfaces, such as bones, teeth and shells,[44,45] and in the inhibition of ice formation in fish living at temperatures below the freezing point of water.[46]

In summary, we see that the old, but until recently empirical, technique of modifying crystal growth by addition of impurities has a wide range of consequences in both theoretical and practical chemistry and materials science.[47] This field of research may be expected to expand rapidly in the future.

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Great Fear of Small Amounts of Elements—The Significance of Analytical Chemistry in our Modern Industrialized Community as Exemplified by Trace Element Analysis

By Günther Tölg* and Rainer P. H. Garten

Dedicated to Professor Rudolf Bock on the occasion of his 70th birthday

Analytical chemistry is consolidating an important position within the framework of our modern industrial community; the frontiers of trace (and ultra-trace) analysis have expanded into new territories, thus demanding a constant change in our mode of thinking in a substance-related manner in analytical chemistry. An outline of the development of analytical chemistry during this century reveals a period of underdeveloped research and education followed by a current phase of impetuous advancement. However, as a result of increasingly antagonistic sectional convictions in the public mind concerning reservations against, as well as efforts towards, efficient technological progress, this advancement evokes new existential risks for analytical chemistry—viz. either to be used in an uncritical way or to fall into discredit following slogans like 'high-performance analytical chemistry is to blame for it all!' A much more constructive consideration says that risks can be estimated and evaluated solely by means of a highly efficient analytical chemistry, when used with a sense of responsibility. Analysts may help to clarify and to cope with the increasing fear of decreasingly smaller amounts of trace elements—in both adverse groups in our community. Strategies necessary to gain this end are outlined with regard to a methodological as well as a political platform.

1. The Role of Analytical Chemistry in our Modern Industrial Society

The chemical, biological, and physical properties of materials and—what is of interest to us in connection with our environment—of complex systems of substances are often dependent upon very small alterations in composition. This dependence forms the basis of many fields of research, e.g. in the life sciences, in the earth sciences, and in materials science; but, as we are learning more and more each day, it also has direct serious consequences for man and his environment in terms of health, working conditions, and other factors determining the quality of his life. Thus, this research and public policy are entering progressively into closer relationships with which not only every responsible, forward-looking scientist and politician, but also every individual citizen must come to an understanding.

In an effort to comprehend these very complicated interrelationships, it is very easy to come to false conclusions

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concerning the function of scientific disciplines for the common good, such as is the case, for example, in analytical chemistry. Even many scientists are scarcely aware of the importance of analytical chemistry for the future development of our quality of life.

All the natural events in our biosphere occur in a multitude of extremely complicated regulated cycles, which in turn are interdependent on very sensitive equilibria. We are increasingly realizing the difficulty, not only of understanding their interactions in detail, and of affecting them only so that the human race can survive intact, but also of assuring the disturbances of these equilibria are limited as much as possible. Very often we do not even recognize the consequences on the affected ecosystems.[1-3]

Our trust in technical progress, built up slowly and with difficulty over the centuries, is shaken nowadays by fast-reacting, alarming reports, which are very often sensationally, but inaccurately presented by the media. The human need for security then motivates some to defend themselves against that which is incomprehensible and even sinister. The anxiety arising from such uncertainty is another only too natural response. The widespread aversion to chemistry ("Modern Inquisition"), will unfortunately not promote the solution of pressing problems. What we need is an accelerated elucidation of the role of chemistry in order to learn factually and circumspectly its advantages and disadvantages (see, e.g., [4]). This, however, presupposes reliable information and data concerning complex processes in the material field. In other words, whenever synthetic or anthropogenically mobilized substances impinge on our lives, both in a positive and in a negative sense, analytical chemistry faces the challenge to make available reliable data for a critical evaluation of changes in material systems. Only in this way, will we make any possible risks calculable. This is also indispensable if we wish to terminate some absurd endeavors either to turn back the wheel of progress or to ignore the fear-provoking consequences of our progress by burying our heads in the sand. Only this will help to lessen the conflict between these two extreme schools of thought, a conflict which is continually becoming more threatening. Thus, analytical chemistry is today taking on an interdisciplinary and society-relevant role;[5,6] this requires for the future—particularly in teaching—an accelerated change of attitude concerning its standing, which has been stagnating for decades (cf. [7,8]). However, an unsatisfactory system can only be improved if its weaknesses are known.

2. Changes in the Catalogue of Functions

As the oldest branch of chemistry, the first functions of analytical chemistry were concerned with the composition of terrestrial materials for the sake of a basic understanding of nature. Its intrinsic value was at first undisputed (cf. [1,9,10]) and led to an extraordinarily successful development in the classical-chemical age. In more recent times, its standing has gradually diminished, in particular as a result of the following developments:[5,7]

1. In the chemical industries it took over more and more of a quality control function whereby routine tasks had the upper hand and scarcely any capacity remained for further methodological developments.
2. Chemical analytical methods had to endure more and more competition from physical methods. This led to further uncoordinated parallel development on both sides, i.e. chemical and physical. But since the teaching of analytical chemistry was mainly in the hands of chemists, the new blood that was recruited was mainly chemically orientated (cf. [8,11]), whereby the synopsis of chemical and physical methods was increasingly lost. The triumphal incursion of physical methods, which proved themselves to be more economical for routine work, into industrial laboratories dominantly in the hands of the self-taught, occurred largely outside the framework of analytical chemistry. It was subsequently sought to replace the fine art of analysis, by instruments or tools, more and more of which were becoming available on the burgeoning instrument market.

   The original unity of methodological development and strategic application of these methods to the solving of problems has been increasingly lost. Physically or technically oriented method specialists and highly specialized instrument manufacturers established themselves, on the one hand, while, on the other, there were more and more "measurement slaves" who tackled problems with "black boxes". From an economical point of view this process could even be justified in the short term because the difficulty of the analyses remained practically the same for a long period of time.
3. The fact that the solution to analytical problems could be, as it were, bought, released research policy makers from the necessity of educating analysts in sufficient numbers and reinforced the view that analytical chemistry was no longer topical as an independent scientific discipline. This opinion is unfortunately still so widely held today that, in spite of the superfluity of constantly perfected methods, the solution of difficult analytical problems has become more and more intractable, because the challenge imposed by the degree of difficulty and scope has risen dramatically.

   The very first environmental problems indicated that it was not just the major and minor components of a synthetic product that were of interest, but the anthropogenically mobilized trace components too.

3. Ambivalent Thinking as a Requirement for the Increasing Employment of Trace-Analytical Information

Our usual, very successful, reductionistic, linear cause-and-effect thinking based on *Newton* and *Descartes*, that at first had only to be extended by dualistic models in quantum mechanics, is revealing itself over a wide area to be too one-sided.[3,9,12,13,14] Here is not the place to lay down why it is necessary to learn to think cybernetically or in cross-linked dynamic systems, but some simple examples will show that the chemistry of trace components encounters the boundaries of all too one-sided thought processes, both with respect to the production of analytical information and to its interpretation.

At least 26 of the naturally occurring elements are now regarded as necessary for life (Fig. 1). Of these, 15 are present in the organism at concentrations of $<0.01\%$. These are collectively categorized under the heading "trace elements" in the biochemical sense. All other elements are ubiquitous in biogenic systems below certain concentration levels, which are laid down within a certain range of scatter by nature; it has not yet been possible to establish physiological effects at these natural concentrations. However, if given concentration thresholds are exceeded, usually because of anthropogenic activities, then, with only a few exceptions, negative effects can be detected on the living conditions of individuals or ecosystems (see, for example, [3, 15–17]).

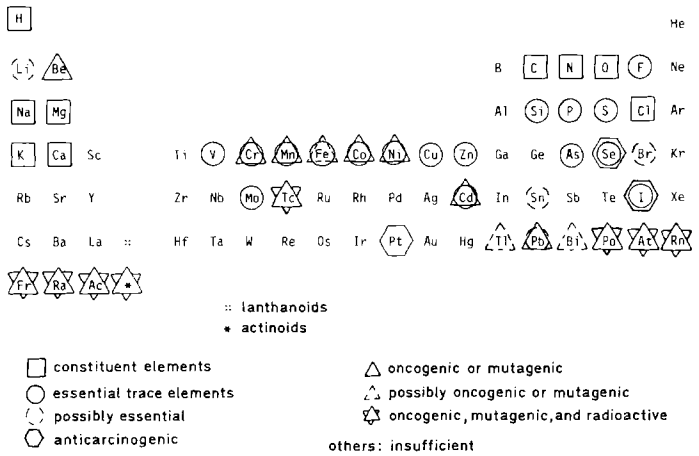


Fig. 1. Periodic table of the elements with essential, oncogenic, and mutagenic trace elements (after [61]).

Each essential trace element only exerts its vital function over a certain concentration range (Fig. 2);[18] too little leads to just as serious a biological problem as too much—under certain conditions either state can lead to mortality. In other words, a natural equilibrium of element concentrations has been set up during the course of evolution between animate and inanimate matter and this setting is restricted in each case to a very narrow range of trace element concentrations for optimal living conditions.

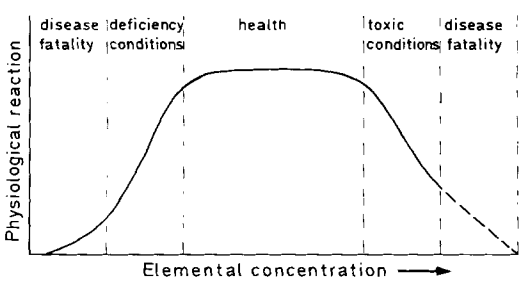


Fig. 2. Ambivalent physiological dose-effect relationship of an essential trace element (after [18]).

This poses the question as to whether the lower limits, below which symptoms of deficiency occur, ought to be defined more closely in future, in order to avoid not only man-made overdosage but also to allow for natural and man-made deficiencies.[19, 20]

Probably the most impressive example at present for demonstrating the ambivalent effects of a trace element, is selenium, the concentration limits of which in the physiologically optimal range differ only by about one order of magnitude.[21] There have also been found distinct indications of such ambivalent behavior for As, Cd, and Pb.[22] It is highly likely that further elements will follow, as analytical techniques improve. Already under discussion is a protective effect of selenium (cf. [21]) against the heavy metals Hg, Cd, or Pb via the formation of physiologically less active compounds. Thus, in order to evaluate the toxicity of heavy metals, which react with selenium yielding extremely stable compounds, it is not only necessary to have a detailed knowledge of the various types of toxic bonding (cf., e.g., [23, 24]) of metals, but also of their concentration in relation to that of selenium, just as, vice versa, the concentration of heavy metals in the system must be taken into account for the evaluation of a selenium deficiency. By analogy, corresponding protective effects by "detoxification", i.e. immobilization of toxic substances, are to be expected for a range of other trace substances, whose damaging effect on living organisms is known at higher dosages if they are observed in isolation.

If it is assumed that all naturally occurring elements have acquired physiological activity during the course of evolution, which is by no means impossible, then there is a considerable degree of obscurity concerning all those elements whose natural concentrations in living systems are too low for their ambivalent function to be demonstrated, because they cannot be determined analytically or because the analysis is very unreliable.

At the moment we can only observe the toxic upper concentration levels of these elements, since these are generally analytically controllable. An exception here is found in the concept of homeopathy, which postulates a positive physiological effect for the smallest possible concentrations of an element and employs these therapeutically. Without wishing here to question the success of such treatments, this one-sided point of view is irrelevant for the trace analyst, at least as far as higher degrees of dilution are concerned (powers > D 10). This has nothing to do with the controversy between conventional medicine and homeopathy, as to whether such low element concentrations can possibly exert any effect. This dispute is pointless, since even the most uncommon elements in the earth's crust, such as for instance Hg, Ag, Au, are present in every organism and every preparation in concentrations that are many orders of magnitude greater than the reported concentrations. For instance, a commercially available preparation purporting to contain silver at a dilution of D 19 ($10^{-17}\%$) actually contained Ag in a concentration of ca. $10^{-7}\%$,[19] i.e. equivalent to the natural concentration of silver in blood serum. The ubiquitous concentration of gold is about one order of magnitude lower. We are on the verge of greatly increasing the ubiquitous concentration of the even less common platinum in the environment (cf. [25, 26]), without being able to predict the consequences.

The next example has deliberately been chosen from the bordering fields of contention between conventional and alternative thinking in chemistry. It ought to demonstrate that not everything is as "healthy" as ideologists assume.

As early as 1967 *Weinig* and *Zink*[27] observed that the concentration of thallium in the urine of vegetarians and smokers is significantly higher than that in control samples from "normally" nourished subjects; it is up to one order of magnitude higher in vegetarian smokers. Tl(I) accompanies potassium, whose atomic radius is very similar. It is therefore preferentially enriched in plants. This finding is of analytical relevance, because the authors determined the concentration of Tl by the very reliable technique of isotope dilution analysis using mass spectrometry, and checked their results by a second independent method. Accordingly, vegetarian smokers are at greater risk than "normal consumers" so far as chronic Tl intoxication is concerned, at least until we know the concentration interval for Tl provided by nature. In the case of selenium, and possibly beryllium,[28] this range most likely lies within only one order of magnitude.

Beryllium provides a further example which illustrates the inadequacies of our conventional way of thinking. A large-scale systematic study of the distribution of beryllium in the environment led certain authors, who shall remain anonymous here, based on their one-sided way of thinking, to the conclusion that beryllium did not constitute a risk for smokers. Their chain of arguments was completely logical. They found that tabacco ash contained very little beryllium. According to the textbooks BeO cannot be volatilized in the combustion process. The analytical methods employed were impeccable; in spite of this the authors made a grave error of judgement.

Had they investigated the urine or the blood of smokers they would have discovered a significant enrichment of volatilized beryllium (cf. Fig. 3), which can on no account be neglected as a risk factor, at least until the toxicology of beryllium and the chemical behavior of Be traces have been fully explored.[28,29]

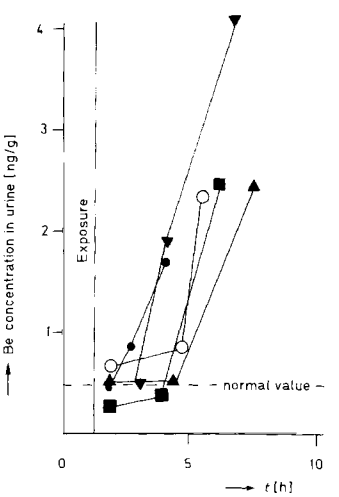


Fig. 3. Time course of Be concentration in the urine of active (●, ■, ▲, ▼) and passive (○) smokers after each hour's inhalation of dense cigarette smoke [29].

4. Criteria of Analytical Quality—Aims and Limits

This section is devoted to a discussion of some significant factors arising from different viewpoints regarding the environmentally related tasks of the trace analyst. The universal analytical method that is ultimately sought for is one that ensures an economical optimal combination of sample preparation, decomposition, separation, and detection, and yields reliable results for all trace elements in all samples; a method with such a degree of universality has not, as yet, been discovered and is unlikely to be so, even in the future. Thus, the major task of the trace analyst is to focus his attention on improving the methodological criteria of quality, that is power of detection, sensitivity, reliability[30-32] and economy,[6,33,34] in order to provide efficient solutions for the innumerable, interdisciplinary problems that exist. He should also recognize today what complicated analytical problems will emerge tomorrow in all fields in which materials are investigated, so as to be able to develop suitable methods in advance. It is only in this way that he will be able to establish himself as a partner of many colleagues in a very wide interdisciplinary field who are dependent on analytical progress, but who are out of their depth in the development of ever more demanding analytical methods.

While the problem of detection power and sensitivity is inherent in the analytical problem, the other two quality criteria, namely reliability and economy, are parameters that depend on the power of detection. Basically the improvement of the detection power and sensitivity of analytical determination has to be looked at from several points of view.

Increasingly sensitive methods of determination also lead to the danger of their misuse. Those who would like to turn back the wheel of history, employ sophisticated analytical procedures to hunt for more pollutants, often in a very uncritical manner. The main effect is to create uncertainty and anxiety and this provokes many of the antagonistically thinking group to believe, in accord with the motto "analytical chemistry is to blame for it all", that there is no sense in developing analytical methods offering higher power of detection. It is to be hoped that those will succeed, both in general and in research policies in particular, who will look at the problem as as whole and will realize that unbiased, efficient analytical chemistry is an indispensable prerequisite for evaluating risks and making them calculable.

But many analysts who honestly try to employ analytical progress as a driving force in the quest for new knowledge, better products, and a healthier life, are also in danger of slowing down necessary progress by false attitudes. Because of their training, many analysts are inclined to oversimplify, to standardize, to generalize, or to fall into the trap of extrapolating data. We should therefore make ourselves more conscious of the fact that it is just these useful, even indispensable human facilities which can be the more dangerous the lower the concentration of the elements to be determined. Obviously, we are constrained to standardize our analytical methods and to make them as simple as possible for economic reasons, in order to guarantee broad compatibility in routine application. But it must be ensured that these methods already function reliably and that each user, who follows the standardized instructions, can also guarantee the accuracy of his results in all the envisaged areas of application. The results obtained in many interlaboratory comparisons (round robin analyses) carried

out in the last few years reveal very impressive interrelationships between the power of detection and the reliability of the results.

The lower the concentration of the elements to be determined in an actual sample, the greater the systematic error that occurs.[5,6,35] Despite the good agreement sometimes found for results obtained by one particular method for a particular sample, normally statistically distributed about the true value, results can be obtained that are very different from the true concentration, as has been shown by round robin analyses comparing various methods and/or various laboratories' results on analyzing the same sample.

A further problem resulting from these systematic errors in the determination of very small traces of an element is illustrated in Figure 4. A large number of determinations have been made of the normal concentration of trace elements in the matrix "human serum", so that the results can be evaluated statistically. The mean concentrations recorded for some essential trace elements by various authors over periods up to 1976 and after 1976 reveal two groups of trace elements:

1. Elements, for which values were obtained which were practically in agreement with each other over both periods. These are the elements Cu, Zn, and also Se, whose determination is unproblematical nowadays. With slight reservations, this also holds for their determination in other biotic matrices. Thus, it is meaningful in these instances to develop standard procedures for their routine analysis.
2. Elements, whose measured normal concentration in the blood serum has been tending to drop to ever lower values up to the present time. They are real problem elements which demand continual attention by the experienced trace analyst.

As long as the systematic errors involved in the determination of these elements prevail over the statistical errors, standard procedures may only be designed with the employment of extreme analytical expert knowledge and critical understanding.

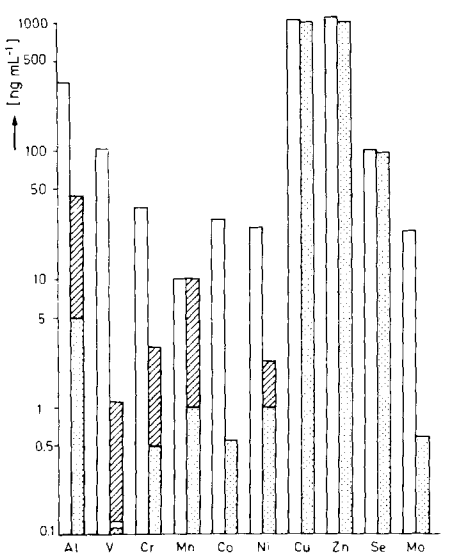


Fig. 4. Comparison of the means of some elemental concentrations in serum, determined in the period before 1976 and after 1976 (according to data assembled by *Versieck* et al. [62]); □ before 1976, ▨ after 1976, ▩ realistic.

5. Pathways to Accuracy in Trace Analysis

Long years of experience and thought concerning the causes and the avoidance of systematic errors in ultratrace analysis can be summarized in one sentence: "Systematic errors of combined procedures are minimized if only absolutely essential unit steps are carried out in closest combination in reaction spaces with the smallest surface areas at the lowest temperatures possible, all apparatus materials are as inert as possible and only a minimum of easily highly purified reagents and additives are employed, all contamination by laboratory air is avoided, and each unit step of such a procedure is carefully investigated for its analytical yield—using radioactive tracers if possible."

This fundamental sentence summarizes our methodological strategy;[35] it therefore requires some comment. The largest systematic errors are expected to arise from impurities, which are introduced into the analytical system from components of the apparatus, from the reagents, and from the atmosphere in the laboratory. They are the greater the more common an element is in the environment (ubiquitous concentration). Irreversible adsorption of trace elements occurs on the vessel walls and losses due to evaporation occur during the whole analytical procedure, which begins with sampling. Some of these errors are in opposite directions and can sometimes compensate each other. Since it is primarily the blank value that limits the power of detection, it must be remembered that it is the ratio of the concentration of the element to be determined in the sample to its concentration in the environment of the analytical system which is decisive rather than the sensitivity of the detector system itself. Thus, in present day ultratrace analysis, it is more meaningful to keep the blank concentration as low as possible than to search for new and more sensitive detectors.[35–38]

Basically, it is only possible to achieve an optimal power of detection for each analytical method when the element to be determined has been isolated. We do not, as yet, possess any methods of determination where the excitation of an analytical signal for the element is not affected in a positive or negative sense by other accompanying elements above a certain threshold concentration. All economical direct instrumental methods (cf., e.g., [31,39]), in which the sample itself is analyzed directly, not only fail to yield optimal detection power, but, under certain circumstances, are also subject to considerable interference by other elements. It is possible to compensate for such interferences, however, but only if reliably investigated standard reference samples are available for calibrating the method[32,40] which are as similar as possible to the analytical samples. In ultratrace analysis, however, this applies in only very few cases (cf. [41]). Consequently, one must resort to less economical and more complicated combined procedures, in which the element of interest is separated as far as possible from other accompanying elements before being determined.[5,37] In contrast to routine methods where systematic errors have already been removed, in ultratrace analysis, only complex combined procedures lead to reliable results, and, in end effect, are more economical than direct instrumental methods yielding inadequate or even false results and their consequences. Systematic errors naturally

occur also in these procedures; they may have different origins which are distributed with different importance over the various individual steps of the procedure.[6, 35, 42]

This catalogue of tasks in modern trace analysis can be extended by some specific examples from our own investigations. They are considerably complex examples involving complicated interdisciplinary problems. We were therefore only able to make modest contributions towards obtaining reliable analytical information and optimal solutions to individual problems. For a scientific interpretation of the data we always seek the cooperation of other suitably qualified colleagues who may not be in a position to develop the analytical part by themselves, while we for our part often feel overtaxed with the scientific interpretation of our results.

5.1. Example: Species and Distribution Analysis of Mercury

Along with Cd, Pb, Tl, and As, mercury, in particular, counts among the most important problem elements which pollute the environment as a result of anthropogenic activities—apart from the not inconsiderable basic emissions caused by volcanism and the weathering of rocks.[43]

In certain industrial areas relatively large amounts of mercury are emitted into the atmosphere during the production and use of its compounds. Much more mercury is emitted, however, by its release from all materials removed by mankind from the earth's crust, during combustion and heating processes (Table 1). Its ubiquitous concentration in these materials is in the middle ng/g range. The growth in industrialization has led to a cumulative increase in these emissions, so that it is not possible with our present state of knowledge to say unequivocally how this increasing Hg-emission, which is unavoidable in our industrial society, will affect the health of living individuals in the next generations; this also applies, but not to such a serious degree, for all other relatively volatile elements. The risks involved are probably more difficult to calculate than the risk which is involved in the peaceful use of nuclear energy. The main reason for this is that the ecological circulation of mercury is exceedingly complex and that mercury behaves biologically very differently in the various compounds in which it appears (see Fig. 5).

Table 1. Comparison of global mercury emissions of natural and anthropogenic origin [43] (based on data from 1970 and 1974).

	Globally released mercury [t/year]
Natural origin:	
Volcanism and weathering in the hydrosphere	500– 5000
Gaseous form from the earth's crust into the atmosphere	25000–150000
Hg-reserve in the oceans: 2×10^8 t	
Evaporation from sea water	23000
Rivers and glaciers	3800
Anthropogenic origin:	
Hg-processing industry	6000– 10000
Preparation of ores and minerals	1500– 20000
Combustion of fossil fuels	100– 8000

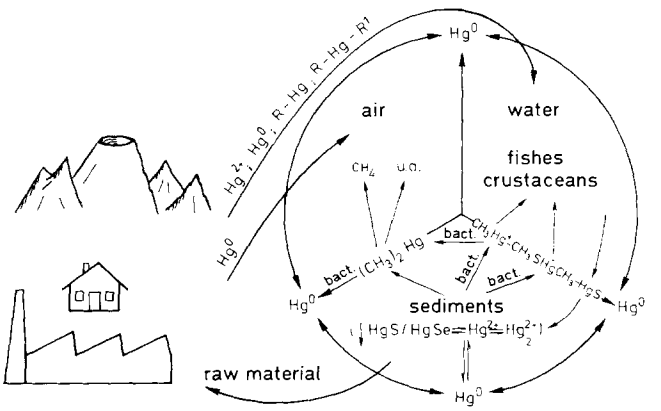


Fig. 5. The circulation of mercury in the environment (according to [63]); u.a. = and other gases.

The route by which organomercury compounds in particular enter the human nutritional chain via water is relatively well understood as a result of the impetus given by the catastrophe in Minimata Bay in Japan in 1954. The methylmercury compounds are greatly enriched by fish in particular (cf. [43, 44]). On the other hand, we understand very little about the mobility of mercury and its compounds in soils, which take the mercury up again from the atmosphere. It is only known that there is a high degree of enrichment in the upper horizons of all soils (cf. Fig. 6).[45] The question as to whether and in what form Hg can be transported into the human nutritional chain via water, has not been investigated sufficiently enough for it to be possible to estimate future risks.

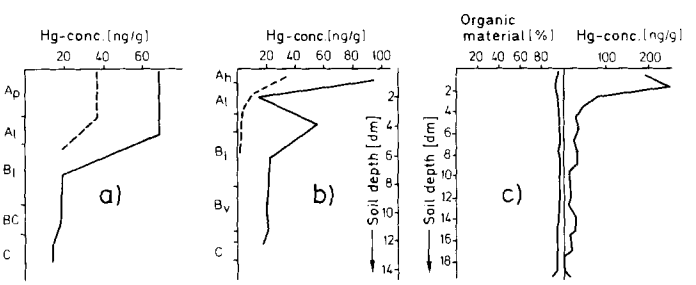


Fig. 6. Typical vertical profiles of mercury concentration in various soils: a) arable; b) forest; c) high bog (broken line: humus content in g/kg) soil horizons: A_p: ploughed top soil; A_h: humus-containing mineral soil; A_l: leached para brown soil; B_l: mean soil horizon with argillaceous illution; B_v: mean soil horizon of mineral weathering; BC: transition horizon; C: living rock [45].

The first, very crude step in our analytical strategy was to learn how to determine as reliably as possible the total Hg-content of all environmentally relevant matrices, i.e. in rocks, soils, water, air, plants, animal organs, tissues, and even in the individual serum protein fractions. It was necessary to strive for a detection power down to the lower pg/g range, at least for the organic matrices, in order to distinguish natural concentrations from anthropogenically originating concentrations. The aforementioned problems of systematic errors due to contamination, adsorption and evaporation were encountered during the solution of this

supposedly relatively simple task. In order to overcome them it was necessary to adhere strictly to our strategy for the ultratrace analysis of elements; combination procedures were designed that were as compact as possible, and performed in a closed system.

As starting point for the combined procedure several decomposition methods were investigated which had been specially developed for ultratrace analysis and which were considered to be practically free from systematic errors.[33,46,47] Combustion or heating the sample in an oxygen plasma excited by microwaves proved almost ideal. The mercury vapor produced during decomposition of the sample (cf. Fig. 7, left) is quantitatively absorbed on a gold absorber (Fig. 7, center) before it is transferred for the actual determination (Fig. 7, right) by pulse heating the Au-absorber. This compact combination of decomposition, enrichment, and actual determination methods in a closed system provides the basis for a very universal, extremely sensitive and reliable determination of the mercury isolated from the sample by a newly developed spectroscopic detector (microwave-induced plasma optical emission spectrometry, MIP-OES), which makes it possible to detect absolute quantities of less than 1 pg Hg.[2,48] With the experience gained so far (several man years) it was possible to commence the following briefly reviewed investigations on the mobility of mercury in soils.

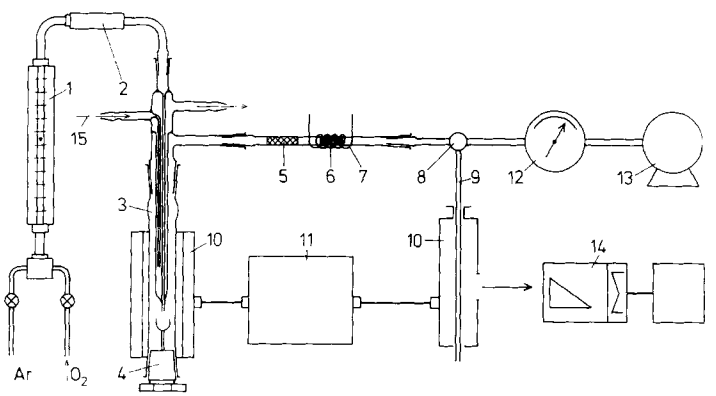


Fig. 7. Combined procedure for mercury determination in biological material and rocks by sample decomposition in microwave induced oxygen plasma (3), enrichment of Hg on an Au absorber (6) and excitation of the optical Hg emission spectrum in a microwave induced argon plasma (Kaiser et al. [48]): 1 rotameter, 2 gas purification, 3 decomposition chamber (quartz), 4 sample container support, 5 quartz wool, 6 Au absorber, 7 heating spiral, 8 three-way cock, 9 quartz capillary, 10 hollow resonator, 11 microwave generator, 12 manometer, 13 vacuum pump, 14 spectrometer, 15 cooling water).

Since soil is exceedingly complex from a chemical point of view we searched, in collaboration with a soil scientist, for a suitable model soil which would be relatively simple to understand, particularly with respect to transport mechanisms.

In the case of upland high bogs, mercury can only be taken up from the atmosphere. Analysis of samples from various depths always gave similar profiles for the distribution of Hg-concentration, which made it possible to recognize the natural background, the anthropogenic portion, and an equilibrium between input from the atmosphere and return of Hg from the upper soil layers into the atmosphere (Fig. 6c).[45]

Using radioactively labeled Hg it was possible to demonstrate that ca. 15% of the mercury taken up by the high bog was released again in the form of metal vapor or methylmercury. It was more difficult to answer the question as to how the mercury behaved that was retained by the peat bog soil. Was it completely fixed in an insoluble form, or did stable soluble complexes form, with humic acids for instance, which could be transported away by drainage water and thus gain access to the water circulation?

It proved possible to isolate the mercury compounds formed in the peat bog soil by employing a complicated separation system (cf. Fig. 8) using HPLC with MIP-OES

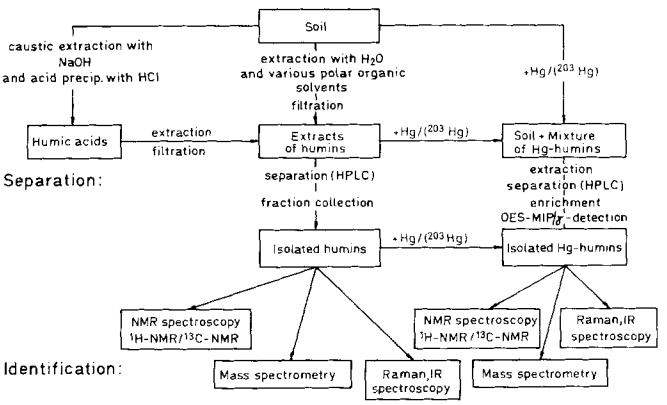


Fig. 8. Isolation and identification of Hg species in soils (after [64]).

as detector. The real breakthrough was the element-specific MIP-OES detector system, which enabled a differentiation between the Hg-containing and the remaining fractions separated chromatographically (Fig. 9).[49]

Furthermore, it was possible to identify the most common mobile Hg-compound occurring in the peat bog soils. According to ultramicro elemental analysis, UV, IR and ^{1}H-NMR spectroscopy it is unequivocally Hg humate.[49] The other four Hg-containing substances detected are present in such minute quantities that their identification will only be possible after further very expensive enrichment processes.

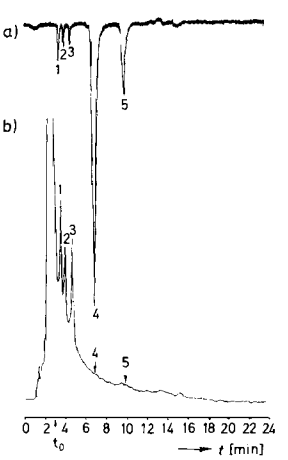


Fig. 9. Chromatographic separation of Hg-species after extraction of Hg-contaminated high peat bog with ethanol. a) MIP-OES detection: Hg(I), $\lambda = 253.6$ nm; b) UV/VIS detection, absorption at $\lambda = 250$ nm, reference wavelength $\lambda = 430$ nm. Details: [49].

About 15% of the total Hg taken up by the peat bog soil is returned to the atmosphere by evaporation within a very short time of residence; ca. 10% is transported away by water as soluble species, mainly humates, and, according to our present knowledge, ca. 75% remains fixed in the peat bog soil. Thus, profile analysis of peat bog soils with suitable corrections can significantly differentiate and make a balance of the anthropogenic input of the Hg in comparison with the natural background.

In spite of these analytical improvements this Hg-problem will be with us for some time until it will be possible to make a realistic estimate of the risks involved, since other relationships are as yet incompletely clarified. One important point is that until now the evaluation of the toxicity of heavy metals has always been focussed on the consideration of a single element, without taking into account its interaction with other elements. But many antagonistic or synergistic effects occur in this field, and they always ought to be taken into account.[50] Hg reacts, in particular, with selenium and sulfur to form selenides or sulfides with virtually no solubility. It is of utmost importance concerning the biological activity of mercury at the site of its action to know the ratio of uptake of antagonistic elements and their species transported in the organism.

5.2. Example: Traces of Selenium between Toxic and Essential

Concentrations of selenium of more than 1 μg/g taken up in the daily nutrition lead to selenosis.

On the other hand, Se-deficiency in the food intake (probably <0.2 μg/g) also causes severe damage to health, since not only does selenium fulfill important enzymatic functions, but, as described previously, it can also bind mercury and render it biologically inactive.[cf. 50,51]

In the case of selenium the analyst must be in a position to be able to make an unequivocal distinction as to whether the very narrow selenium concentration limits, laid down by nature for optimal biological effect, are maintained, exceeded, or not reached. Above all, the remaining uncertainties in the analytical data for the very low relevant concentration range make it difficult to evaluate the risks involved in selenium deficiency. Even the normal natural concentration range is difficult to determine satisfactorily, as has been confirmed by recent round robin analyses.[50]

Consequently, an analytical procedure has been sought which is economically acceptable for routine work and which enables the determination of selenium in a wide spectrum of matrices, in the ng/g range and below, as reliably as possible. Many methods promised success here because selenium can be detected very sensitively using any of the common analytical techniques (Fig. 10). The real difficulty lies in the employment of a critical comparison to find the starting point for a method which is as sensitive and reliable as possible while at the same time economical and universally applicable to all matrices of interest in an ecological survey, from geological to biological materials, so as to yield results that are as comparable as possible.

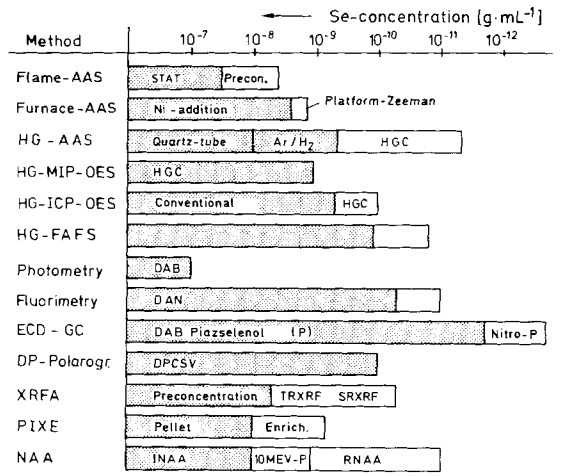


Fig. 10. Concentration ranges of the most sensitive methods for the trace determination of selenium (according to Tölg [50]): STAT: slotted tube atomic trapping; HG-AAS: Hydride generation atomic absorption spectrometry; HGC: Hydride generation and condensation; HG-MIP-OES: HG-microwave induced plasma-optical emission spectrometry; HG-ICP-OES: HG inductively coupled plasma-OES; HG-FAFS: HG flame atomic fluorescence spectrometry; DAB: 3,3'-diaminobenzidine; DAN: 2,3-diaminonaphthalene; ECD-GC: electron capture detector gas chromatography; DPP: differential pulse polarography; DPCSV: differential pulse cathodic stripping voltammetry; XRFA: X-ray fluorescence analysis; TRXRF: total reflection XRFA; SRXRF: synchrotron radiation XRFA; PIXE: proton induced X-ray emission spectrometry; INAA: instrumental neutron activation analysis; 10MEV-P: proton activation analysis ($E_P = 10$ MeV); RNAA: radiochemical neutron activation analysis.

Just as in our experiences with the determination of Hg and many other elements, we found confirmation of the principle that the most sensitive and reliable analysis can only be achieved after prior isolation of the selenium. The strategy followed for selenium determination is comparable with that for the determination of mercury, since selenium is easily separated by evaporation during the decomposition of the sample.

Once again it is a matter of an optimal combination of decomposition, separation, and determination methods. This combination has been achieved in many different ways. Only one of them will be described briefly here which possesses the optimal quality criteria for determin-

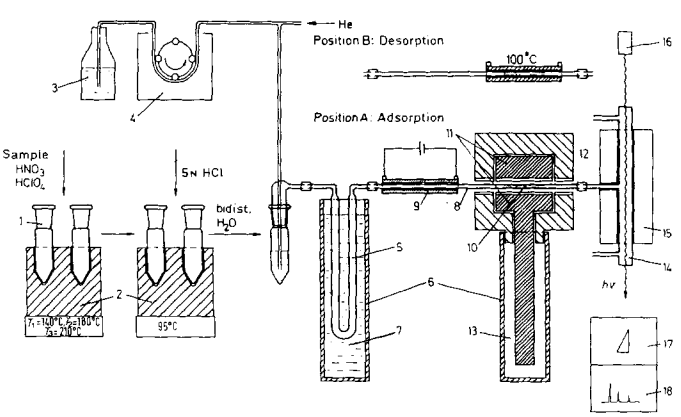
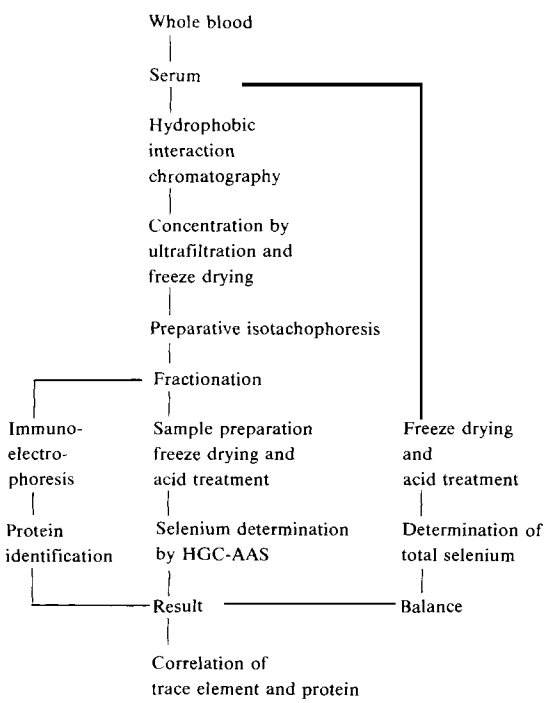


Fig. 11. HGC-AAS apparatus for the determination of selenium in the pg·mL^{-1} range (according to J. Piwonka [52]): 1. Quartz flask, 2. heating block, 3. reducing solution, 4. peristaltic pump, 5. quartz U tube, 6. Dewar flask, 7. cold trap (−70°C), 8. quartz adsorption tube, 9. heater, 10. adsorption trap Chromosorb W30/60, 11. cold block (Al, −196°C), 12. insulation, 13. liquid N_2, 14. quartz cuvette, 15. furnace, 16. EDL-lamp, 17. atomic absorption spectrometer, 18. recorder.

ing selenium reliably in all biotic matrices in the lower pg-range. The high detection power of the AAS method, which is only exceeded by the gas-chromatographic determination of selenium as piazselenol using the electron capture detector, is based on a simple preconcentration step. As a supplement to conventional hydride AAS, after a special decomposition of the sample in oxygen, hydrogen selenide is released and collected in an absorber tube by freezing onto Chromosorb (HGC-AAS). The hydrogen selenide collected can then be transferred in a pulse-like fashion to the atomization cuvette by simply heating up the absorber tube (Fig. 11).[52]

It is now possible to determine selenium in blood serum protein fractions by a complicated combined analytical procedure (cf. Scheme 1).[53] Thus, very sensitive procedures are available for the determination of Hg and Se, and their antagonistic effects can be investigated even in the serum protein fractions.



Scheme 1. Flow diagram for the separation and determination of selenium in the protein fractions of blood serum (after [53]).

The procedure is even suitable for the micro-distribution analysis of selenium in sections of a single hair or in finger nails. Very good reproducibility was obtained in the investigation of different hairs from a single subject, but when the selenium content of hairs from various subjects was determined surprisingly large variations were found. The cause of this could be traced to selenium contamination[50] (cf. [54]), which could only be incompletely removed by even the most careful cleansing process. Other authors[55] revealed in a gradient analysis, scanning a proton microprobe (PIXE) across the hair's cross section that selenium was strongly enriched at the surface of the hair, and definitely originated from selenium-containing shampoos (cf. Fig. 13). It was concluded from the thickness of the layer that the selenium had diffused into the hair. However, the detection power of PIXE does not suffice for the determination of selenium in the interior of the hair strand.

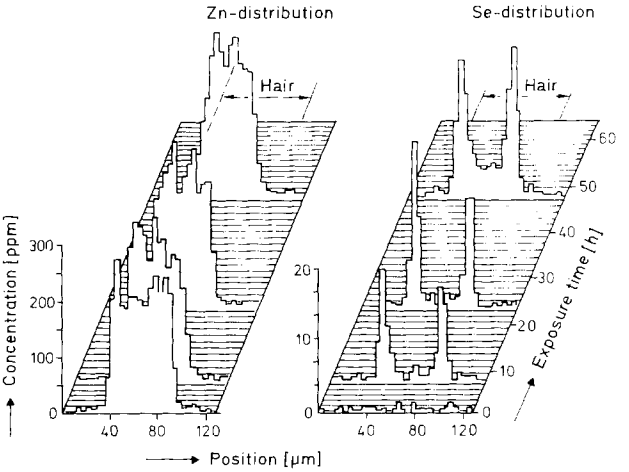


Fig. 12. Concentration distribution of Zn and Se across the cross-section of hair segments (distances in µm) after various periods of treatment with a selenium-containing shampoo. X-ray emission analysis with a proton microprobe PIXE (after [55]).

6. Future Challenges

The problems discussed here as examples are similarly imposed in other fields of analysis also, for example in the analysis of semi-conductors, metals, ceramics and plastics; here also, the positive and negative effects caused by previously ignored impurities are recognized.[56] In all these fields, interest centers not only on ever decreasingly lower concentration ranges of a total impurity but also on its distribution in samples and on sample surfaces.[57–59] The decisive question is often the mode of bonding of an element,[23,60] the formation of the compound, or the metabolism of active agents in very complex systems, which can only be elucidated by including analyses of microstructures, surfaces, and bonding properties. There is danger arising, whenever a single-minded course is followed without observing critically the sum total. This also applies to the interpretation of analytical data; and here, in particular, it can be said that the whole is more than the sum of its parts. Once again, an appeal must be made for closer partnership between specialized analysts and scientists of all spheres who need reliable data. Only such cooperation will lead to the urgently required progress which can repair the currently disturbed relationship between man and his environment.

The inter-methodological approach in basic analytical research itself urgently needs intensification. This presupposes, apart from an improvement in research capacity, a high degree of critical and creative thought concerning analytical strategies, which can only be worked out by highly qualified analysts—both chemically and physically orientated—with the necessary background knowledge (see [11]). The primary task is the furtherance of junior analytical scientists. However, this will only succeed, if a concerted effort is made to promote efficient analytical chemistry; and this will call on those responsible for research policies as well as those interested in reliable analytical

data, viz. all users of such data, expert colleagues in universities, in civil authorities, in industry, and in scientific and medical institutes.

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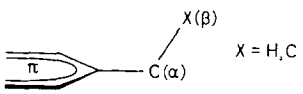
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Hyperfine Coupling to ^{13}C Nuclei in Alkyl Substituents—A Contribution to the Problem of C–C and C–H Hyperconjugation**

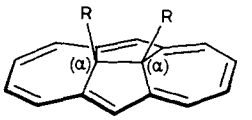
By *Fabian Gerson** and *Walter Huber*

The concept of "hyperconjugation" was introduced by *Mulliken*[1] to describe the interaction between a π-MO and a σ-MO of appropriate symmetry (pseudo-π-MO). The theoretical foundations of this interaction were recently discussed by *Radom*.[2] Of particular interest is hyperconjugation in ions that occur as intermediates in chemical reactions. The course of the reaction often depends on the preferred conformations of such ions which, in turn, are determined by the relative "hyperconjugative abilities" of the C–X σ-bonds. According to MO calculations of rotational barriers in simple alkyl cations[3] and anions[4] as model systems, these "abilities" are greater for C–C than for C–H bonds. ESR spectroscopy is especially suitable for testing predictions of this kind, since the hyperfine coupling constants of the β-^{13}C atoms ($^{13}C(\beta)$-hfc's), like those of the β-H atoms ($^{1}H(\beta)$-hfc's), predominantly arise from hyperconjugation of the singly occupied π-MO (SOMO) with the σ-MO of the C(α)–X(β) bond.

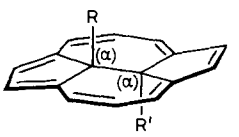


An insight into the relative "hyperconjugative abilities" of the C–H and C–C σ-bonds can thus be gained from the corresponding $^{1}H(\beta)$- and $^{13}C(\beta)$-hfc's. With the exception of a recently reported value for the radical cation of $(^{13}CH_3)_2CO$,[5] however, no hfc's of $^{13}C(\beta)$ have so far been available to provide a comparison with those of $^{1}H(\beta)$. Ideally suited model systems are the three pairs of radical ions of bridged [14]annulenes, the cations **1a**$^{\oplus\ominus}$ and **1b**$^{\oplus\ominus}$,[6] as well as the anions **2a**$^{\ominus\ominus}$, **2b**$^{\ominus\ominus}$[7] and **3a**$^{\ominus\ominus}$, **3b**$^{\ominus\ominus}$.[8]

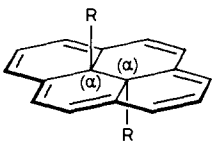
These radical ions, which have been characterized by their ^{1}H-hfc's, offer several advantages. The carbon framework is fairly rigid. On going from **a** to **b** within each pair, there is no change either in the π-spin distribution or in the orientation of C(α)–X(β) bonds relative to the cyclic π-system (X = H for R = H in **a** and X = C for R = CH_3 in **b**). Furthermore, these radical ions are a typical example of a particularly favored hyperconjugation. Not only are the



1a, R = H(β)
1b, R = C(β)H_3



2a, R = H(β), R' = C(β)H_3
2b, R = R' = C(β)H_3



3a, R = H(β)
3b, R = C(β)H_3

C(α) atoms simultaneously bound to two π centers having large LCAO coefficients of the same sign for the SOMO, but also the directions of the C(α)–X(β) bonds are almost parallel to that of the $2p_z$ axes at the two centers.[9] The strong hyperconjugative interaction is manifested by the exceptionally large $^{1}H(\beta)$-hfc's, $a(^{1}H)$, for **1a**$^{\oplus\ominus}$, **2a**$^{\ominus\ominus}$, and **3a**$^{\ominus\ominus}$ (Table 1). A reexamination of the ESR spectra of **1b**$^{\oplus\ominus}$, **2b**$^{\ominus\ominus}$, and **3b**$^{\ominus\ominus}$[10] reveals the existence of satellite lines stemming from ^{13}C isotopes in two equivalent sites. The corresponding, unusually large ^{13}C-hfc's, $a(^{13}C)$, are assigned to the C(β)-nuclei (Table 1). For **2b**$^{\ominus\ominus}$, the assignment is confirmed by the ESR spectrum of the radical anion enriched (90%) with ^{13}C isotopes in the C(β) positions ($^{13}C_2$-**2b**$^{\ominus\ominus}$).[11] In the case of **1b**$^{\oplus\ominus}$, the assignment is supported by the fact that the corresponding satellite lines are missing in the ESR spectrum of **1a**$^{\oplus\ominus}$. Unfortunately, an analogous argument cannot be used for **3b**$^{\ominus\ominus}$, because ^{13}C-satellite lines in the spectrum of **3a**$^{\ominus\ominus}$ cannot be examined due to the instability of the radical anion.[8a]

Table 1. $^{1}H(\beta)$- and $^{13}C(\beta)$-hfc's, $a(^{1}H)$ and $a(^{13}C)$, respectively, in mT [a] for the radical ions **1a**, **b**$^{\oplus\ominus}$, **2a**, **b**$^{\ominus\ominus}$, and **3a**, **b**$^{\ominus\ominus}$.

	1a$^{\oplus\ominus}$	**2a**$^{\ominus\ominus}$	**3a**$^{\ominus\ominus}$
$a(^{1}H)$	2.81 [6]	2.14 [7]	1.91 [8a]
	1b$^{\oplus\ominus}$	**2b**$^{\ominus\ominus}$	**3b**$^{\ominus\ominus}$
$a(^{13}C)$	2.74	1.72	1.43

[a] Experimental error: ±1%.

The $^{13}C(\beta)$-hfc's, $a(^{13}C)$, are almost as large as the corresponding $^{1}H(\beta)$-hfc's, $a(^{1}H)$ (Table 1).[12] With respect to the relative "hyperconjugative abilities" of the C–C and C–H bonds, it is, however, more informative to compare the spin populations ρ_C and ρ_H at the C(β) and H(β) atoms in question. Whereas conversion of $a(^{1}H)$ into ρ_H is straightforward, calculation of ρ_C requires an exact measurement of the anisotropy parameter $B(^{13}C)$ in addition to the isotropic value $a(^{13}C)$.[13] This requirement is met in the case of **2b**$^{\ominus\ominus}$ by the use of the labeled derivative $^{13}C_2$-**2b**$^{\ominus\ominus}$.

Figure 1 shows the ESR spectrum of $^{13}C_2$-**2b**$^{\ominus\ominus}$ in a liquid solution, along with the ENDOR signals associated with $a(^{13}C)$.[14] The second-order splitting observed for these signals is, to our knowledge, the first such finding in a ^{13}C-ENDOR experiment. In view of the small width of the ESR and ENDOR lines, the anisotropy of the $^{13}C(\beta)$-

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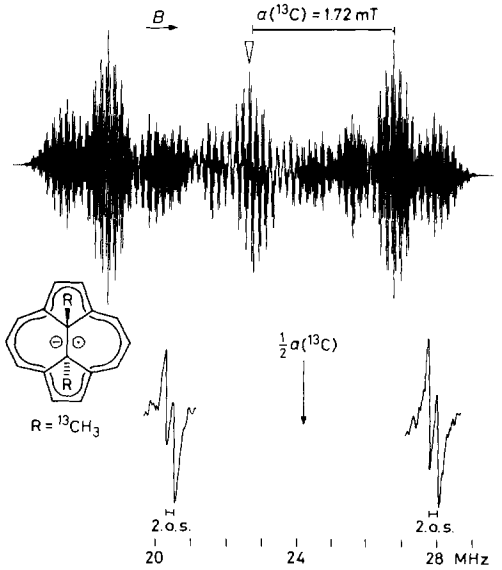


Fig. 1. ESR (top) and ^{13}C-ENDOR (bottom) spectra of $^{13}C_2$-**2b**$^{\ominus\ominus}$ in liquid solution. Solvent: 1,2-dimethoxyethane; counterion: $K^{\oplus}$; $T = 193$ K. The triangle in the ESR spectrum indicates the position for the ENDOR experiment. 2.o.s. = second-order splitting. Recorded with a Varian E-9 ESR spectrometer and a Bruker ER-252 ENMR system connected to a Bruker ER-200-D-SRC-9 spectrometer. [14]

hfc's should be rather small. This conclusion is confirmed by the ESR and ENDOR spectra of $^{13}C_2$-**2b**$^{\ominus\ominus}$ in a glassy solution (Fig. 2). The difference $A_{\parallel}(^{13}C) - A_{\perp}(^{13}C) = 3.4_5$ MHz (0.12_3 mT), which is derived from the ENDOR signals, gives an anisotropy parameter $B(^{13}C)$ of only $\frac{1}{3}0.12_3$ mT $= 0.04_1$ mT.[13] From the experimental ^{13}C(β)-hfc's ($a(^{13}C) = 1.72$ and $B(^{13}C) = 0.04_1$ mT)[12] and the atomic parameters for the C-2s- and C-2p-orbitals[15] (135 and 3.8 mT, respectively)[15] the partial populations $\rho_C(2s) = 1.72$ mT/135 mT $= 0.013$ and $\rho_C(2p) = 0.04_1$ mT/3.8 mT $= 0.011$ are calculated. This result is compatible

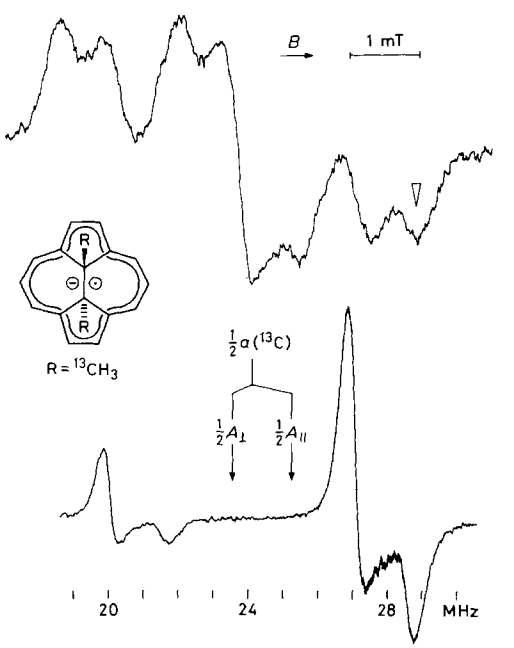


Fig. 2. ESR (top) and ^{13}C-ENDOR (bottom) spectra of $^{13}C_2$-**2b**$^{\ominus\ominus}$ in glassy solution. Solvent: 2-methyltetrahydrofuran; counterion: $K^{\oplus}$; $T \approx 113$ K. The triangle in the ESR spectrum indicates the position for the ENDOR experiment. Taken with a Varian E-9 ESR spectrometer connected to a Varian EN-DOR-1700 system.

with an sp-hybridization rather than with the sp^3-hybridization expected for a methyl C atom. Interestingly, it is reminiscent of the formulation $-C{\equiv}H_3$ used for a methyl substituent by *Mulliken*[1] nearly 50 years ago.

The total spin population ρ_C at a C(β) atom in **2b**$^{\ominus\ominus}$ thus amounts to $0.013 + 0.011 = 0.024$, while the corresponding value ρ_H for the H(β) atom in **2a**$^{\ominus\ominus}$ is $\rho_H(1s) = 2.14$ mT/50.7 mT $= 0.042$,[12] where 2.14 and 50.7 mT are the hfc's of ^{1}H(β) in **2a**$^{\ominus\ominus}$ (Table 1) and of the ^{1}H nucleus in atomic hydrogen,[16] respectively. Should the spin populations, $\rho_C = 0.024$ and $\rho_H = 0.042$, be interpreted in terms of the "hyperconjugative abilities" of the C–C bonds being markedly smaller than those of the C–H ones, which is at variance with the previous predictions of MO models?[3,4] Or, do the radical ions **1a,b**$^{\oplus\ominus}$, **2a,b**$^{\ominus\ominus}$, and **3a,b**$^{\ominus\ominus}$ represent a special case, so that the conclusions drawn from the present results are not general? An answer to these questions demands further investigations.

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CAS Registry numbers:
2b$^{\ominus\ominus}$, 92541-66-7; **2b**-$^{13}C^{\ominus\ominus}$, 96412.48.5

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An Intermediate and Its Secondary Products in a Nickel-Catalyzed Synthesis of [4]-Radialenes

By *Ludwig Stehling* and *Günther Wilke**

Dedicated to Professor Schulte-Frohlinde on the occasion of his 60th birthday

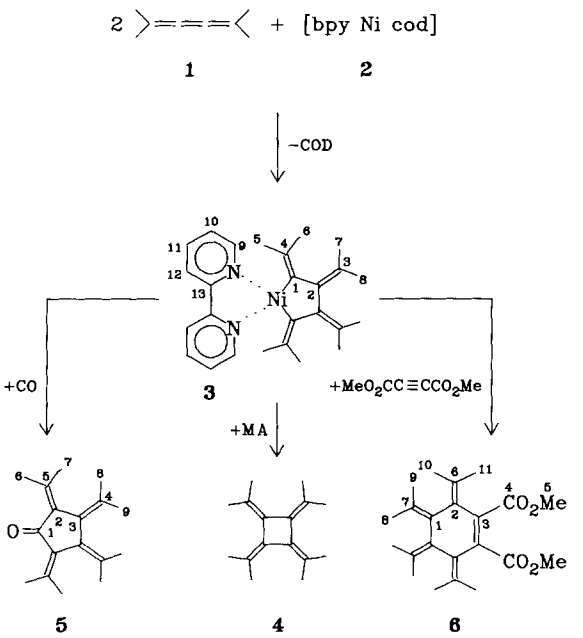
1,2,3-Butatrienes can be catalytically cyclodimerized to [4]-radialenes[1] or cyclotrimerized to [6]-radialenes in the presence of $[(Ph_3P)_2Ni(CO)_2]$.[1,2] In the cyclotrimerization of butadiene on "naked" nickel it was possible for the first time to trap an intermediate of a catalytic cyclooligomerization.[3] Subsequently, numerous other intermediates, in general metallacycles,[4] have been isolated from related

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catalytic reactions. Thus, metallacyclopentanes are formed on reaction of 2,2'-bipyridyl-1,5-cyclooctadienenickel(0) **2** with 3,3-dimethylcyclopropene[5] or methylcyclopropane;[6] the structure of the former metallacycle was determined X-ray crystallographically.[5]

2,5-Dimethyl-2,3,4-hexatriene **1** reacts smoothly with **2** in tetrahydrofuran (THF) at 5 °C with displacement of 1,5-cyclooctadiene (COD) to give the nickelacyclopentane **3**, which can be isolated in crystalline form in over 80% yield. The structure of **3** was confirmed by ^{1}H- and ^{13}C-NMR spectra and X-ray structural analysis.[7,8]

3 is formed by the oxidative addition of two triene molecules to nickel(0) with concomitant CC coupling. In the presence of maleic anhydride (MA) a reductive elimination takes place, leading to formation of the [4]-radialene **4**.[9] The Ni–C σ-bonds in **3** take part in insertion reactions followed by reductive elimination. Thus, reaction of **3** with CO leads to formation of 2,2'-bipyridyldicarbonylnickel and the cyclopentanone derivative **5**, whose structure is confirmed by IR/Raman, NMR, and mass spectra.[10] On reaction of methyl acetylenedicarboxylate with **3**, insertion and reductive elimination leads to the cyclohexene derivative **6**, which has also been unequivocally characterized.[11]



In the catalytic cyclooligomerization[1] of 2,5-dimethyl-2,3,4-hexatriene **1** mentioned initially, **4** is formed in only 11% yield along with 38% cyclotrimers.[2] The reaction described here in contrast, affords **4** in yields of more than 90% without necessitating a separation from by-products.

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1, 2431-31-4; **2**, 55425-12-4; **3**, 96453-21-3; **4**, 88919-66-8; **5**, 96446-08-1; **6**, 96446-09-2; MA, 108-31-6; CO, 630-08-0; $MeO_2CC{\equiv}CCO_2Me$, 762-42-5; 2,2'-bipyridyldicarbonylnickel, 14917-14-7.

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[8] **3**: 15.65 g (48.44 mmol) of **2** was dissolved in THF (350 mL) under argon and treated with a solution of **1** (10.48 g, 96.88 mmol) in THF (150 mL). After ca. 12 hours' stirring at 5 °C, the solution was evaporated to 40 mL, treated with 200 mL of pentane, cooled to −78 °C, and the resulting precipitate filtered cold on a frit, and dried. Yield: 17.4 g (40.35 mmol), 83.3%. ^{13}C-NMR ([D$_8$]THF, TMS, 75.5 MHz): $\delta = 151.17$, 150.52 (s, C-1, C-2); 108.32 (s, C-3); 121.69 (s, C-4); 26.47 (q, C-5); 23.12, 22.40, 22.08 (q, C-6, C-7, C-8); 152.33 (d, C-9); 127.20, 121.84 (d, C-10, C-12); 135.92 (d, C-11); 153.74 (s, C-13); MS: *m/z* 430 (M^+, decomp.).
[9] **4**: 2.11 g (4.89 mmol) of **3** was dissolved in THF (40 mL) under argon and treated with solid maleic anhydride (MA) (0.96 g, 9.78 mmol). Reaction was allowed to proceed for ca. 12 h, the THF removed by evaporation, and the residue taken up in pentane. After filtration through a frit, the filtrate was evaporated to dryness. Yield of crude product: 0.9 g (4.62 mmol) 94%. After sublimation in vacuo (60–80 °C): 0.75 g (3.47 mmol), 78.8% pure product. ^{1}H-NMR ([D$_8$]toluene): $\delta = 1.83$ ([2] ($CDCl_3$): $\delta = 1.80$); ^{13}C-NMR ($CDCl_3$): $\delta = 138.3$, 115.5, 23.8 ([2]: $\delta = 138.3$, 115.5, 23.8); MS: *m/z* 216 (M^+); UV (*n*-hexane): $\lambda_{max} = 269$ nm ($\lg\varepsilon = 4.62$), 259 sh (4.16), 280 sh (4.21), 304 sh (3.83) ([2]: UV (cyclohexane): $\lambda_{max} = 272$ nm ($\lg\varepsilon = 4.279$), 260 sh (4.176), 283 sh (4.230), 307 sh (3.857)).
[10] **5**: 2.94 g (6.82 mmol) of **3** was dissolved in THF (80 mL) and treated with 458.3 mL (20.46 mmol) CO. The THF was then removed and the residue was taken upon in pentane, filtered through a frit, and the filtrate evaporated to dryness. The residue was sublimed in a vacuum (80–100 °C): 1.1 g (4.5 mmol), 66% pure product. ^{13}C-NMR ($CDCl_3$, TMS, 75.5 MHz): $\delta = 194.05$ (s, C-1); 136.51, 136.05 (s, C-2, C-3); 125.07 (s, C-4); 140.89 (s, C-5); 25.97, 23.06, 22.72, 20.38 (q, C-6, C-7, C-8, C-9); MS: *m/z* 244 (M^+, 63%); IR (KBr): $\nu = 1696$ (s) (CO), 1661 (w), 1644 (w), 1619 (s) (C=C) cm^{-1}; m.p. 111 °C.
[11] **6**: 1.21 g (2.8 mmol) of **3** was dissolved in toluene under argon and treated with methyl acetylenedicarboxylate. After 4 hours' stirring the mixture was filtered through a frit. The filtrate was evaporated to dryness and the residue was taken up in pentane, filtered through a frit, and the solvent removed from the filtrate. Yield: 0.6 g (1.67 mmol), 59.8%. ^{13}C-NMR ($CDCl_3$, TMS, 75.5 MHz): $\delta = 133.42$, 133.35, 129.51, 126.18 (s, C-1, C-2, C-6, C-7); 132.38 (s, C-3); 169.87 (s, C-4); 52.12 (q, C-5); 25.05, 21.47, 20.93, 20.30 (q, C-8, C-9, C-10, C-11); MS: *m/z* 358 (M^+, 29%); IR (KBr): $\nu = 1734$ (s), 1721 (s) (CO), 1609 (m), 1537 (m) (C=C) cm^{-1}; m.p. 159 °C.

Nitrogen Monoxide as a Source for Oxo Ligands—Acetylene-Oxo Complexes of Tungsten**

By *Helmut G. Alt** and *Heidi I. Hayen*

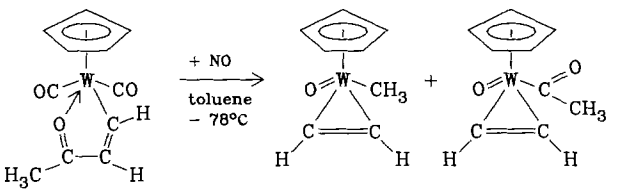
The conventional way to prepare organometallic oxo complexes involves the thermally or photochemically induced reaction of carbonyl complexes with air or with oxygen.[1-4] In special cases, the hydrolysis of alkyl transition-metal complexes is also suitable.[5]

We report here the reaction of the alkenyl ketone complex **1** with nitrogen monoxide in toluene. Nitrogen monoxide is not coordinated to the metal as an intact complex ligand, but rather provides its oxygen for the formation of a terminal oxo ligand. Simultaneously, the alkenyl ketone ligand fragments into an acetylene and a methyl or acetyl ligand.

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The mechanism of this instantaneous reaction is still unclear. Nitrogen monoxide, which is readily reduced, could react via a transient hyponitrito complex to form dinitrogen monoxide,[6, 7] thus acting as a source of oxygen.[8] However, no N_2O is detected in the reaction gas. Complex **1** does not react with NO_2 to form **2a** and **3a**. With air, only a small amount of **3a** is formed after 30 min.



1 **2a** (25%) **3a** (47%)

In order to prepare acetylene-oxo complexes of type **2**, the reaction of the acetylene-alkyl-carbonyl complexes **4a**–**c** with NO (as a source of oxygen) can also be used.

$$[LW(CO)(C_2H_2)Me] \xrightarrow[-CO]{+NO} [LW(O)(C_2H_2)Me]$$

4 **2**

a: L = η^5-C_5H_5, 37%, **b**: L = η^5-C_5H_4Me, 17%, **c**: L = η^5-C_5Me_5, 74%

For L = C_5H_5 and C_5H_4Me, the acetylene-nitrosyl complexes **5**[9] are formed in 38 and 61% yield, respectively. No oxo complexes result from the reaction of the chromium and molybdenum analogues of **1** with NO under the same reaction conditions. The reaction of **6a** with NO did not afford a tractable product; complex **6b** reacts with NO to give the dinitrosyl complex **7**.

$[LW(CO)(C_2H_2)NO]$
5, L = η^5-C_5H_5, η^5-C_5H_4Me

$[(C_5R_5)(CO)_2M\{HC{=}CH{-}C(O)Me\}]$
6; **a**, R = H, M = Mo; **b**, R = Me, M = Cr

$[(C_5Me_5)Cr(NO)_2(NO_2)]$ **7** $[W(O)(C_2H_2)(S_2CNR_2)_2]$ **8**, R = Me, Et

$[Re(O)(C_2Me_2)I]$ **9** $[(C_5H_5)W(NO)_2(HC{=}CHCOMe)]$ **10**

$[(C_5H_5)W(CO)_3]_2$
11

In the IR spectra (cf. [10]) of the acetylene-oxo complexes **2a**–**c** and **3a**, a relatively intense band is observed at 940 cm^{-1}, which is characteristic of the W=O vibration.[1–5] The ν(CC) absorption of the C_2H_2 ligand appears as a strong band in the region 1580–1630 cm^{-1}. Similar values have been reported for the alkyne-oxo complexes **8**[4] and **9**.[11] Especially noticeable in the ^{1}H-NMR spectra[10] is the large downfield shift of the signals of the methyl ligands. This is due to the positive charge induced on the central metal atom by the oxo ligand. A similar effect is observed for the chemical shifts of the C_2H_2 hydrogen atoms in the ^{1}H-NMR spectrum and for those of the C_2H_2 carbon atoms in the ^{13}C-NMR spectrum.

The alkyne ligand in the oxo complex **8**, R = Me,[4] has a relatively low barrier for rotation around the metal-alkyne bond ($\Delta G^{\neq}$ = 66.4 kJ/mol); the C_2H_2 signals of the complexes **2a**–**c** and **3a** do not change upon heating of the samples to 130 °C (in [D_8]toluene under pressure). This indicates that the complexes **2a**–**c** and **3a** exhibit high tungstacyclopropene character and that tungsten is present in its highest formal oxidation state +6.

Selective nitrosylation of **1** is achieved when nitrosyl-chloride is used as a nitrosylation reagent: in this case, equal proportions of the stable alkenyldinitrosyl complex **10**[13] and the known compound **11** are formed.

Experimental Procedure

All operations were carried out under inert atmosphere with dry solvents. Reaction of **1** with NO: **1** (0.24 g, 0.64 mmol) [12] was dissolved in 20 mL of toluene. The solution was cooled to –78 °C and allowed to react with excess NO gas. The solution immediately changed from dark red to orange. Subsequent column chromatography (silica gel/pentane) afforded the yellow oxo complex **2a** (eluted with ether) and the orange acetyl compound **3a** (eluted with tetrahydrofuran). Both solutions were evaporated to dryness under high vacuum. **2a**: m.p. = 77–80 °C (under argon), *m/z* 306 (relative to ^{184}W), yield 0.05 g (25%). **3a**, oil at room temperature, *m/z* 334 (relative to ^{184}W), yield 0.10 g (47%).

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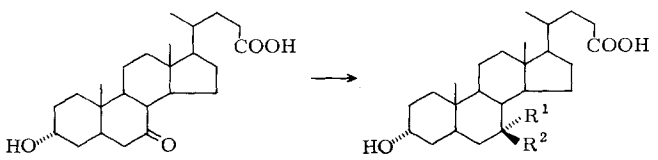
CAS Registry numbers:
1, 63325-53-1; **2a**, 96395-41-4; **2b**, 96395-42-5; **2c**, 96395-43-6; **3a**, 96395-44-7; **4a**, 62798-73-6; **4b**, 96395-45-8; **4c**, 96395-46-9; **5**, (l = η^5-C_5H_5), 87862-57-5; **6**, (l = η^5-C_5H_4Me), 96395-47-0; **6a**, 64466-36-0; **6b**, 96395-48-1; **7**, 96395-49-2; **10**, 96395-50-5; **11**, 12091-65-5; nitrogen monoxide, 10102-43-9; nitrosyl chloride 2696-92-6.

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[10] **2a**: IR: ν(CC) = 1585 (THF), ν(W=O) = 940 cm^{-1} (KBr). ^{1}H-NMR ([D_6]acetone, –20 °C, 2.04 internal standard): δ = 6.07 (s, C_5H_5), δ(A) = 10.35 (d, q; q; ^4J(HH) = 1.3 Hz), δ(B) = 8.90 (d) (AB system, J(A,B) = 0.5 Hz; ^2J(WH) = 9.7 and 7.0 Hz; C_2H_2), 1.71 (d, ^4J(HH) = 1.3 Hz; CH_3). ^{13}C{^{1}H}-NMR ([D_6]acetone, –20 °C, 29.75, internal standard): δ(C_5H_5) = 105.3, δ(C_2H_2) = 152.6, 148.4, δ(CH_3) = 2.3; ^1J(WC) = 89.7 Hz. – **3a**: IR: ν(C=O) = 1630, ν(CC) = 1630 (THF), ν(W=O) = 950 cm^{-1} (Nujol). ^{1}H-NMR ([D_6]acetone, –20 °C, 2.04, internal standard): δ = 6.10 (s, C_5H_5), δ(A) = 10.38, δ(B) = 8.80 (d) (AB system, J(AB) = 0.5 Hz; ^2J(WH) = 6.8 and 6.6 Hz; C_2H_2); 2.75 (s, CH_3). ^{13}C{^{1}H}-NMR ([D_6]acetone, –20 °C, 29.75 internal standard): δ(C_5H_5) = 105.9, δ(C=O) = 261.4, δ(C_2H_2) = 144.0, 139.3; ^1J(WC) = 23.9 and 58.1 Hz, δ(CH_3) = 52.1.
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[13] IR: ν(NO) = 1780, 1625, ν(C=O) = 1605 cm^{-1} (THF). ^{1}H-NMR ([D_6]acetone, –20 °C, 2.04 internal standard): δ = 6.23 (s, 5 H, C_5H_5), δ(A) = 7.80 (d, 1 H), δ(B) = 5.12 (d, 1 H) (AB system, J(AB) = 6.1 Hz), δ = 1.90 (s, 3 H, Me). ^{13}C-NMR ([D_6]acetone, –20 °C, 29.25 internal standard): δ = 105.7 (C_5H_5), 175.5 (CO), 148.4, 92.5 (–CH=CH–), 27.7 (Me). MS: *m/z* 414 (relative to ^{184}W), decomp. 171 °C.

Reduction of Ketones by Alkali Metals in Tertiary Alcohols: Unexpected Cation Effect on the Stereochemistry**

By *Claudio Giordano,** *Giulio Perdoncin,* and *Graziano Castaldi*

Although the reduction of ketones by alkali metals is a classical process, the overall mechanism and the factors that govern the stereochemistry of the products are not completely understood.[1] The stereochemical course of the reduction has practical applications: for example, the reduction of 3α-hydroxy-7-oxo-5β-cholanic acid **1** by alkali metals is the key step in the industrial production of 3α,7β-dihydroxy-5β-cholanic acid **2**. The reduction of **1**, carried out using a large excess of sodium in alcohols, provides **2** and **3** in the ratio 80—85/20—15 in almost quantitative yield.[2] In order to increase the stereoselectivity toward the formation of **2**, we have investigated the factors that influence the stereochemistry of this reduction.[3]



1

2, R^1 = H, R^2 = OH
3, R^1 = OH, R^2 = H

We describe here the stereochemistry of the reduction of **1** by alkali metals in tertiary alcohols (see Table 1). When the reduction is carried out in *tert*-amyl or *tert*-butyl alcohol, higher stereoselectivity toward the formation of **2** is observed with potassium, rubidium, and cesium than with sodium. This effect is not observed in primary and secondary alcohols.

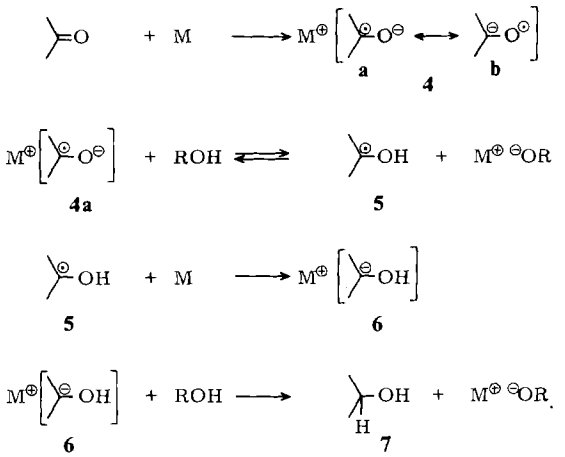
Table 1. Reduction of **1** by alkali metals M in *tert*-amyl alcohols [a].

1 [mmol]	MO*t*Am [mol] [b]	*t*AmOH [mL]	M [mmol]	**2** : **3** [c]
25.60	—	200	Na [0.217]	80 : 20
25.60	—	200	K [0.141]	94 : 6
2.56	—	20	Rb [0.025]	96 : 4
2.56	—	20	Cs [0.025]	96 : 4
25.60	M = K [0.136]	200	Na [0.436]	94 : 6
2.56	M = Rb [0.014]	20	Na [0.044]	95 : 5
2.56	M = Cs [0.014]	15	Na [0.044]	95 : 5

[a] The reduction was carried out with vigorous stirring, under nitrogen, and at reflux temperature. The metal was added in 10 minutes in the amount required to reach conversion higher than 90%. [b] Alkali metal *tert*-amylates were obtained by dissolving the desired amount of the metal in *tert*-amyl alcohol before adding **1**. [c] The product ratio was determined by HPLC analysis [2].

The reduction with sodium in tertiary alcohols in the presence of potassium, rubidium, or cesium salts gives the same stereoselectivity as observed for the reduction with potassium, rubidium, or cesium metals, respectively. In contrast, the stereoselectivity in the reduction of **1** with potassium, rubidium, or cesium is only slightly affected by the presence of sodium salts. This interesting cation effect in alcoholic medium has not been previously reported for the reduction of ketones by alkali metals.

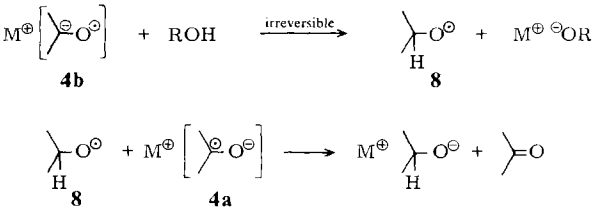
How can the mechanism of the reduction accomodate these experimental results? The first step of this reduction is the transfer of an electron to the ketonic carbonyl group generating the ketyl **4**.[4] The ketyl exists in equilibrium with a dimeric (or higher) species, which for aliphatic ketyls strongly favors dimeric or polymeric ion pairs.[5] In the presence of a relatively acidic proton donor (e.g., a tertiary alcohol) an α-hydroxyalkyl radical **5** is formed, according to the classical mechanism, via protonation of the ketyl on oxygen.[1,5] Subsequently, **5** undergoes a second electron transfer leading to the carbanion **6**, which is rapidly protonated to form **7**[1] (Scheme 1).



Scheme 1. Classical mechanism for the reduction of ketones with alkali metals in tertiary alcohols.

As an alternative to this mechanism, we would like to consider the possibility that the radical anion **4** is protonated on a different site. It has been reported that the protonation of the ketyl **4** occurs on oxygen rather than on carbon.[6] However, the observation that a stable ketyl dimer of 2,2,6,6-tetramethylcyclohexanone, on quenching with water, rapidly disproportionates to a molecule of alcohol and a molecule of ketone[7] suggests that the protonation might occur on carbon. Obviously, the protonation on oxygen is favored. However, it is a reversible process, whereas the protonation on carbon is irreversible under our experimental conditions. The latter protonation would lead to the formation of an electrophilic alkoxy radical **8**, which could be easily reduced by the ketyl **4** (Scheme 2). On the other hand, the protonation on oxygen would lead to a nucleophilic α-hydroxyalkyl radical **5**, which could not be reduced by the ketyl **4** so easily.[8]

The radical **5** is much more acidic (5 pK_A units lower) than the parent alcohol.[9] The ketyl **4** will be present in



Scheme 2. Alternative mechanism for the reduction of ketones with alkali metals in tertiary alcohols (first step as in Scheme 1).

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higher concentration in tertiary alcohols than in primary or in secondary ones,[10] thus favoring the reduction of **8**. In the classical mechanism,[1] the stereochemistry of the product is determined by the protonation of the carbanion **6**, which is a strong base, whereas, in our proposed mechanism, it is determined by the protonation of the more weakly basic ketyl **4** on carbon. Thus, the new mechanism better accomodates the observed cation effect in the reduction of **1** by alkali metals in tertiary alcohols.

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1, 4651-67-6; **2**, 128-13-2; **3**, 474-25-9.

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NaGe—High-Pressure Formation of the NaPb-Type Structure**

By *Jürgen Evers,* Gilbert Oehlinger, Gerhard Sextl,* and *Armin Weiss*

The 1:1 compounds of the alkali metals Na, K, Rb, and Cs with Si, Ge, Sn, and Pb crystallize at normal pressure (NP) in four structure types. In the monoclinic NaSi-type structure,[1] the monoclinic NaGe-type structure,[1] and the cubic KGe-type structure,[2] 6:6 coordination is observed, in contrast to the tetragonal NaPb-type structure with 7:7 coordination.[3] Recently, the six binary phases with the KGe-type structure were transformed under high pressure (maximum 4 GPa) into the NaPb-type structure.[4] The NP phases are approximately 4% less densely packed than the high-pressure (HP) phases. This increase in density is in agreement with the pressure-coordination rule that the HP phases exhibit higher coordination (7:7) than the NP ones (6:6). We report here on the high-pressure transformation of NaGe, the only known binary phase with the NaGe-type structure, into the NaPb-type structure.

NaGe was prepared at NP under argon by fusion of stoichiometric amounts of the elements in a molybdenum crucible equipped with a cover. In order to prevent the evaporation of sodium during the synthesis, the Mo crucible was placed in a vacuum-tight iron crucible fitted with a copper gasket. The crucibles were heated in a high-vacuum furnace to 800—850°C. NaGe is rapidly decomposed by air and water. Therefore, all preparative operations involving the open iron crucible must be carried out under purified argon in a glove box. A belt-type apparatus was used to generate high pressures and high temperatures (maximum 4 GPa, 500°C, boron nitride crucibles). After rapid cooling to room temperature and subsequent release of pressure, the HP phase of NaGe can be metastably quenched to ambient conditions. Heating of this phase to 300°C results in quantitative retransformation into the NP phase.

The X-ray Guinier pattern (Huber G 644 with computer control, $Cu_{K\alpha 1}$ radiation) can be tetragonally indexed. It shows the characteristic sequence of reflections for the NaPb-type structure.[3] Best agreement between observed and calculated intensities was achieved with the positional parameters given in Table 1 (32 reflections, $R = 0.07$). In the ternary phases $NaGe_xSn_{1-x}$, which were studied in steps of $\Delta x = 0.25$ from $x = 0$ to $x = 1$, the NaPb-type structure is stable at NP for $0.00 \leq x \leq 0.25$ and at HP over the whole range $0.00 \leq x \leq 1.00$.

Table 1. Crystallographic data for NaGe (NP) of the NaGe type [1] and NaGe (HP) of the NaPb type.

	Normal-pressure phase [1]	High-pressure phase
Space group	$P2_1/c$	$I4_1/acd$
Lattice parameters [pm]	$a = 1233$ $b = 670$	$a = 984.0 \pm 0.3$
	$c = 1142$	$c = 1609.6 \pm 0.6$
Angle [°]	$\beta = 119.9$	
Number of formula units per unit cell	16	32
Unit-cell volume [pm³]	817.8×10^6	1559×10^6
$\rho_{calcd.}$ [g/cm³]	3.11	3.26
$\rho_{measured}$ [g/cm³]	3.14	3.25
Positions	$4Na_I$, $4Na_{II}$, $4Na_{III}$, $4Na_{IV}$, $4Ge_I$, $4Ge_{II}$, $4Ge_{III}$, $4Ge_{IV}$ in 4e	16 Na_I in 16f; x = 0.627; 16 Na_{II} in 16e; x = 0.875; 32 Ge in 32g; x = 0.065; y = 0.136; z = 0.930

The crystallographic data for the monoclinic NP phase of the NaGe-type structure and for the tetragonal HP phase of the NaPb-type structure are summarized in Table 1. NaGe (HP) is isotypic with NaSn[5] and NaPb.[3] For these three sodium compounds, the axial ratio c/a changes continually. It is 1.64 in NaGe (HP), 1.66 in NaSn ($a = 1046$, $c = 1739$ pm),[5] and 1.68 in NaPb ($a = 1058$, $c = 1775$ pm).[3] Furthermore, the corresponding silicides and germanides of the larger alkali metals K, Rb, and Cs[4] as well as their stannides and plumbides[6] crystallize in the NaPb type at NP. In this case, c/a remains constant at 1.63.

Tetragonal NaGe (HP) with the NaPb-type structure has an approximately 5% higher density than monoclinic NaGe (NP) with the NaGe-type structure (Table 1). This increase in density involves an increase in the coordination number from 6:6 to 7:7. Nevertheless, the Ge partial structures of both polymorphs of NaGe consist of isolated tetrahedra of tricoordinated germanium atoms. Possibly, the semiconducting properties of these phases will be lost when 8:8 coordination in NaGe is stabilized at pressures very much higher than 4 GPa. Such a coordination is already present at NP in LiGe,[7] LiSn,[8] and LiPb.[9] In

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LiGe, the Ge partial structure consists of a three-dimensional network of tricoordinated germanium atoms. However, the electric conductivity now shows metallic behavior. In LiSn and LiPb, no tricoordinated arrangement of the Sn and Pb atoms, respectively, is found. The Sn atoms still have four Sn neighbors in LiSn; the Pb atoms in LiPb have even six Pb neighbors. In this case, metallic phases are present.

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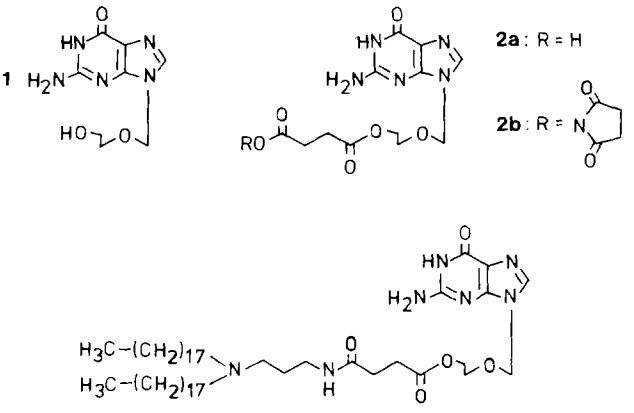
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A Nucleolipid with Antiviral Acycloguanosine as Head Group—Synthesis and Liposome Formation**

By *Helmut Rosemeyer, Michael Ahlers, Brigitta Schmidt,* and *Frank Seela**

Nucleoside analogues in which the glyconic moiety is replaced by an acyclic side chain exhibit strong antiviral activity. 9-(2-Hydroxyethoxymethyl)guanine (acycloguanosine, acyclovir), **1**, which bears only the C-1′–O–C-4′–C-5′ chain of D-ribofuranose is one of the most potent antiviral substances, especially against herpes simplex (type I and II.)[1] Depot and/or transport forms of acycloguanosine[2,3] have to ensure the release of the unchanged pharmacon in vivo. The selective toxicity of **1** for virus-infected cells is based on the fact that it acts as a substrate for a virus-coded thymidine kinase which phosphorylates specifically the 5′-hydroxyl group. A modification of this hydroxyl group abolishes the activity almost completely, while structural alterations of the nucleobase lead to strongly reduced activity.[4]

An anionic acycloguanosine-phospholipid conjugate has recently been described.[5] We report here the synthesis and liposome formation of the nucleolipid **3** which carries acycloguanosine as head group and the likewise antiviral *N,N*-dioctadecyl-1,3-propanediamine as lipid moiety. Between the lipid and acycloguanosine, a succinate spacer is incorporated which can be cleaved at the head group by the action of either esterases or dilute base with liberation of the pharmacon.[2,3] This hydrolyzable amphiphilic acycloguanosine derivative can be solubilized in the form of liposomes bearing the drug as a hydrophilic head.[6,7] Amphiphilic drug conjugates show altered resorption characteristics and body distribution, and liposomes of such conjugates can be taken up by tumor cells via various mechanisms.[8]



3

Reaction of acycloguanosine, **1**, with succinic anhydride leads to the crystalline succinate **2a**, which can be converted into its activated ester **2b** by reaction with *N*-hydroxysuccinimide in the presence of dicyclohexylcarbodiimide. Compound **2b** was isolated or coupled in situ with the primary amino group of *N,N*-dioctadecyl-1,3-propanediamine. The latter was obtained by alkylation of dioctadecylamine with acrylonitrile and subsequent reduction with $LiAlH_4$.[9] The reaction of this lipid with the activated ester **2b** was complete within 6 h; pure **3** was obtained after silica gel chromatography in 62% yield as a colorless wax.

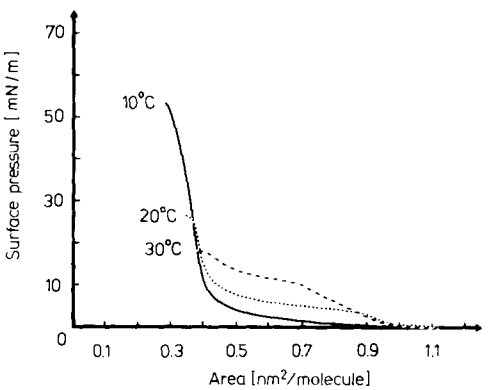


Fig. 1. Surface pressure–area isotherms of the nucleolipid **3** at three different temperatures.

For the characterization of the amphiphilic behavior of **3**, the nucleolipid was spread as a monolayer at the gas-water interface on a Langmuir film balance.[10] Figure 1 shows the resulting surface pressure–area isotherms at three temperatures. Whereas below 10°C the nucleolipid forms only a condensed film with a collapse pressure of about 53 mN/m, the 20°C and 30°C isotherms also show a liquid-like phase. The area value at the collapse point of the condensed phase amounts to 0.42 nm^2/molecule and is in the normal range of double-tailed lipids. Along an isobar with a surface pressure of 10 mN/m phase transition appears at 22°C.

Ultrasonication of mixtures of **3** with either cholesterol (30 mol-%) or dicetyl phosphate (100 mol-%) in water (15 min, 50°C) or manual shaking results in the formation

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of opaque solutions.[6] After filtration (millipore-filter, 0.45 μm), about 80% of the nucleolipid can be separated as liposomes from low-molecular-weight material by gel chromatography and obtained as an opaque, UV-active solution ($\lambda_{max} = 262$ nm), which is stable for at least four weeks. Electron micrographs show their spherical structure. Liposomes obtained by the "handshaking method" have a mean diameter of about 2000—5000 Å, those obtained by ultrasonication approximately 300—1000 Å.

The finding that the nucleolipid **3** forms liposomes only in the presence of cholesterol or dicetyl phosphate as mediator may be due to the relatively low hydrophilicity of the head group. A steric hindrance of liposome formation by acycloguanosine can be excluded because the area value of the condensed film of **3** (0.42 nm^2/molecule) is in the normal range of double-tailed lipids.

Experimental Procedure and Physical Data

2b: The succinate **2a** [2] (325.3 mg, 1 mmol) and *N*-hydroxysuccinimide (115.3 mg, 1 mmol) are dissolved in dry, amine-free dimethylformamide (10 mL) and cooled to about 5 °C. Dicyclohexylcarbodiimide (206 mg, 1 mmol) is then added and the reaction mixture stirred for 24 h at room temperature. During this time the precipitated dicyclohexylurea is occasionally removed by filtration. The solvent is evaporated in vacuo, the residue dissolved in water (100 mL), and the precipitated crude product filtered. Recrystallization (2-propanol) afforded 312 mg (79%) of the crystalline ester **2b**; m.p. 130—133 °C. Thin layer chromatography (TLC) (silica gel, $CHCl_3$/MeOH, 8:2, v/v) $R_f = 0.6$; UV (MeOH) $\lambda_{max} = 253$, 272 nm (sh) ($\varepsilon = 14300$, 9800 M^{-1} cm^{-1}); ^{1}H-NMR (250 MHz, [D$_6$]Me_2SO) $\delta = 10.64$ (s, 1H, NH), 7.80 (s, 1H, H-8), 6.51 (s, 2H, NH_2), 5.37 (s, 2H, H-1'), 4.12 (t, 2H, H-4' or H-5', $J = 4.0$ Hz), 3.66 (t, 2H, H-4' or H-5', $J = 4.1$ Hz), 2.91 (t, 2H, CH_2-succinate, $J = 5.9$ Hz), 2.80 (s, 4H, 2 × CH_2-succinimide), 2.65 (t, 2H, CH_2-succinate, $J = 5.9$ Hz); ^{13}C-NMR (62.9 MHz, [D$_6$]Me_2SO) $\delta = 170.6$, 169.6, and 167.8 (3C=O), 156.4 (C-6), 153.6 (C-2), 151.2 (C-4), 137.2 (C-8), 116.4 (C-5), 71.7, 66.2 and 62.9 (CH_2N-9, CH_2O, CH_2CO_2), 27.9 and 25.6 (2CH_2-succinate), 25.2 (2CH_2-succinimide).

3: The succinate **2a** (325.3 mg, 1 mmol) and *N*-hydroxysuccinimide (230.6 mg, 2 mmol) are dissolved in 15 mL of dry dimethyl sulfoxide (DMSO) and converted into the ester **2b** as described above. When the reaction is complete (TLC) about 10 mL of the solvent is removed in vacuo and the residue is diluted with $CHCl_3$ (20 mL). After addition of *N,N*-dioctadecyl-1,3-propanediamine (650 mg, 1.12 mmol), the reaction mixture is stirred for 6 h at room temperature. Silica gel chromatography (6 × 40 cm, $CHCl_3$/MeOH, 95:5, v/v) gave a main zone, which, after pooling the appropriate fractions and evaporation of the solvent, afforded 550 mg (62%) of **3** as a colorless wax; m.p. 67—68 °C (not corrected). TLC (silica gel, $CHCl_3$/MeOH, 9:1, v/v) $R_f = 0.45$; UV ($CHCl_3$) $\lambda_{max} = 257$, 272 nm (sh) ($\varepsilon = 13700$, 9300); ^{13}C-NMR (62.9 MHz, $CDCl_3$) $\delta = 172.9$ and 170.6 (2C=O), 158.7 (C-6), 154.2 (C-2), 152.0 (C-4), 137.6 (C-8), 117.2 (C-5), 72.6, 67.2, and 63.1 (CH_2N-9, CH_2O, CH_2CO_2), 48.0, 46.3, and 41.1 (NCH_2), 31.9—22.6 (aliphatic CH_2), 13.9 (2CH_3).

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1, 59277-89-3; **2a**, 59298-42-9; **2b**, 96328-27-7; **3**, 96328-28-8; succinic anhydride, 108-30-5; *N*-hydroxysuccinimide, 6066-82-6; *N,N*-dioctadecyl-1,3-propanediamine, 15337-59-4

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Synthesis, Structure, and Ligand Motion of $[Cr(CO)_2\{P(OCH_3)_3\}(\eta^4\text{-}2,4\text{-dimethyl-}1,3\text{-pentadiene})]$, a Complex with a C—H—Cr Bridge**

By *Günther Michael, Jürgen Kaub,* and *Cornelius G. Kreiter**

Organotransition-metal complexes that, in addition to σ- or π-bonds, exhibit 3z2e bonding between a C—H moiety of the ligand and the central metal atom[1] are models for the attack of a coordinatively unsaturated complex fragment on a C—H bond. Such complexes are crucial for the understanding of the activation of C—H bonds by transition metals.

The photochemical reaction of the chromium complex **1** with 2,4-dimethyl-1,3-pentadiene (**2**) in *n*-pentane at 203 K does not yield a $[Cr(CO)_3\{P(OCH_3)_3\}(\eta^4\text{-diene})]$ complex, as is the case with other dienes,[2] but rather the product **3** containing one CO ligand less.[3] In **3**, the diene is coordinated to the central chromium atom through both its π-bond system and a methyl group.

$$\underset{\mathbf{1}}{[Cr(CO)_5\{P(OCH_3)_3\}]} + \underset{\mathbf{2}}{C_7H_{12}} \xrightarrow[-3CO]{h\nu} \underset{\mathbf{3}}{[Cr(CO)_2\{P(OCH_3)_3\}(\eta^4\text{-}C_7H_{12})]}$$

The reaction mixture must be rapidly separated by chromatography on silica gel at 230 K, since spontaneous decomposition of **3** sometimes occurs upon longer standing. Pure **3** forms deep red crystals, which are soluble in *n*-pentane or toluene. In toluene, **3** is stable for a short period at temperatures of up to 390 K.

The IR spectrum of **3** exhibits two CO stretching vibrations having the same intensity (1915, 1840 cm^{-1}; *n*-pentane), which indicate an angular $Cr(CO)_2$ group.

The ^{1}H-NMR spectrum of **3** is temperature dependent (Table 1). The low-temperature spectrum is obtained at 124 K. Particularly noticeable is the fact that the resonances of the 5-methyl protons are split into three multiplets, a, b, and c (Table 1), with geminal coupling constants of $J_{ab} = 10.0$, $J_{ac} = 15.0$, and $J_{bc} = 18.0$ Hz. The strong shielding of one of these methyl protons shows its interaction with chromium. At 240 K, the methyl protons in the 5-position are apparently equivalent due to rapid exchange ($\Delta G^{\ddagger}_{200} = 28.6 \pm 0.3$ kJ/mol). Increasing the temperature to 390 K results in collapse of the signals of the methyl groups in the 2- and 4-positions and of those of the methylene protons in the 1-position and the methyl protons in the 5-position ($\Delta G^{\ddagger}_{300} = 68.1 \pm 0.1$ kJ/mol).

The X-ray structure determination of **3** (Fig. 1) supplements the spectroscopic results. Complex **3** has a distorted octahedral ligand sphere. The 2,4-dimethyl-1,3-pentadiene ligand occupies three facial coordination sites with its π-system (b and c) and with a C—H bond of the methyl group in the 5-position (a). The bulky $P(OCH_3)_3$ ligand is found in the d position.

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[**] Hindered ligand motion in transition-metal complexes, Part 27. This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie. Part 26: G. Michael, J. Kaub, C. G. Kreiter, *Chem. Ber.*, in press.

Table 1. ^{1}H-NMR spectroscopic data of **3**. Chemical shifts in δ relative to TMS. Intensity and, where determinable, ^{31}P-^{1}H coupling constants [Hz] in parentheses. Measurements at 124 and 240 K in [D_6]dimethyl ether, measurement at 390 K in [D_8]toluene.

1*Z*	1*E*	2, 4	3	5	$P(OCH_3)_3$	*T* [K]
−0.06 (1)	3.43 (1)	2.11 (3) 2.30 (3)	5.46 (1)	0.12 (a) (1, 2.0) −1.58 (b) (1, 4.5) −10.03 (c) (1, 13.0)	3.67 (9, 11.1)	124
−0.12 (1, 5.3)	3.35 (1, 8.0)	2.15 (3) 2.31 (3)	5.31 (1)	−3.75 (3, 6.5)	3.70 (9, 11.0)	240
[a]	[a]	2.11 (6)	5.07 (1)	[a]	3.57 (9, 11.0)	390

[a] The averaged-out signal of the protons in the 1- and 5-positions is very broad and not observable.

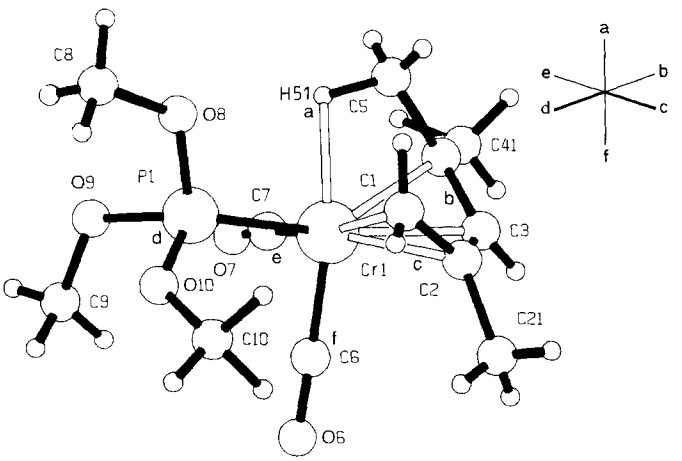
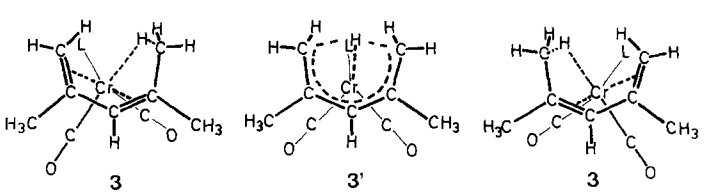


Fig. 1. Crystal structure of **3**. $P2_1/n$, $a = 822.2(2)$, $b = 1183.9(3)$, $c = 1611.9(3)$ pm, $\alpha = 90.0$, $\beta = 99.31(2)$, $\gamma = 90.0°$, $\rho_{calcd.} = 1.41$ g cm^{-3}. CAD4 (Enraf-Nonius) ω-scan ($2\theta \leq 55°$), $Mo_{K\alpha}$. 2658 independent, 3228 measured reflections, $R = 0.054$, $R_w = 0.043$. The positions of the hydrogen atoms on C10 were calculated; all remaining protons were located by X-ray analysis and freely refined. Selected distances [pm] and angles [°]: Cr–C1 224.6(4), Cr–C2 219.9(4), Cr–C3 216.0(4), Cr–C4 214.0(4), Cr–C5 239.9(4), Cr–H51 194(3), Cr–P 225.3(1), Cr–C6 179.3(4), Cr–C7 182.4(4), C1–C2 138.7(5), C2–C3 141.4(5), C3–C4 137.3(6), C4–C5 148.8(5); P–Cr–H51 80.3(8), C6–Cr–H51 169.9(9), Cr–Cr–H51 91.8(9), P–Cr–C6 91.9(1), P–Cr–C7 92.1(1), C6–Cr–C7 82.0(2), Cr–H51–C5 101.1. C1–C4 extend across a plane (±2.2 pm); C5 directed towards the Cr out of the plane (+29.8 pm), C21 and C41 are directed away (−30.2, −12.8 pm). Further details of the crystal structure investigation are available on request from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2, on quoting the depository number CSD 51353, the names of the authors, and the journal citation.

The temperature-dependent ^{1}H-NMR spectra of **3** show two hindered ligand motions which are independent of each other. One is a hindered rotation of the terminal methyl group, which was similarly observed for $[\{P(OCH_3)_3\}_3Fe(\eta^3\text{-butenyl})]^+$.[4] The activation barrier of $\Delta G^{\ddagger}_{200} = 28.6 \pm 0.3$ kJ/mol is a measure for the strength of the Cr–H–C bond.

3 is chiral and is present as an enantiomeric pair. Owing to the second dynamic process (Scheme 1), an apparent C_s symmetry is observed on a time average; this means that enantiomerization takes place.

Thus, the position of the diene skeleton changes relative to the three other ligands and a 1,5-sigmatropic hydrogen shift occurs in the 2,4-dimethyl-1,3-pentadiene ligand. Since the energy barrier of $\Delta G^{\ddagger}_{300} = 68.1 \pm 0.1$ kJ/mol is much lower than that for free conjugated dienes,[5] the chromium is presumably involved in the 1,5-hydrogen shift. The ^{1}H-NMR spectroscopic results can be explained by the existence of the species **3'**, a transient intermediate. On the basis of the experimental data it cannot be determined whether the $P(OCH_3)_3$ ligand and the two CO ligands undergo synchronous def-efd positional exchange during the 1,5-hydrogen shift or whether the three facial ligands are rotated more quickly with respect to the rest of the molecule.



Scheme 1. L: $P(OCH_3)_3$.

Complex **3** shows that the steric demands of organic ligands are apparently the determining factor in the formation of organotransition-metal complexes containing C–H-metal bridges. The 5-methyl group of the 2,4-dimethyl-1,3-pentadiene ligand in **3** displaces a CO ligand in the a position and reduces the electron deficiency on chromium by formation of the C–H–Cr bond. Although this bond to the metal can be easily broken, the C–H bonds of the 5-methyl group are strongly activated, thereby enabling a facile 1,5-hydrogen shift to occur, presumably via chromium.

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CAS Registry numbers:
1, 18461-34-2; **2**, 1000-86-8; **3**, 96445-04-4.

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[2] M. Kotzian, C. G. Kreiter, G. Michael, S. Özkar, *Chem. Ber.* 116 (1983) 3637.

[3] *Experimental procedure:* An *n*-pentane solution (500 mL) containing **1** (500 mg, 1.58 mmol) and **2** (1.5 mL) was irradiated at 203 K for 1 h with a UV lamp (TQ 150, Original Hanau Heraeus Quarzlampen GmbH). A stream of nitrogen was vigorously bubbled through the solution in order to remove the photochemically evolved carbon monoxide. The dark red reaction mixture was filtered through filter flakes, treated with 50 mL of ether, and evaporated at 253 K. The residue was dissolved in 5 mL of

pentane/ether (1:3) and chromatographed at 230 K on silica gel with pentane/ether (3:1). Unreacted **1** was eluted initially followed by **3**. The red solution containing **3** was evaporated; the product was dissolved in pentane/ether (4:1) and the resulting solution slowly cooled from 252 K to 193 K. The deep red crystals that separate out were washed several times with 1 mL portions of pentane at 193 K and dried under high vacuum (188 mg, 36%).

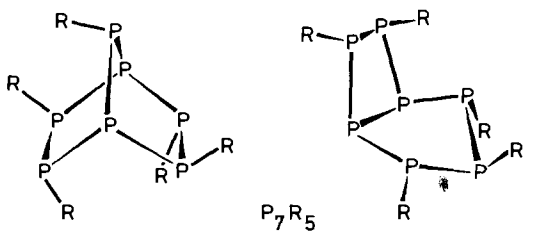
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P_7tBu_5—The First Bicyclo[3.2.0]heptaphosphane**

By *Marianne Baudler,* Michael Michels, Josef Hahn,* and *Manfred Pieroth*

Dichloro(organo)phosphanes react with metals in the presence of phosphorus(III) chloride to give polycyclic organophosphanes P_nR_m ($m < n$).[1] In the case of small alkyl groups (R = Me, Et, *i*Pr), with $RPCl_2$ and PCl_3 in the molar ratio 5:2, the 2,3,5,6,7-pentaorganobicyclo[2.2.1]heptaphosphanes **1**[1,2] are formed. We have now found a novel P_7R_5 structure type in the penta-*tert*-butylheptaphosphane **2**, and at the same time the first polycyclic phosphane skeleton containing an annelated four-membered ring.[1a]



P_7R_5

1, R = Me, Et, *i*Pr

2, R = *t*Bu

2 is formed in about 20% yield on dehalogenation of a mixture of *tert*-butyl(dichloro)phosphane and PCl_3 with magnesium.

$$5\,tBuPCl_2 + 2\,PCl_3 + 8\,Mg \longrightarrow \underset{\mathbf{2}}{P_7tBu_5} + 8\,MgCl_2$$

In addition, mainly $(PtBu)_4$,[3a] $(PtBu)_3$,[3b] P_6tBu_4,[4] P_8tBu_6,[5] P_4tBu_3H,[6a] and P_5tBu_4H[6b] are formed. The best initial yield of **2** (ca. 25%) is obtained when $tBuPCl_2$ is allowed to react with PCl_3 in the molar ratio 2:1 (not 2.5:1!) in boiling tetrahydrofuran (THF). **2** can be isolated in analytically pure form by chromatographic separation of the product mixture.

The heptaphosphane **2** is a pale yellow solid (m.p. 132°C, decomp. sealed tube) which is stable at room temperature and is sensitive to light and oxidation; it is readily soluble in hydrocarbons and THF, and moderately soluble in methanol. The mass spectrum (10 eV, 70°C) shows, aside from the M^+ ion (*m/z* 502; 100%), only $(M-C_4H_9)^+$. The IR spectrum[7] is distinctly different from that of **1** (R = Me[2]) in the region of the P–P stretching and deformation vibrations.

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The constitution and spatial structure of **2** follow from detailed NMR studies. The $^{13}C\{^1H,^{31}P\}$-NMR spectrum[8] provides proof of the nonequivalence of the five *tert*-butyl groups. The ^{31}P- and ^1H-signals[8] belonging to identical $>PtBu$ groups were assigned on the basis of a "reverse ^{31}P-^1H shift-correlated" 2D-NMR spectrum,[9] which also indirectly characterizes the ^{31}P signals of the bridgehead atoms. The complete analysis of the $^{31}P\{^1H\}$-NMR spectrum (Fig. 1) is additionally based on a COSY 45 experiment,[10] by which the relative signs of the coupling constants have been determined (RMS value of the spectrum calculation: 0.3; all transitions assigned).

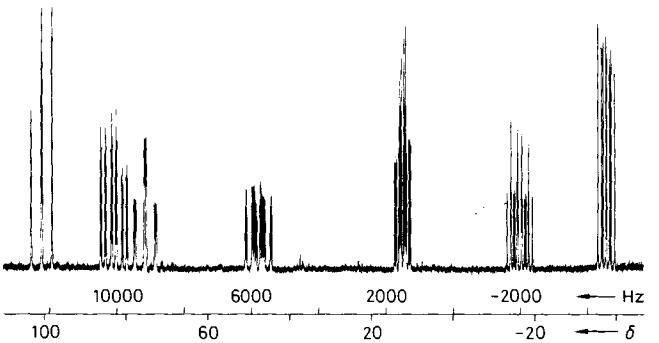
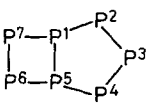


Fig. 1. Observed 121.497-MHz $^{31}P\{^1H\}$-NMR spectrum of **2** in [D$_6$]benzene at 27°C.

Table 1. ^{31}P-NMR parameters [a] of **2** in [D$_6$]benzene (15%) at 27°C.



δ	^1J(PP)	^2J(PP)	^3J(PP)
+ 51.3 (P^1)	−305.9 (P^1P^2)	+ 16.5 (P^1P^3)	+47.3 (P^2P^6)
+ 79.0 (P^2)	−303.5 (P^2P^3)	+ 23.1 (P^1P^4)	− 0.9 (P^3P^6)
+104.2 (P^3)	−320.7 (P^3P^4)	+ 17.6 (P^1P^6)	0.0 (P^3P^7)
+ 86.7 (P^4)	−328.5 (P^4P^5)	+ 22.0 (P^2P^4)	+ 0.1 (P^4P^7)
− 12.7 (P^5)	−123.0 (P^5P^6)	+ 3.9 (P^2P^5)	
+ 16.0 (P^6)	−156.6 (P^6P^7)	+ 9.9 (P^2P^7)	
− 33.9 (P^7)	−244.5 (P^1P^7)	+ 11.5 (P^3P^5)	
	−192.3 (P^1P^5)	+139.4 (P^4P^6)	
		+110.0 (P^5P^7)	

[a] *J* [Hz]; signs assuming negative ^1J(PP)-couplings.

The positions of the signals and, above all, the values of the ^1J(PP) coupling constants (Table 1) identify **2** as a bicyclic compound containing a five-membered ring and an annelated four-membered ring. The large positive $^2J(P^4P^6)$ coupling indicates that the lone pairs of electrons at the respective P atoms are directed towards each other.[4,11] Accordingly, the four-membered ring is strongly inclined towards the five-membered ring and the *t*Bu group at P^6 is in the *exo* position. The relationships $^2J(P^5P^7) \gg {}^2J(P^1P^6)$ and $^3J(P^2P^6) \gg {}^3J(P^4P^7) \approx {}^3J(P^3P^6)$ reveal the *endo* position of the *t*Bu group at P^7 and the arrangement of the substituents of the five-membered ring. Due to steric interactions between the *t*Bu groups in the 3,7 position, the four-membered ring and five-membered ring are distorted with respect to each other at the zero-bridge P^1–P^5. This mani-

fests itself in the different values of $^2J(P^1P^3)$ and $^2J(P^3P^5)$ and, in particular, in the large coupling constants $^2J(P^5P^7)$ and $^3J(P^2P^6)$ caused by the resulting folding of the four-membered ring; the five-membered ring is assumed to have a twisted envelope conformation. Due to the asymmetry of the molecule, **2** exists as an enantiomeric mixture. Transformations between (+)- and (−)-form by concomitant inversion at P^6 and P^7 do not take place at room temperature.

That **2** is a 2,3,4,6,7-penta-*tert*-butylbicyclo[3.2.0]heptaphosphane[12] can be explained by a destabilization of the structure type **1** as a result of increasing steric interactions with increasing bulkiness of the substituents at P^6 and P^7. Differing skeletal structures for R = Me, Et, *i*Pr, and R = *t*Bu have already been found in the P_8R_6 class of compounds.[1a] In the case of **2**, for the first time a molecular polycyclic phosphane is forced to form an annelated four-membered ring as structural unit for steric reasons.[1a] A framework consisting of two annelated P_4 rings, on the other hand, is so unfavorable energetically that the compound P_6tBu_4 related to **2** is not a bicyclo[2.2.0]- but a bicyclo[3.1.0]hexaphosphane.[4]

Experimental

A solution of $tBuPCl_2$ (50.9 g, 0.32 mol) and PCl_3 (22.0 g, 0.16 mol) in THF (200 mL) is added dropwise within 2 h to 500 mL of vigorously stirred boiling THF containing magnesium turnings (14.0 g, 0.58 mol; previously etched by evaporating a few grains of iodine). The yellow mixture is refluxed for a further 1 h, and, thereafter, allowed to cool to room temperature before complete removal of the solvent under reduced pressure. The residue is then taken up in 800 mL of *n*-pentane and the undissolved material filtered off, washed with pentane (3 × 400 mL) and the solvent removed from the combined filtrates. The yellow, viscous residue is dissolved in 100 mL of pentane, and P_8tBu_6 allowed to separate out by crystallization at room temperature (1 d). After filtration, the filtrate is evaporated down to 40 mL and then chromatographed twice on Al_2O_3 using pentane with ^{31}P-NMR spectroscopic control. Final purification is achieved by preparative HPLC (Nucleosil-5-C18 column, methanol, receiver: −78 °C). The solvent is rapidly condensed off (bath: −30 °C, cooling trap: −196 °C, pressure: 0.3 torr), leaving 0.59 g of pure **2** (2% referred to $tBuPCl_2$; not optimized).

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CAS Registry numbers:
2, 96482-81-4; $tBuPCl_2$, 25979-07-1; PCl_3, 7719-12-2.

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[3] a) K. Issleib, M. Hoffmann, *Chem. Ber.* 99 (1966) 1320; b) M. Baudler, J. Hahn, H. Dietsch, G. Fürstenberg, *Z. Naturforsch. B* 31 (1976) 1305.
[4] M. Baudler, Y. Aktalay, K.-F. Tebbe, T. Heinlein, *Angew. Chem.* 93 (1981) 1020; *Angew. Chem. Int. Ed. Engl.* 20 (1981) 967.
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[6] a) M. Baudler, B. Makowka, *Z. Naturforsch. B*, in press; b) M. Baudler, H. Tschäbunin, *Z. Anorg. Allg. Chem.* 511 (1984) 77.
[7] IR (<600 cm^{-1}, KI pellet): 585 (w), 524 (vw), 509 (vw), 490 (vw), 398 (w, sh), 391 (m), 371 (w, sh), 367 (w), 350 (vw), 337 (vw) cm^{-1}.
[8] $^{13}C\{^1H,^{31}P\}$-NMR ([D_6]benzene, 27 °C, 75.47 MHz): 33.9, 33.7, 33.6, 33.2, 32.5 (PC), 32.7, 32.0, 31.4, 30.1, 29.0 (PCC). — $^1H\{^{31}P\}$-NMR ([D_6]benzene, 24 °C, 300.13 MHz): 1.45 (P^2tBu), 1.56 (P^3tBu), 1.39 (P^4tBu), 1.25 (P^6tBu), 1.37 (P^7tBu).
[9] a) A. Bax, R. H. Griffey, B. L. Hawkins, *J. Magn. Reson.* 22 (1976) 345; b) W. E. Hull, private communication.
[10] A. Bax, R. Freeman, *J. Magn. Reson.* 44 (1981) 542.
[11] a) M. Baudler, G. Reuschenbach, J. Hahn, *Chem. Ber.* 116 (1983) 847; b) M. Baudler, T. Pontzen, *Z. Naturforsch. B* 38 (1983) 955; c) M. Baudler, J. Hellmann, T. Schmidt, *ibid. B* 38 (1983) 537.
[12] A bicyclo[2.2.1]heptaphosphane structural framework was initially assumed for the compound identified only by mass spectroscopy [1c].

Pentacarbonylolefin- and Pentacarbonyldiolefinrhenium Complex Cations; Synthesis and Structure of the 2-Butene-1,4-diyl-Bridged Carbonyldirhenium Complex *trans*-$[(OC)_5ReCH_2CH{=}CHCH_2Re(CO)_5]$**

By *Wolfgang Beck**, *Klaus Raab*, *Ulrich Nagel*, and *Wolfgang Sacher*

Dedicated to Professor Helmut Behrens on the occasion of his 70th birthday

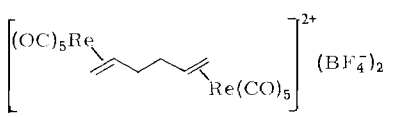
Reaction of pentacarbonyltetrafluoroboratorhenium(I) with ethene and propene under very mild conditions (1 bar, 20 °C) affords the olefin complexes $[(OC)_5Re(olefin)]^+BF_4^-$.[1] We have now found that the Lewis acid "$Re(CO)_5^+$" can add to the C=C bond of various mono- and diolefins.

$$[(OC)_5ReFBF_3] + L \xrightarrow[20\,^\circ C]{CH_2Cl_2} [(OC)_5Re(L)]^+BF_4^-$$
1

a, L = 1-pentene; **b**, L = cyclohexene; **c**, L = 1,5-cyclooctadiene; **d**, L = 1,3-butadiene; **e**, L = 1,4-cyclohexadiene

With 1,5-hexadiene and 1,5-cyclooctadiene we could also isolate the diolefin-bridged complexes **2**, which, because of their sparing solubility in acetone, can be separated from the monomeric compounds **1**. Compared to the ν(C=C) bands of the free olefins, those of the coordinated olefins in the IR spectra of **1** and **2** are, as expected, shifted by ca. 100 cm^{-1} to lower wave numbers (Table 1).

2a



2b

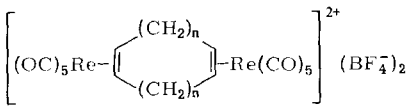


Table 1. IR data [cm^{-1}] of **1**–**4** (in Nujol).

	ν(CO)	ν(C=C)
1a	2168 m, 2105 w,sh, 2057 vs,br	1530 m
1b	2174 m, 2055 vs, br	1530 w
1c	2170 m, 2050 vs, br	1530 m, 1642 w
1d	2168 m, 2104 w, 2055 vs, br	1529 m, 1628 w
1e	2165 m, 2040 vs, br	1539 m, 1660 vw
2a	2165 m, 2055 vs, br	1535 m
2b	2165 m, 2040 vs, br	1529 w
3 [a]	2132 m, 2082 m, 2067 vw, 2037 s, 2017 sh, 2007 sh, 1981 vs, 1932 sh, 1920 s/m	1514 w, 1595 m (>C=O)
4 [a]	2120 m, 2030 sh, 1993 vs, 1960 s, 1923 vw	

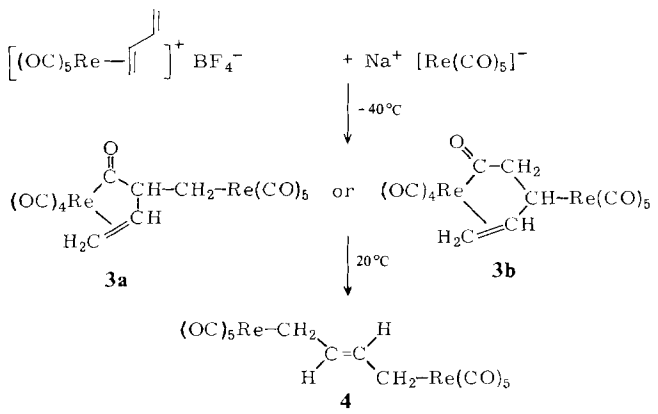
[a] In KBr.

The addition of nucleophiles to the coordinated olefin in complex cations is an important reaction principle, even on an industrial scale.[2] With carbonylmetalates as nucleophiles, this reaction principle enabled the first successful

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[**] Organometallic Lewis Acids, Part 17. This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie. — Part 16: K. Raab, W. Beck, *Chem. Ber.*, in press.

preparation of ethanediyl-bridged complexes.[1,3] A novel example of this type of reaction is the addition of pentacarbonylrhenate(1−) to the η^2-coordinated 1,3-butadiene in **1d**, which leads to the formation of the 2-butene-1,4-diyl-bridged complex **4** as stable product.



At low temperatures (−40°C), a complex **3** is first formed, which, according to the IR- and ^{1}H-NMR-spectrum,[4] can be formulated as a product of kinetically controlled 1,2-addition with CO insertion.[5] The structures of **3a** and **3b** are both consistent with the spectroscopic data of **3**. Complex **3** already isomerizes in solution at room temperature to give **4**. Elimination of CO does not occur under these mild conditions. In the direct photochemical reaction of $Re_2(CO)_{10}$ and $Mn_2(CO)_{10}$ with butadiene, the CO-deficient compounds $[(OC)_5MC_4H_6M(CO)_4]$ and $[(OC)_4MC_4H_6(CO)_4]$ (M = Mn, Re)[6,7] were isolated; here, butadiene functions as a σ-η^1-, π-η^3- or η^2,η^2-bridge. Thus, in **4** the previously unknown σ-η^1,σ-η^1-type C_6H_4-bridge is realized.

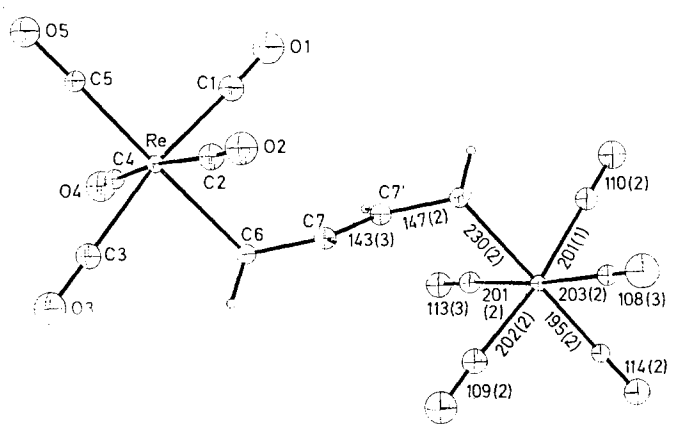


Fig. 1. Low-temperature molecular structure (at −90 °C) of **4**, 50% probability level (H atoms only schematic), atomic distances [pm]. $P\bar{1}$, $a = 612.6(3)$, $b = 660.1(3)$, $c = 1244.0(6)$ pm, $\alpha = 83.44(4)$, $\beta = 88.85(4)$, $\gamma = 61.47(3)°$, $V = 0.4387(3)$ nm^3, $Z = 1$, $\lambda(Mo_{K\alpha}) = 71.069$ pm; ω scan, $\Delta\omega = 0.8°$, $2° \leq \omega \leq 29.3°$ min^{-1}; $4° \leq 2\vartheta \leq 55°$; 4299 measurements, 2001 independent ($I \geq 2\sigma(I)$) reflections, 53 parameters. The absorption ($\mu = 140.2$ cm^{-1}) was corrected (crystal dimensions $0.08 \times 0.3 \times 0.3$ mm^3; Parametral face indexes: {001} 72 Friedel pairs as measured values). $R = 0.111$, $R_w = 0.115$, $w = [\sigma^2(F_0) + 0.001\,F_0^2)^{-1} \cdot (1 - \exp[-5(\sin\vartheta/\lambda)^2]]$. The hydrogen atoms are located at calculated sites and not refined. A refinement of the structure with anisotropic thermal parameters gave $R = 0.072$. Further details of the crystal structure investigation are available on request from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2, on quoting the depository number CSD 51 195, the names of the authors, and full citation of the journal.

4 (Fig. 1) has a center of symmetry corresponding to a crystallographic center of symmetry. The four C-atoms of the *trans*-2-butene bridge lie in a plane, from which the rhenium atoms are located at a distance of 198 pm; this corresponds to a C7′−C7−C6−Re torsion angle of 109°. The C7−C7′ bond is apparently longer than normal C=C double bonds, while the C6−C7 bonds are shorter than normal C−C single bonds. The angles C7′−C7−C6 (124(2)°) and C7−C6−Re (114(1)°) are widened; as in the case of $[(CO)_5Re-CH_2-CH_2-Re(CO)_5]$,[1] this can be attributed to the bulkiness of the $Re(CO)_5$ moiety.

Experimental:

1d: A Schlenk tube containing $[(OC)_5ReFBF_3]$ [8] (0.58 g, 1.40 mmol) was evacuated and then filled with anhydrous 1,3-butadiene gas (1 bar). 10 mL CH_2Cl_2 was then added to the contents of the tube through counterflowing butadiene and the resulting suspension stirred for 2 d at 1 bar. The colorless **1d** was centrifuged off, washed with CH_2Cl_2 (2 × 10 mL), and dried in a high vacuum. Yield 96%. **3**, **4**: 1.24 g (2.65 mmol) **1d** was dissolved with stirring in ca. 30 mL acetonitrile (previously cooled to −40°C). The solution was then treated dropwise with a tetrahydrofuran solution of $Na[Re(CO)_5]$ (prepared from 0.89 g (1.36 mmol) $Re_2(CO)_{10}$ and 2.5 mL 0.8% sodium amalgam in 7 mL THF at 0°C, reaction time 90 min). After a short while a yellow precipitate started to separate out. During the addition the temperature was slowly lowered to −45°C and on completion of addition the mixture was kept at −50 to −45°C. After 3 hours' stirring, the precipitate was recovered at this temperature (either by centrifugation or by filtration on a frit), washed twice with acetonitrile/THF (4:1; pre-cooled to −50 to −45°C) at ca. −50°C, and then dried in a high vacuum, firstly at −40°C and then at room temperature. The yellow substance consisted mainly of **3**. Yield 42–63%. **3** and **4** were separated chromatographically at −10°C (stationary phase: silica gel 60). Yellow **4** was completely eluted with CH_2Cl_2. Thereafter, **3** (also yellow), which hardly moved in CH_2Cl_2, was eluted with acetone.

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1a, 78610-83-4; **1b**, 95251-14-2; **1c**, 95251-16-4; **1d**, 95251-18-6; **2a**, 95251-20-0; **2b**, 95251-22-2; **2c**, 95251-24-4; **3a**, 95251-25-5; **3b**, 95251-26-6; **4**, 95251-27-7; $[(OC)_5ReFBF_3]$, 78670-75-4; $Na[Re(CO)_5]$, 33634-75-2; $Re_2(CO)_{10}$, 14285-68-8; 1-pentene, 109-67-1; cyclohexene, 110-83-8; 1,5-cyclooctadiene, 111-78-4; 1,3-butadiene, 106-99-0; 1,5-hexadiene, 592-42-7; 1,4-cyclohexadiene, 428-41-1.

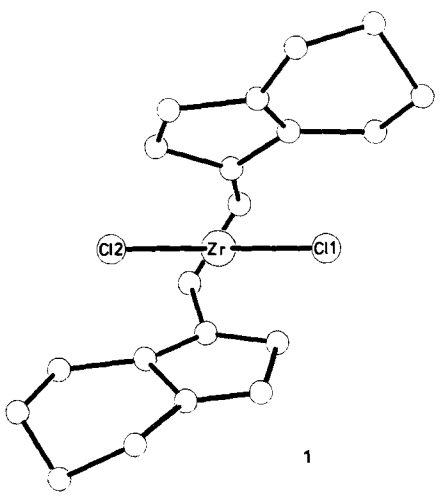
[1] K. Raab, U. Nagel, W. Beck, *Z. Naturforsch. B 38* (1983) 1466.
[2] Cf., for example, J. P. Collman, L. S. Hegedus: *Principles and Applications of Organotransition Metal Chemistry*, University Science Books, Mill Valley, CA 1980, p. 604.
[3] W. Beck, B. Olgemöller, *J. Organomet. Chem. 127* (1977) C45; B. Olgemöller, W. Beck, *Chem. Ber. 114* (1981) 867.
[4] The ^{1}H-NMR spectrum of **3** (AMPXYZ spin system) was in good agreement with the simulated spectrum.
[5] CO-insertion or decarbonylation is rare in the case of alkyl- and acylcarbonylrhenium complexes (cf. G. Wilkinson, F. G. A. Stone, E. W. Abel: *Comprehensive Organometallic Chemistry, Vol. 4*. Pergamon, Oxford 1982, p. 228). In the case of pentacarbonyl(2-cyclopropene-1-carbonyl)rhenium, however, carbonylation already takes place at 20°C, via allylic rearrangement, which also seems possible in the case of **3** (P. J. Desrosiers, R. Hughes, *J. Am. Chem. Soc 103* (1981) 5593; *104* (1982) 4842; R. P. Hughes, J. W. Reisch, A. L. Rheingold, *Organometallics 4* (1985) 241.
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[7] E. Guggolz, F. Oberdorfer, M. L. Ziegler, *Z. Naturforsch. B 36* (1981) 1060.
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Polymerization of Propene and Butene with a Chiral Zirconocene and Methylalumoxane as Cocatalyst**

By *Walter Kaminsky,* Klaus Külper, Hans H. Brintzinger,* and *Ferdinand R. W. P. Wild*

Hitherto, only atactic polypropylene could be prepared with soluble bis(cyclopentadienyl)zirconium(IV)/methylalumoxane Ziegler-Natta catalysts.[1,2] *Ewen*[3] has recently shown that mixtures of, e.g., 63% isotactic and 37% atactic polypropylene are formed with the sterically rigid ethylenebis(1-indenyl)titanium dichloride (mixture of meso form and racemate).[4]

If, however, the chiral ethylenebis(4,5,6,7-tetrahydro-1-indenyl)zirconium dichloride **1** (Fig. 1) is used in combination with methylalumoxane ($[Al(CH_3)-O]_n$) as cocatalyst, highly isotactic polypropylene is obtained. The racemate of **1** was used for this polymerization. The fraction of polymer soluble in toluene can be reduced to 0.2 wt.-%, which is considerably lower than the 2—7% achievable with heterogeneous $TiCl_4/MgCl_2/Al(C_2H_5)_3/C_6H_5CO_2C_2H_5$-based catalysts.[6]



1

Fig. 1. Crystal structure of chiral $[C_2H_4(4,5,6,7\text{-tetrahydro-1-indenyl})_2ZrCl_2]$ **1**. [5]

Table 1. Polymerization of propene or butene with **1** and methylalumoxane. Conditions: 8.4×10^{-6} mol/L *rac*-**1** in 330 mL toluene, 70 mL α-olefin, 1.6×10^{-2} mol/L Al-units of methylalumoxane (M_η 1200) at various temperatures (Pol = polymer, M_η = average molecular weight).

Olefin	T [°C]	t [min]	Yield [g]	Activity $\left[\frac{\text{kg Pol}}{\text{mol Zr}\cdot\text{h}}\right]$	M_η
Propene	−20	360	1.5	80	300000
Propene	−10	270	4.5	300	280000
Propene	0	255	12.5	880	130000
Propene	8	180	13.0	1300	85000
Propene	15	170	26.7	2900	55000
Propene	20	120	31.3	4750	41000
Propene	60	90	38.7	7700	12000
1-Butene	−10	330	9.1	500	150000
1-Butene	+20	200	29.2	2640	50000

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Remarkable is the high activity of the chiral catalyst **1** (Table 1). Thus, less than 10^{-5} mol/L suffices for the production of 7700 kg polypropylene per mole of Zr per hour at 60°C.

Under comparable conditions only 2730 kg of atactic polypropylene is formed per mole of Zr per hour with bis(cyclopentadienyl)dimethylzirconium. That is, the chiral zirconocene **1** affords not only isotactic polypropylene, but also has a polymerization activity 2—3 times greater than catalysts that form only atactic polypropylene. The rates of polymerization of ethylene : propene with bis(cyclopentadienyl)zirconium compounds are of the order of 25 : 1, whereas with zirconocene this ratio drops to ca. 10 : 1.[7,8] This means that propene is polymerized relatively far better by zirconocene **1** than by bis(cyclopentadienyl)zirconium compounds.

Table 2. Composition of some polypropylenes prepared with **1** (see Table 1).

M_η	M_w	M_w/M_n [a]	Atactic fraction [%] [b]	Isotacticity index [%] [c]	Viscosity number [cm³/g] [d]
280000	305000	2.6	0.25	91	242
130000	144000	2.4	0.2	88.1	132
55000	62000	2.0	0.7	87.3	110
41000	45000	1.9	1.0	86.0	76

[a] GPC measurements at 135°C in trichlorobenzene. [b] Fraction soluble in saturated hydrocarbons (b.p. 130°C) according to *Kloos* et al. [9]. [c] IR spectroscopically, according to *Luongo*. [10] [d] At 135°C in decalin.

Besides the high activity of **1** towards propene, which reaches values at least equal to those achieved by heterogeneous catalysts, the properties of the polypropylene thus formed are also remarkable (Table 2). In contrast to industrial polypropylene, which has a molecular weight distribution M_w/M_n of at least 5, with **1** we have produced products with molecular weight distributions of only 1.9 to 2.6. The fraction soluble in hydrocarbons amounts to less than 1% in all cases. The IR-spectroscopically determined isotacticity index of 86 to 91% is also very high. The crystallinity of the highly isotactic polypropylene is largely determined by the stereochemical uniformity of the polymerization. High-resolution ^{13}C-NMR spectroscopy affords an insight into the pattern of the sequences in the polymer chain. Isotactic sequences (mm triads) are found to be present to the extent of 95%, heterotactic sequences (mr triads) to the extent of 3.2%, and syndiotactic sequences (rr triads) to the extent of 0.9%. Notable is the very small amount of rr triads compared to mr triads. In the case of commercially available polypropylene the mr/rr ratio is of the order of 1, and rr is greater by a factor of about 5.

This means that the propene molecules are inserted highly stereospecifically with this homogeneous Ziegler-Natta catalyst. Defects in the insertion are minimal, as is confirmed by the high isotaxy of 97.5% and an average length of the isotactic sequences of more than 60 monomer units.

1-Butene can also be polymerized highly effectively with the zirconocene **1**/methylalumoxane catalyst (cf. Table 1). Thus, polymerization activity is still 2640 kg of polybutene per hour per mole of Zr at 20°C. Although the polymers have molecular weights of 150000 or 50000, they are soluble in toluene. The consistency is wax-like to crystalline, but not clear and viscous like atactic polybutane, which was produced with bis(cyclopentadienyl)zirconium compounds and measured ^{13}C-NMR spectroscopically.

Hence, both unusually highly isotactic polypropylene as well as isotactic polybutene can be produced with **1** and methylalumoxane; the activity of the catalyst is high. The narrow molecular weight distribution, an additional effect, might be of interest from an industrial processing point of view.

Experimental

1: Tetrahydrofuran (THF) (60 mL) was distilled into a three-necked flask at −196 °C and treated, with stirring, with 4.9 g (21 mmol) of $ZrCl_4$. A solution of the dilithium salt of bis(1-indenyl)ethane (21 mmol) in THF (50 mL) was then added dropwise to the mixture under N_2, at room temperature. After 2 hours' stirring, hydrogen chloride was passed into the mixture and, immediately thereafter, the excess HCl was removed *in vacuo*. The mixture was then treated with diethyl ether (20 mL) and petroleum ether (10 mL). The resulting light-yellow, crystalline product was filtered off and washed successively with 4N hydrochloric acid, water, ethanol, and diethyl ether and dried *in vacuo*; yield 3.1 g of (*R,S*)-ethylenebis(1-indenyl)zirconium dichloride. 1 g of this substance was hydrogenated, as described for the analogous titanium compound [4], for 30 min with 75 mg PtO_2 and 25 mL CH_2Cl_2 at 100 bar H_2; yield 650 mg of **1** (characterized by X-ray structure analysis [5]).

Polymerization of propene: A solution of methylalumoxane (320 mg, 5.6 mmol Al) and **1** (3.3×10^{-6} mol) in 1 mL of toluene was added to 330 mL toluene contained in a 1 L glass autoclave fitted with a thermostat and magnetic stirrer and previously dried out and purged with argon. After 20 minutes' ageing, purified propene (70 mL) was distilled into the contents of the autoclave at 20 °C. The solution gradually clouded, and white polypropylene precipitated out. After 120 min the contents of the autoclave were treated with ethanol, filtered, and the filter cake washed with dilute HCl and dried in vacuo; yield 31.3 g of isotactic polypropylene. On removal of toluene from the filtrate there remained a further 0.3 g of polypropylene.

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1, 96363-63-2; $ZrCl_4$, 10026-11-6; dilithium salt of bis(1-indenyl)ethane, 96363-64-3; isotactic polybutene, 25036-29-7; isotactic polypropylene, 25085-53-4

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Electrochemical Oxidation of Anthracene and 9,9′-Bianthryl to the Respective Dication and Tetracation**

By *Michael Dietrich, John Mortensen,* and *Jürgen Heinze**

The electrochemical reduction of unsubstituted arenes to stable, highly charged anions was recently described for the first time.[1] Thus, for example, it was possible to detect electrochemically the tetraanion of 9,9′-bianthryl **1** and the hexaanion of decacyclene. Independently, *Müllen* et al.[2] had previously converted **1** as well as a series of annulene derivatives to their tetraanions by the use of alkali metals and, on the basis of NMR spectroscopic results, found new applications of the Hückel $4n+2$ rule for such highly charged perimeter systems.

Until now it had not been possible to obtain the corresponding tetracations either chemically or via electrochemical oxidation. The highly charged cations react easily with nucleophilic impurities or, as is usually the case, with the nucleophilic solvent. The proper choice and purification of the solvent is therefore even more crucial than for the cathodic reduction. In 1979, *Tinker* and *Bard*[3] described the anodic oxidation of thianthrene and other arenes in liquid SO_2 and were able to show that this solvent is excellently suited to the generation of reactive cations owing to its low nucleophilicity.

It has now been possible, using an optimized sample preparation procedure (purification of SO_2 solely with Al_2O_3),[1,4] to generate anodically in liquid SO_2 the extremely reactive dication of anthracene $\mathbf{2}^{2+}$[5] as well as, for the first time, the tetracation of **1** and to characterize these species by cyclic voltammetry.

All measurements were carried out in SO_2/Bu_4NPF_6 with a Pt electrode. The potentials were calibrated using an internal ferrocene standard and then referred to the standard Ag/AgCl reference electrode.

Owing to the high reactivity of $\mathbf{2}^{+}$, only quasi-reversible voltammograms of the $\mathbf{2}/\mathbf{2}^{+}$ redox pair have been observed for scan rates of 100 mV/s at −70 °C. A mean life-time of 0.5 s for the cation was derived from the peak-current ratios.[7]

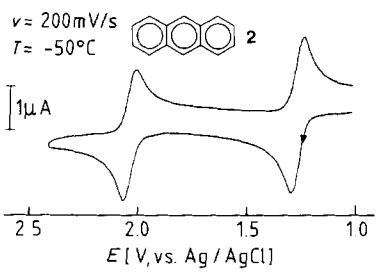


Fig. 1. Cyclic voltammogram of the oxidation of **2** in SO_2 (working electrode: Pt).

Figure 1 shows the voltammogram for the oxidation of **2** at −50 °C. Two clearly defined reversible steps are apparent; a ΔE^0 of 770 mV (−50 °C) for these two steps gives a semiquinone formation constant of 2.48×10^{17}. The peak-current ratios indicate a radical cation life-time that extends far beyond the time scale of cyclic voltammetry; for the dication, the average life-time under the experimental conditions was estimated to be ca. 10 s. The extremely high reactivity of the dication is shown by the observation that, in SO_2 dried with P_2O_5, $\mathbf{2}^{2+}$ always reacts via irreversible subsequent reactions. Remarkably, the peak height for the dication formation is somewhat smaller than that for the monocation formation; this indicates a reversible dimerization ($K \approx 50$ L·mol^{-1}) of the radical cation with the substrate, as is also found for pyrene and other arenes.[1]

The oxidation of **1** leads, in four reversible redox steps (Fig. 2), to what is, to the best of our knowledge, the first tetracation of an unsubstituted arene.[8] Since formation of the tetracation also involves the transfer of four electrons, **1** represents, in principle, an eight-step redox system. The standard potential difference ($E_1^0 = 1.267$; $E_2^0 = 1.482$;

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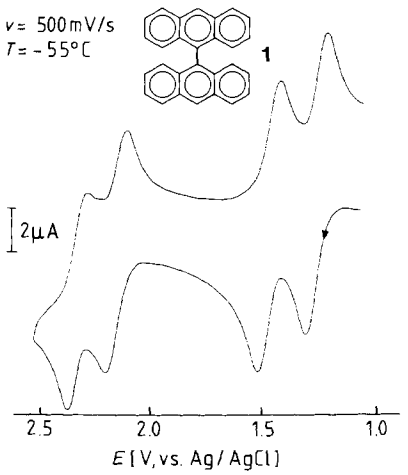


Fig. 2. Cyclic voltammogram of the oxidation of **1** in SO_2 (working electrode: Pt).

$E_3^0 = 2.170$; $E_4^0 = 2.348$ V vs. Ag/AgCl) between the first and the fourth redox step of **1** amounts to 1.080 V at $-50\,^{\circ}C$. This correlates very well with the value of 1.070 V that is observed for the reduction of **1** in tetrahydrofuran in the presence of Na^+/[15]crown-5. The effective ionic radii of the counterions PF_6^- and Na^+/[15]crown-5, namely, 3.5 and 3.6 Å, respectively (perpendicular to the plane of the crown ether), are similar; this indicates that the electrostatic shielding effects (ion pair effects) are the same in positively and negatively charged redox systems.

The life-time of the electrochemically generated tetracation $\mathbf{1}^{4+}$ is about 1 s under the experimental conditions. We presume that traces of nucleophilic impurities, such as F^-, initiate subsequent reactions.

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[8] Since, in **1**, two anthryl groups are joined at the 9,9'-positions, $\mathbf{1}^{4+}$ can also be formally viewed as a double dication. This presumes, however, that the two charged anthryl groups do not interact with each other, an assumption that is not supported by the experimental results. The electronic interaction energies of the tetracation and the tetraanion of **1** [1] attain values of up to 0.6 eV depending on the type of counterion, which determines the charge deshielding in the anthryl moiety.

Comparison of Theoretical and Experimental Deformation Densities in S–O Bonds**

By *Hartmut Fuess,* Jan W. Bats, Durward W. J. Cruickshank,* and *Miriam Eisenstein*

The distribution of electrons in a chemical bond between atoms may be studied by careful X-ray structure analysis.[1a] In such investigations, deformation densities are determined as differences between the total measured electron density and that of a set of spherical atoms whose positions in a crystal lattice are known. A comparison between experimental and theoretical densities has to take into consideration the fact that atoms or molecules in a crystal are influenced by intermolecular forces and by thermal vibrations. The quantum-chemical calculations, however, are usually carried out for an atom or molecule at rest. Therefore, the experimental results have to be corrected for thermal vibrations before a meaningful comparison between the theoretical and experimental densities can be made. The electron densities obtained by this procedure are called static deformation densities.[1b] Alternatively, inclusion of thermal motion in the theoretical static densities gives results that may directly be compared with the experimental results. These thermally smeared electron densities are called dynamic densities.

The comparisons reported up to now have dealt essentially with organic molecules containing C–H, C–O, and C–C bonds.

We report here on quantum-chemical calculations and experimental determinations of the deformation density in the sulfur-oxygen bond, which is present in several different anions. Marked similarities are found between the experimental electron-density maps for $Na_2S_2O_3$ and the theoretical maps for H_3NSO_3 (Fig. 1).

The experimental work[2a] on $Na_2S_2O_3$, space group $P2_1/a$, forms part of a series of careful crystallographic studies on sulfur-oxygen bonds in thiosulfates[2] and in a sulfite.[3] The densities for $Na_2S_2O_3$ are static deformation densities based on a multipole refinement[4] of 3456 reflections up to a resolution of $\sin\theta/\lambda = 1.0$ Å^{-1}. Position parameters for oxygen were obtained from neutron diffraction data. The reported densities were obtained by a Fourier transform of calculated structure factors. In addition, the densities for the three chemically equivalent sulfur-oxygen bonds were averaged.

The theoretical work forms part of a series of careful studies[5] on sulfur-oxygen bonds in H_3NSO_3, SO_3^-, and SO_2 and its ions. The theoretical electron-density maps shown here were calculated for sulfamic acid using extended double-zeta basis sets, which included two sets of d functions for each S, O, and N atom and two sets of p functions for each hydrogen.

Comparison of the experimental and theoretical maps (Fig. 1) shows, in particular, that the shapes of the respec-

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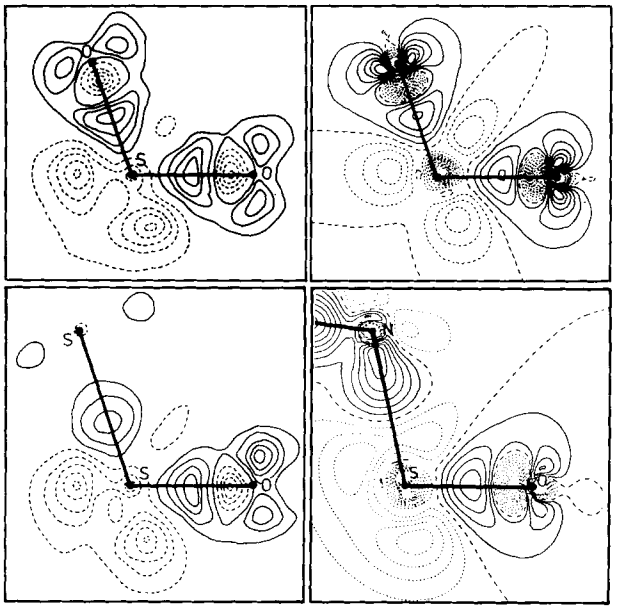


Fig. 1. Left: experimental static deformation density in $Na_2S_2O_3$, resolution 1.0 $Å^{-1}$. Right: theoretical static deformation density in H_3NSO_3. Contour interval 0.1 $e/Å^{-3}$. The zero contour (dashed) is omitted in the experimental map but included in the theoretical map. Top: electron deformation density in the O–S–O plane. Below: electron deformation density in the X–S–O plane (X = S, N). Solid lines and dotted (or dashed) lines represent positive and negative densities, respectively.

tive maxima in the S–O bond and the minima near sulfur are similar in all maps. Also, the deformation density in the vicinity of the S–O bonds shows approximate axial symmetry in both experimental and theoretical maps.

In the molecular XSO mirror planes (Fig. 1, bottom), the maxima and minima in $Na_2S_2O_3$ and H_3NSO_3 are similar. The S–O bond maxima even have similar slight skewnesses, and the asymmetry of the lone pairs of electrons on oxygen in $Na_2S_2O_3$, with the higher density on the S–S side, is also apparent in the theoretical maps.

The biggest difference between theory and experiment is that in the theoretical maps for sulfamic acid the theoretical maxima for the nonbonding electrons on oxygen are appreciably higher in the OSO plane than in the XSO plane, whereas in the experimental maps for thiosulfate this is not the case. The difference between sulfamic acid, which may be regarded as the zwitterion $(H_3N)^+(SO_3)^-$, and $S_2O_3^{2-}$ is not unexpected. First, it is consistent with differences we have found theoretically between SO_2^- and SO_2^{2-} (the maps for H_3NSO_3 and SO_3^- being very similar). Secondly, it is consistent with the differing bond character in the two molecules. In sulfamic acid the S–N bond length corresponds to that of a single bond, while the S–O length of 1.441 Å shows considerable double-bond character. This explains the non-uniform distribution of nonbonding electrons on the oxygen atom. In the thiosulfate anion the S–S bond length of 2.007 Å indicates some double-bond character, and the S–O length of 1.479 Å is typical for that in a sulfate group. Thus, a more uniform distribution of non-bonding electrons is to be expected near the oxygen atom in the thiosulfate.

In the experimental maps the densities of the oxygen non-bonding electrons are nearly as spread out as those of the bonding electrons, whereas in the theoretical maps the densities of the oxygen non-bonding electrons exhibit small sharp peaks. The method of experimental analysis, however, does not permit resolution of such sharp features near the atoms.

Quantum-chemical calculations on a double-zeta basis (omitting the p functions on hydrogen and all d functions) give poor agreement with the experimental results.

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CAS Registry numbers:
$Na_2S_2O_3$, 7772-98-7; H_3NSO_3, 5329-14-6.

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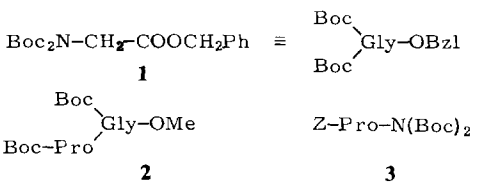
Exhaustive *tert*-Butoxycarbonylation of Peptide Nitrogens**

By *Leif Grehn* and *Ulf Ragnarsson**

We have recently described an efficient and convenient method for the preparation of Boc-pyrroles and Boc-indoles (Boc = *tert*-butoxycarbonyl) using Boc_2O in dry acetonitrile or dichloromethane[1] with 4-dimethylaminopyridine (DMAP) as catalyst.[2,3] By this procedure we have also synthesized tryptophan derivatives protected on the indole nitrogen and shown that such compounds may be useful for peptide synthesis in solution.[4] However, when excess Boc_2O was used in these preparations, several byproducts were frequently obtained. Spectral evidence indicated that these crude mixtures contained substances with Boc groups on amide nitrogens. To elucidate the scope of this reaction, we have now investigated the action of Boc_2O/DMAP on some simple model substrates.

It was found that the urethane moiety in Boc-Gly-OBzl was completely acylated using only a slight excess of Boc_2O/DMAP in acetonitrile, affording the *N,N*-diacyl compound **1** in high yield. **1** is surprisingly stable and could be handled without special precautions. Since diacylation of amino nitrogens is relatively difficult to accomplish in most cases, this novel approach may prove useful for the preparation of diacylamino derivatives in general. In particular, mixed diacyl analogues might be available by stepwise synthesis.

When Boc-Pro-Gly-OMe was treated with 1.1 equivalent of the reagent mixture, acylation occurred smoothly at the only available nitrogen atom, giving **2** in excellent yield.



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The outcome of this reaction thus appears to open up new possibilities for the facile protection of peptide bonds with Boc groups. In the same way, both amide hydrogens in Z-Pro-NH_2 (Z = benzyloxycarbonyl) could easily be replaced by Boc employing 2.2 equivalents of Boc_2O. The product **3**, like **1** and **2**, was sufficiently stable to withstand normal workup including aqueous extractions (Table 1). Both Boc groups were smoothly removed from **3** with 33% trifluoroacetic acid in dichloromethane within 45 min (TLC) at room temperature.

Table 1. Yield and physical data of the Boc derivatives **1**—**3**. All new compounds gave satisfactory elemental analyses (C, H, N). The yields are based on the crude product, which was pure by TLC (toluene:acetonitrile, 2:1). ^{13}C-NMR ($CDCl_3$, $\delta(CDCl_3) = 77.0$).

1: 95% yield, m.p. = 30.5—31.0°C (petroleum ether, 10 mL/g, active charcoal, −70°C); ^{13}C-NMR: 169.0 (ester CO), 151.8, 83.1, 27.9 (Boc), 135.4, 128.5, 128.3, 66.8 (benzyl), 47.4 (Gly CH_2)

2: 100% yield, m.p. = 93.0—93.5°C (as for **1** but 50 mL/g); $[\alpha]_D^{25}$ −41.2 ($c = 1$, DMF); ^{13}C-NMR: 175.6/175.2 (peptide CO), 169.5/169.2 (ester CO), 154.4/153.8, 84.2/84.0, 28.4/28.2 (peptide Boc), 151.8/151.7, 79.4, 27.8 (α-Boc), 61.0/60.8 (Pro, αC), 30.9/30.2 (Pro, βC), 23.5/22.8 (Pro, γC), 46.9/46.5 (Pro, δC), 52.1 (ester Me), 45.3 (Gly CH_2) [a]

3: 87% yield; oil (as for **1**, but 25 mL/g). The white precipitate melts below 0°C but later solidifies at room temperature; $[\alpha]_D^{25}$ −31.2 ($c = 1$, DMF); ^{13}C-NMR: 173.5/173.2 (amide CO), 149.1, 85.0, 27.5 (Boc), 154.6/154.1, 136.8, 128.3, 127.8, 127.3, 66.9 (Z), 60.6/59.8 (Pro, αC), 30.8/29.9 (Pro, βC), 23.6/22.9 (Pro, γC), 47.1/46.6 (Pro, δC) [a]

[a] Doubling of signals due to the presence of two conformers [8].

Acyclic diacylamines have been reported previously but such compounds are often unstable and may revert to monoacylamines.[5,6] Peptide bonds carrying trifluoroacetyl groups are known but they are also sensitive to hydrolysis.[7] With respect to stability, therefore, the new Boc compounds are superior to earlier diacylamines. Moreover, their lipophilic properties enhance their solubilities in solvents frequently used in peptide synthesis.

Experimental Procedure

DMAP (12 mg, 0.1 mmol) was added to a stirred solution of the peptide derivative (1.0 mmol) in dry acetonitrile (2—3 mL) followed by Boc_2O (240 mg, 1.1 mmol). After stirring for 5 h at room temperature, all peptide starting material was consumed (TLC, toluene:acetonitrile, 2:1). The brownish reaction mixture was evaporated at room temperature and the oily residue partitioned between ether (50 mL) and 1 M aqueous $KHSO_4$ (25 mL). The organic extract was thoroughly washed in turn with 1 M aqueous solutions of $KHSO_4$ and $NaHCO_3$ and finally brine and dried over $MgSO_4$. Evaporation to complete dryness (high vacuum, room temperature) left a light yellow oil, which was chromatographically pure. Recrystallization from petroleum ether (decolorizing carbon) gave an analytically pure product (see Table 1).

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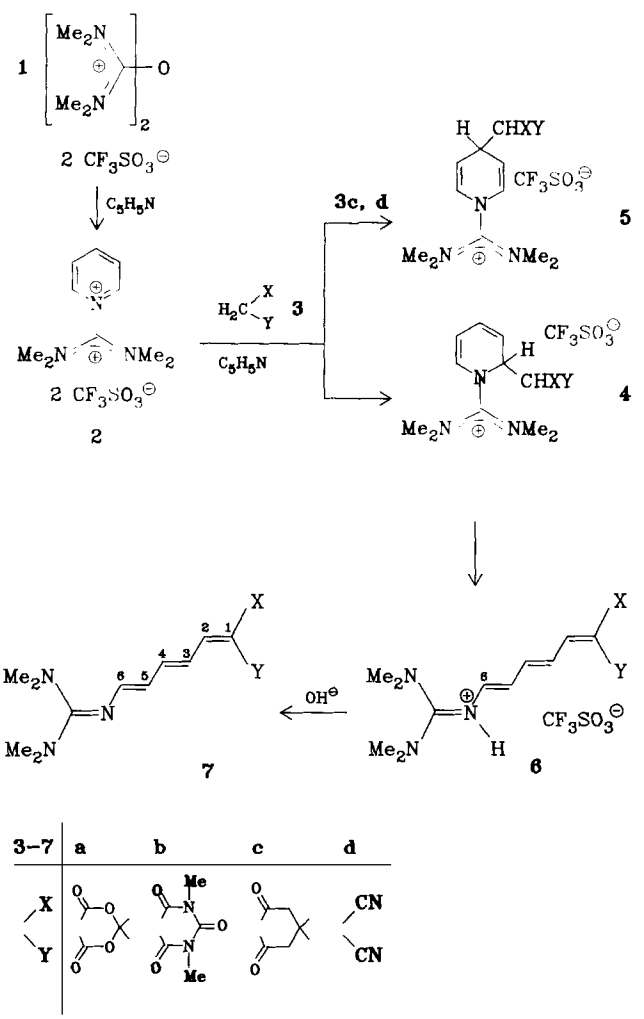
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Azahexamethineneutrocyanines from a *N*-(Tetramethylformamidinio)pyridinium Salt**

By *Gerhard Maas** and *Bernhard Feith*

Nucleophilic ring-opening reactions of quaternary pyridinium salts which initially involve α-addition of the nucleophile are always likely to succeed if the heterocycle bears a strong electron-attracting substituent on the nitrogen atom.[1] It would appear that pyridinium salts bearing a cationic substituent, have—with the exception of one (2-pyridinio)pyridinium salt[2]—so far never been used for such rearrangements.

We have now found that the *N*-(tetramethylformamidinio)pyridinium salt **2**, which is readily accessible from the "dication ether" salt **1**[3] and pyridine, is also attacked at the α-C atom by the anions of active methylene compounds **3**; as usual the primary product **4** undergoes ring-opening to give **6**. *N*-protonation of the isolated compound **6b** was verified by a weak vicinal coupling with H-6. On reaction with bases the deep-colored azaneutrocyanines **7a**—**d** are formed. Their all-*trans* configuration is proven by the X-ray structure analysis of **7a** (see Fig. 1)



3–7	a	b	c	d
X	O	O	O	CN
Y	O	O	O	CN

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and also follows from the $^3J_{H,H}$ coupling constants, which—as far as recognizable—differ by less then 1.5 Hz (see Table 1).

Table 1. Some physical and spectroscopic data of **7a—d** and **6b** [a].

7a: dark red crystals with shiny violet surfaces; m.p. 164°C; ^{1}H-NMR ($CDCl_3$): $\delta = 1.70$ (s, 6H, CMe), 2.96 (s, 12H, NMe), 6.10 (t, H-5), 7.33 (t, H-4), 7.48 (t, H-3), 7.53 (d, H-6), 7.94 (d, H-2); $J(2,3) = J(3,4) = 12.7$, $J(4,5) = J(5,6) = 11.7$ Hz; IR: 1703, 1616, 1520 cm^{-1}; UV/VIS [b]: 525 nm ($\lg\varepsilon = 4.94$), 527 (5.07), 521 (5.16), 471 (5.21)

7b: dark red crystals with shiny bluish-violet surfaces; m.p. 174—175°C; ^{1}H-NMR ($CDCl_3$): $\delta = 2.95$ (s, 12H, NMe_2), 3.32 (s, 6H, NMe), 6.12 (dd, H-5, $J(5,6) = 11.7$, $J(4,5) = 12.7$ Hz), 7.34 (dd, H-4, $J(3,4) = 13$, $J(4,5) = 12.7$ Hz), 7.46 (d, H-6, $J(5,6) = 11.7$ Hz), 7.75 (t, H-3, $J(2,3) = J(3,4) = 13$ Hz), 8.00 (d, H-2, $J(2,3) = 13$ Hz); IR: 1703 (m), 1622 cm^{-1} (br, s); UV/VIS [b]: 541 nm ($\lg\varepsilon = 5.00$), 546 (5.06), 539 (5.15), 535 (4.90)

7c: dark red crystals with shiny metallic-green surfaces; m.p. 152°C; ^{1}H-NMR ($CDCl_3$): $\delta = 1.05$ (s, 6H, CMe), 2.43 (s, 4H, CH_2), 2.96 (s, 12H, NMe_2), 6.15 (t, H-5), 7.34 (m, H-4), 7.41 (d, H-6), 7.64—7.82 (AB part of ABX, H-2 and H-3); $J(4,5) = J(5,6) = 12.2$ Hz; IR: 1612 cm^{-1} (br, s); UV/VIS [b]: 544 nm ($\lg\varepsilon = 4.84$), 552 (4.94), 546 (5.01), 5.41 (4.90)

7d: dark red crystals with shiny metallic-green surfaces; m.p. 116°C; ^{1}H-NMR ($CDCl_3$): $\delta = 2.94$ (s, 12H, NMe_2), 5.99 (t, H-5), 6.41 (dd, H-3), 7.07 (dd, H-4), 7.28 (d, H-2), 7.35 (d, H-6); $J(2,3) = 12.6$, $J(3,4) = 13$, $J(4,5) = 12.2$, $J(5,6) = 12.2$ Hz; IR: 2215/2200 (s, C≡N), 1600 (m), 1495 cm^{-1} (s); UV/VIS [b]: 506 nm ($\lg\varepsilon = 4.75$), 510 (4.81), 511 (5.00), 506 (4.93)

6b: orange powder; m.p. 265°C; ^{1}H-NMR (CD_3CN): $\delta = 3.00$ (s, 12H, NMe_2), 3.25 (s, 6H, NMe), 6.35 (dd, H-5, $J(5,6) = 13.5$, $J(4,5) = 12.5$ Hz), 6.78 (d, broadened by NH-coupling, H-6), 7.25 (t with long-range coupling, H-4), 7.86—8.04 (AB part of an ABX system, H-2, H-3), 8.45 (br, NH); IR: 1655, 1530 cm^{-1} (both s)

[a] ^{1}H-NMR: 200 MHz, TMS as standard. IR: KBr pellet. All compounds gave correct elemental analyses. [b] The longest wavelength absorption bands in benzene, chloroform, acetone, and ethanol (95%) are given. IR: ν; UV/VIS: λ.

The products of γ-addition to the pyridinium ring **5c** and **5d** could be detected in the reaction solution by NMR spectroscopy. Under kinetically controlled conditions, **5d** is formed almost exclusively, but rearranges into **4d** or **6d**.[4]

The equal possibility of carbanionic attack at the formamidinium carbon of **2**, which would lead via elimination of a pyridine molecule to a push-pull olefin or a *O*-(formamidinio)enol,[5] surprisingly does not take place in the cases presented here.

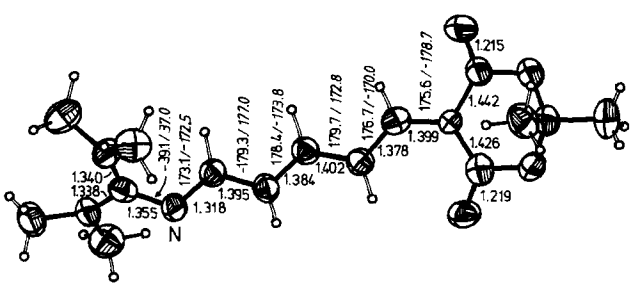
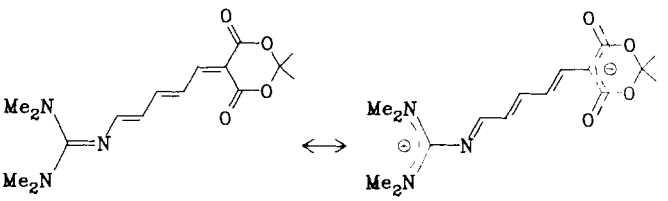


Fig. 1. ORTEP plot (50% probability) of a molecule of **7a**. The second independent molecule has almost a mirror-image configuration. The torsion angles [°] for the molecule (italics: corresponding values for the second molecule) and the average bond lengths [Å] are shown. The mean errors of the average values are 0.004—0.005 Å. The *NCN* fragment of the formamidinium group is rotated by 42° (in the second molecule by 35°) and the *CCC* plane of the heterocyclic acceptor by 5° (14°) with respect to the least-squares plane of the polyene chain (NC_5).

The bonding in neutrocyanines can, in general, be described in terms of a mesomerism of the type **7aA** ↔ **7aB**. The X-ray structure analysis of **7a**[6] (see Fig. 1) clearly shows that almost complete bond equalization has taken place (dipole moment $\mu = 5.66$ D in dioxane). It follows from the weak alternance that the resonance structure **7aB** even dominates. This bonding is favored in the crystal by a relatively large twisting of the NCN plane of the formamidinium group with respect to the least squares plane of the (in the second independent molecule not quite planar) NC_5 polyene chain.



7aA **7aB**

Consistent with their polymethine-like character, **7a—d** show only a slight solvatochromism of the longest wavelength absorption bonds, which, with increasing polarity of the solvent are shifted, first bathochromically and then hypsochromically.

Experimental

A solution of **1** [3] (3.0 mmol) and pyridine (7.5 mmol) in acetonitrile (25 mL) was stirred for 2 h at room temperature and then treated with 3.0 mmol of the CH-acidic compound **3**. On completion of reaction [**3a**: 3.5 h; **3b**: 30 min (**6b** crystallizes from the solution and can be isolated, yield 96%); **3c**: 2.5 h; **3d**: 60 h] the solvent was removed in vacuo and the residue taken up in 100 mL of chloroform. The solution was washed with 2 × 10 mL of NaOH (10%) or with aqueous ammonia (25%), whereupon it turned red-violet in color. It was then washed with water until neutral and finally dried over magnesium sulfate. After evaporation to dryness the residue was recrystallized from tetrahydrofuran (yield: **7a**: 70%; **7b**: 72%; **7c**: 69%; **7d**: 77%); for further data, see Table 1.

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CAS Registry numbers:
1, 78581-29-0; **2**, 96532-49-9; **3a**, 2033-24-1; **3b**, 769-42-6; **3c**, 126-81-8; **3d**, 109-77-3; **4a**, 96555-19-0; **4b**, 96532-51-3; **4c**, 96532-53-5; **4d**, 96532-55-7; **5c**, 96555-21-4; **5d**, 96532-57-9; **6a**, 96532-59-1; **6b**, 96532-61-5; **6c**, 96532-63-7; **6d**, 96532-65-9; **7a**, 96532-58-0; **7b**, 96532-60-4; **7c**, 96532-62-6; **7d**, 96532-64-8; pyridine, 110-86-1.

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[6] **7a**: triclinic, space group $P\bar{1}$, $a = 7.851(1)$, $b = 11.697(2)$, $c = 20.051(3)$ Å, $\alpha = 103.69(1)$, $\beta = 87.63(1)$, $\gamma = 101.63(1)°$, $\rho_{calc} = 1.218$ g cm^{-3}, $Z = 4$ (two

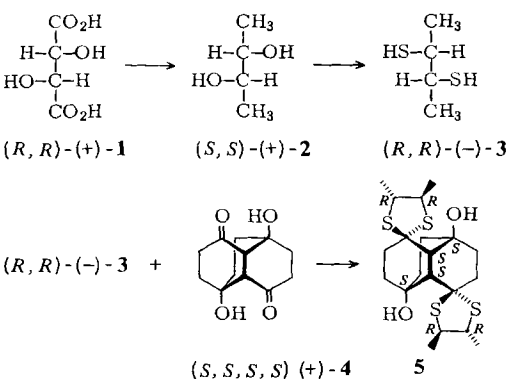
independent molecules). Enraf-Nonius CAD4 diffractometer, monochromatized $Mo_{K\alpha}$ radiation, 4292 independent reflections with $2.0 \leq \theta \leq 22.0°$, full matrix refinement with 2616 reflections [$I > 2\sigma(I)$]; $R = 0.0676$, $R_w = 0.0491$ [$w = k \cdot (\sigma^2 + 0.0009 F_0^2)^{-1}$]. Further details of the crystal structure investigation are available on request from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2 on quoting the depository number CSD 51288, the names of the authors and the full citation of the journal.

On the Absolute Configuration of (+)-Tartaric Acid

By *Hartmuth Buding, Bertold Deppisch, Hans Musso,** and *Günther Snatzke*

The absolute configuration of (+)-tartaric acid from grape juice was determined in 1951 by *Bijvoet* et al.[1] for the rubidium salt using the anomalous dispersion of zirconium K_α X-rays. This result was questioned by *Tanaka* et al.[2] in 1972, but *Dunitz*[3] has shown it to be correct. In the meantime new structure determinations on tartrates[4] have appeared and there is independent evidence that macroscopic crystal forms can be related to molecular chirality by X-ray methods.[5] According to *Prelog* et al.[6] each new example that reconfirms Bijvoet's method is welcome. Therefore, we present results that led us unintentionally to the determination of the (*R,R*) configuration for (+)-tartaric acid **1**.

(+)-2,3-Butanediol **2** was obtained from (+)-**1** by reduction of the carboxy groups according to a conventional procedure,[7] and was then transformed into (−)-2,3-butanedithiol **3** by the method of *Corey* and *Mitra*.[8] The reaction of **3** with the racemic diketone **4** yielded a mixture of diastereomeric bisdithioacetals. The second component eluting on chromatography was shown by *Bijvoet*'s X-ray diffraction analysis to be the enantiomer **5**.[9] The chiral centers in (−)-**3** therefore have the (*R,R*) configuration. Since the formation of **3** from (+)-**2** must involve a Walden inversion, (+)-**2** has the (*S,S*) configuration and the starting material is therefore (*R,R*)-(+)-**1**.



Independently, the (*S,S,S,S*) configuration was determined for the carbon framework of the tricyclic ketone (+)-**4** (obtained by hydrolysis of **5**) from the negative Cotton effect that is observed.[9] The (*R,R*) configuration of (+)-**1** and the (*S,S,S,S*) configuration of (+)-**4** are linked here by the structure determination of **5**. In this way (*R,R*)-(+)-**1** is reconfirmed through the optical activity of (*S,S,S,S*)-**4**.

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Direct Structural Proof for the Pentazole Ring System in Solution by ^{15}N-NMR Spectroscopy**

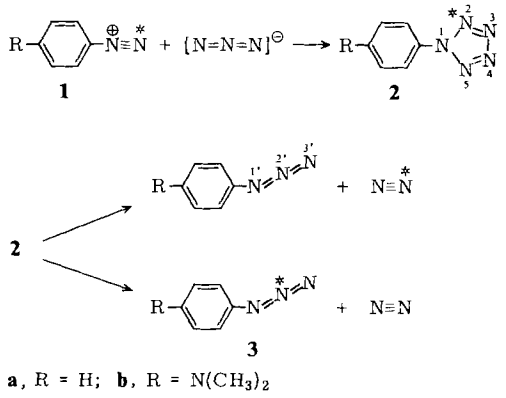
By *Raffaello Müller, John D. Wallis,* and *Wolfgang von Philipsborn**

Benzenediazonium chloride **1a** reacts with lithium azide in methanol to produce phenyl azide **3a** and molecular nitrogen. *Huisgen* and *Ugi*[2] discovered that the reaction proceeds by two mechanisms. For one of them it was proposed that phenylpentazole **2a** is an intermediate.[3] Its symmetry accounts for the equal distribution of an ^{15}N label, originally in the terminal N atom of the diazonium salt, between the decomposition products phenyl azide **3a** and molecular nitrogen (Scheme 1). Subsequently, a series of crystalline *p*-substituted phenylpentazoles was isolated[4] at low temperature (−30 °C), and recently the structure of the most stable of these, *p*-dimethylaminophenylpentazole **2b**, was confirmed by X-ray crystallography at 128 K.[5] We have now used ^{15}N-NMR spectroscopy to observe this unstable compound in solution at 238 K and to monitor its decomposition at higher temperatures.

The natural abundance ^{15}N-NMR spectrum of a solution of a crystalline sample of **2b** in $CDCl_3$ measured at 40.56 MHz (9.4 T) and 238 K is shown in Figure 1a. Even at this temperature the pentazole has partially decomposed during the long measurement time (40 h) to molecular nitrogen and *p*-dimethylaminophenyl azide **3b**. The nitrogen

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Scheme 1.

produces a broad resonance at $\delta = -73$[6,7] and the presence of **3b** is confirmed by comparison with the spectrum of an authentic sample (Fig. 1b). The assignment of the four resonances of **3b** is based upon literature data on phenyl azides.[8] These were the only resonances observed when the spectrum was remeasured after the sample had been left at room temperature for 24 h. The four remaining signals in Figure 1a are ascribed to the pentazole derivative **2b**, one to the $-N(CH_3)_2$ group ($\delta = -324.6$) and three to the all-nitrogen five-membered ring (N-1: $\delta = -80.0$, N-2,5: $\delta = -27.1$, N-3,4: $\delta = +4.9$, Table 1).

The resonance at $\delta = -80.0$ is assigned to the only tricoordinated N atom N-1, by analogy with other azoles.[9] Using additive shielding increments[10] evaluated from

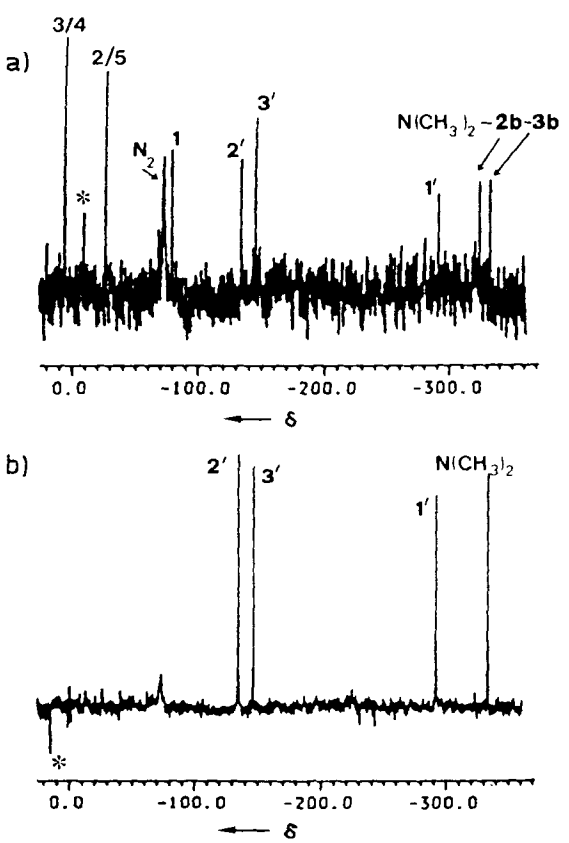


Fig. 1. ^{15}N-NMR Spectra (40.56 MHz) of a) pentazole **2b**, 0.04 M in $CDCl_3$, 238 K (see also Table 1 [a]) and b) authentic azide **3b**, 0.21 M in $CDCl_3$, 253 K (see also Table 1 [b]). The weak signal at $\delta = -73$ is probably due to N_2 originating from decomposed azide; the asterisk indicates electronic spikes.

Table 1. ^{15}N chemical shifts in δ values (± 0.3 ppm) relative to external $CH_3{}^{15}NO_2$; solvent $CDCl_3$ [15].

	T [K]	N-1	N-2,5, N-2′	N-3,4	$N(CH_3)_2$
2b	238	− 80.0	− 27.1	+ 4.9	− 324.6 [a]
3b	238	− 292.2	− 134.6	− 146.2	− 333.2 [a]
	297	− 292.7	− 134.4	− 147.0	− 335.0 [a, b]
^{15}N-**2b**	253		− 27.5		[c]
^{15}N-**3b**	273		− 135.3		[d]
	295		− 135.0		[d]

[a] Data from a solution of 80 mg of crystalline **2b** dissolved in 10 mL of $CDCl_3$, 0.07 M in $Cr(acac)_3$. [b] Data of an authentic sample of **3b**, 348 mg in 10 mL $CDCl_3$, 0.07 M in $Cr(acac)_3$. [c] Data from a crystalline sample of [2(5)-^{15}N]-pentazole **2b**, 99% ^{15}N, 25 mg in 10 mL of $CDCl_3$, 0.06 M in $Cr(acac)_3$. [d] Same sample as in [c], after decomposition.

azoles, a range of $\delta = -70$ to -90 for N-1 is predicted. The shielding of the tricoordinated N atoms decreases in the series 1-methylpyrazole ($\delta = -180.8$),[11] 2-methyl-1,2,3-triazole ($\delta = -134.0$),[9] 2-methyltetrazole ($\delta = -105.3$),[9] and the pentazole **2b** ($\delta = -80.0$). The assignments of N-2,5 and N-3,4 were made on the basis of the spectrum (Fig. 2a) of a sample of **2b** labeled with ^{15}N at N-2, which was prepared from the corresponding diazonium salt **1b** labeled at the terminal nitrogen.[12] The resonances of N-2,5 and N-3,4, while in the expected range predicted by extrapolation from triazoles and tetrazoles, could not be reproduced by application of additive shielding increments.[10] On decomposition of **2b**, the ^{15}N label appeared as expected in the central position of the N_3 group of **3b** and in the molecular nitrogen[13] (Fig. 2b).

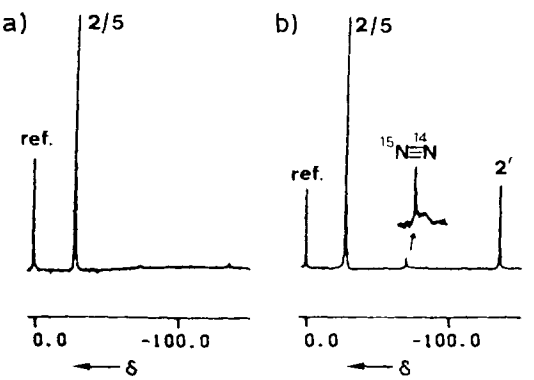


Fig. 2. ^{15}N-NMR Spectra (40.56 MHz) of a) [2(5)-^{15}N]-pentazole **2b**, 0.013 M in $CDCl_3$, 253 K (see also Table 1 [c]) and b) labeled pentazole **2b** (0.013 M, $CDCl_3$) during decomposition to [2-^{15}N]-**3b** and labeled $^{15}N \equiv {}^{14}N$ [13] at 273 K.

It is thus confirmed that **2b** also contains a pentazole ring in solution. The electron-attracting power of the pentazole group is demonstrated by the deshielding of the dimethylamino N atom ($\delta = -324.6$) compared to that in *N,N*-dimethylaniline ($\delta = -338 \pm 2$). A similar effect is observed when the pentazole group is replaced by CN ($\delta = -325.4$) or CHO ($\delta = -323.1$), and an even greater effect is produced by an NO_2 group ($\delta = -316.5$).[14] The crystallographic results indicate that the inductive effect of the pentazole group is similar to that of the nitro group. Hence, it may be concluded from the ^{15}N-NMR data that the pentazole substituent is not as good a π-acceptor as the nitro group.

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1b·Cl$^-$, 100-04-9; **2b**, 58402-54-3; ^{15}N-**2b**, 96445-25-9; **3b**, 18523-44-9; ^{15}N-**3b**, 96445-26-0; LiN_3, 19597-69-4.

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[7] The ^{15}N resonance of labeled $^{15}N \equiv {}^{14}N$ was reported to appear as a relatively sharp line at $\delta = -70.5$ (in cyclopropane, 233 K, recalculated rel. to CH_3NO_2 as ext. standard); cf. J. G. Green, G. R. Dubay, N. A. Porter, *J. Am. Chem. Soc. 99* (1977) 1264. For a discussion of the chemical shifts and line widths of N_2 see also [13].
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[13] The signal of the labeled $^{15}N \equiv {}^{14}N$ appears as a sharp line at $\delta = -70.1$ in good agreement with [7]. It is assigned to truly dissolved N_2 and is only observed with labeled material because of the low concentration. The broad N_2 absorption centered at $\delta = -73$ in Figures 1 and 2b probably results from gaseous N_2 in micro-bubbles and the associated local field inhomogeneity.
[14] J. Dorie, B. Mechin, G. Martin, *Org. Magn. Reson. 12* (1979) 229. The published chemical shift data were recalculated relative to $CH_3{}^{15}NO_2$ as an ext. standard.
[15] The ^{15}N-NMR spectra were measured on a Bruker AM-400 w.b. spectrometer at 40.56 MHz in 20-mm tubes with $Cr(acac)_3$ as a relaxation reagent (AT = 0.8 s, α = 23°, no proton decoupling).

Disulfur Monoxide as Complex Ligand—Preparation and Molecular Structure of $[(\eta^5\text{-}C_5Me_5)Mn(CO)_2(S_2O)]$**

By *Max Herberhold,* Bertram Schmidkonz, Manfred L. Ziegler,* and *Thomas Zahn*

Dedicated to Professor Helmut Behrens on the occasion of his 70th birthday

Free disulfur monoxide, S_2O, which is stable in the gas phase below 1 torr for several days, decomposes to SO_2 and polysulfur oxides.[1] Like the isovalent and isoelectronic SO_2, it is non-linear.[1]



S_2O can be formed as a complex ligand by the oxidation of S_2 ligands. However, the S_2O complexes reported so far only allow tentative conclusions to be made regarding the coordinating properties of S_2O, since no structural investigations are available for the mononuclear complexes **1**[2] and **2**,[3] and since the binuclear complex **3**,[4] whose structure has been confirmed by X-ray analysis, contains S_2O bridges.

$6(dppe)_2Ir(S_2O)]Cl$ **1**, dppe: bis(diphenylphosphino)ethane

$[Cp_2Nb(S_2O)Cl]$ **2**, Cp: η^5-cyclopentadienyl

$[Mo(S_2O)(S_2C-NEt_2)_2]_2$ **3**

We have prepared the brown disulfur complex **5** by reaction of the tetrahydrofuran(THF)-stabilized complex fragment $[Cp^*Mn(CO)_2]$ ($Cp^* = \eta^5$-pentamethylcyclopentadienyl), which is formed via photolysis of **4** in THF,[5] with excess sulfur. **5** was then converted to the red complex **6** by air oxidation.[6] The mononuclear neutral complex **6** is a suitable model compound for the study of the S_2O ligand.

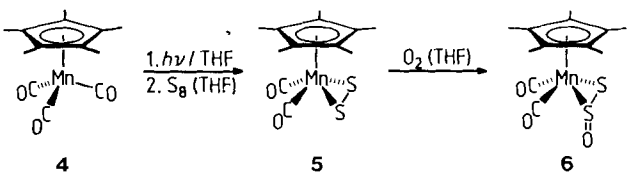


Table 1. Spectroscopic data for the complexes **4**—**6**.

	4	**5**	**6**
IR			
ν(CO) [cm^{-1}] [a]	2002 s	1993 vs	2000 vs
	1917 vs	1946 vs	1952 vs
k(CO) [N·cm^{-1}] [b]	15.28	15.67	15.77
^{1}H-NMR [c]			
$\delta(C_5(CH_3)_5)$	1.85	1.76	1.71
^{13}C-NMR [c]			
$\delta(C_5(CH_3)_5)$	10.2	9.8	9.3
$\delta(C_5(CH_3)_5)$	95.4	102.0	100.9

[a] In THF. [b] Calculated according to F. A. Cotton, C. S. Kraihanzel, *J. Am. Chem. Soc. 84* (1962) 4432. [c] In $CDCl_3$, 0°C.

Table 1 summarizes the characteristic IR and NMR data of the complexes **4**—**6**. According to the force constants k(CO) of the carbonyl vibrations, which can be calculated from the ν(CO) frequencies, the back-bonding from the metal to the CO ligands decreases upon replacement of a CO group in **4** with S_2 or S_2O. The acceptor character of S_2 is higher than that of CO; this observation was also made in an earlier study on $[CpRe(CO)_2S_2]$.[7] Apparently, S_2 is able to withdraw more charge from the complex fragment $[Cp^*Mn(CO)_2]$ than carbon monoxide. A further, but somewhat smaller increase in the acceptor ability occurs upon oxidation of the S_2 ligand to S_2O.

According to the X-ray structure determination of **6** (Fig. 1), the disulfur monoxide ligand is coordinated to the metal via both sulfur atoms. The Mn—S bonds are long and somewhat different; the sulfur atom bearing the oxygen, S(2), exhibits pyramidal geometry and is further away from the metal than the terminal S(1). The S—S axis is roughly parallel to the ring plane of the Cp* ligand. The oxygen atom of the S_2O ligand is directed away from the Cp^* ring; the dihedral angle S_2O/C_5Me_5 is 54.3°. In comparison to free S_2O, the S—S and S—O bonds of coordi-

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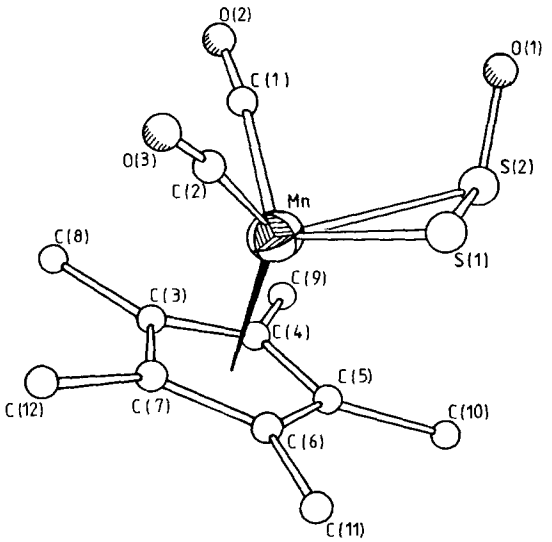
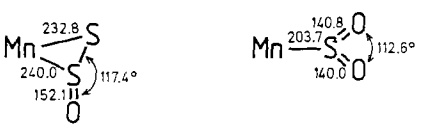


Fig. 1. Molecular structure of **6** in the crystal. $Pbn2_1$-C_{2v}^9, $Z=4$, $a=843.1(4)$, $b=1229.9(4)$, $c=1394.3(1.1)$ pm; $R_{iso}=0.139$, $R_{aniso}=0.056$, $R_w=0.048$. — Selected structural data ([pm] and [°], respectively): Mn–S(1) 232.8(5), Mn–S(2) 240.0(5), S(1)–S(2) 201.3(8), S(2)–O(1) 152.1(13); S(1)–Mn–S(2) 50.4(2), Mn–S(1)–S(2) 66.7(2), Mn–S(2)–S(1) 63.0(2), Mn–S(2)–O(1) 114.6(5), S(1)–S(2)–O(1) 117.4(6). Further details of the crystal structure investigation are available on request from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2, upon quoting the depository number CSD 51386, the names of the authors, and the journal citation.

nated S_2O in the complex **6** are longer, whereas the SSO angle remains unchanged. The S–S distance (201.3(8) pm), however, is markedly shorter in **6** than for the S_2O bridges in **3** (mean value 210.0(5) pm), which were interpreted tentatively as S_2O anions in a molybdenum(III) complex.[4] In the manganese complex **6**, S_2O can be looked upon as a side-on π-bound ligand.



Scheme 1. Left: part of **6**; right: part of $[CpMn(CO)_2SO_2)]$ **7** [8].

In contrast, the SO_2 ligand in **7** is only bonded via the central sulfur atom. The involvement of multiple bonding must be assumed for the Mn–S bond because of the trigonal-planar sulfur geometry and the short Mn–S distance.[8,9] The SO_2 plane lies perpendicular to the ring plane of the Cp ligand. The S–O distances are somewhat shorter than those of free SO_2 and the OSO angle is smaller.[8]

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4, 34807-89-1; **5**, 96482-53-0; **6**, 96502-41-9; sulfur, 7704-34-9.

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[6] *Experimental procedure:* A solution of **4** (600 mg, 2.2 mmol) in 150 mL of anhydrous N_2-saturated THF was irradiated with a high-pressure mercury lamp (Q700 Original Hanau) until the ν(CO) absorptions of **4** had vanished (ca. 3 h). After addition of sulfur (200 mg, 6.3 mmol), the solution was stirred for 1 h, its color changing from the original wine-red to dirty green. Subsequently, air was passed through the solution for 30 min, followed by an additional 5–8 h of stirring under air. The resulting brownish red solution was evaporated and the residue chromatographed on a silica gel column (CCR 60 Grace, 20 × 1.5 cm). The column was first washed with pentane and then the sulfur-containing complexes (including **5**) were eluted as a greenish brown band with CH_2Cl_2 and **6** as a red band with THF. Recrystallization from THF/diethyl ether at −78 °C afforded red crystals of **6** (150 mg, 21%), which decompose at 140–145 °C. — IR (KBr) 1995 (vs), 1950 (vs) (ν(CO)), 1056 (m) (ν(SO)), 546 (m) (ν(SS)) cm^{-1}. — FD-MS: m/z 326 (M^+). — EI-MS: m/z 326 (4%, M^+), 310 (6%, $Cp^*Mn(CO)_2S^+$), 270 (36%, $Cp^*Mn(S_2O)^+$), 254 (16%, $Cp^*MnS_2^+$), 238 (3%, Cp^*MnSO^+), 222 (37%, Cp^*MnS^+), 206 (17%, Cp^*MnO^+), 190 (4%, Cp^*Mn^+), 119 (100%, $C_9H_7^+$). — Correct elemental analysis (C, H, O, S, Mn).

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Reaction of Small Molecules with the Binuclear Complex $[(\mu\text{-}C_5H_5)(\mu\text{-}Br)Pd_2(PR_3)_2]$: Addition without Cleavage of the Metal-Metal Bond**

By *Peter Thometzek, Karin Zenkert,* and *Helmut Werner**

The addition of small molecules such as CO, CO_2, or SO_2 to compounds containing metal-metal bonds and the possible reversibility of this process is of current interest, e.g., in connection with the removal of these molecules from gas mixtures. We chose as a model system the sandwich-type binuclear complexes **1a**, **b**,[1] in which the bridging bromide can be easily replaced, for example, by a thiolate or carbonylmetalate anion.[2]

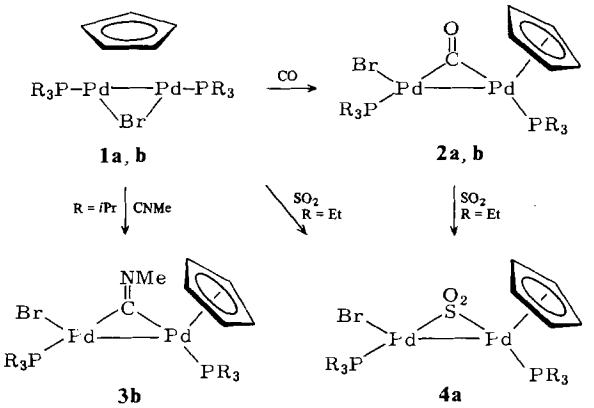
The reaction of **1a**, **b** with CO in pentane or toluene produces nearly quantitatively in a few minutes the novel CO-bridged binuclear complexes **2a**, **b**.[3] These ruby-red, rather air-stable solids are soluble in all the standard organic solvents except alkanes. In contrast to the reactions of $[(\mu\text{-dppm})_2M_2X_2]$ ($dppm=CH_2(PPh_2)_2$; M = Pd, Pt; X = Cl, Br)[4a] and $[(\mu\text{-dppm})_2Rh_2(CO)_2]$[4b] with CO, the addition of carbon monoxide to **1a**, **b** is not accompanied by cleavage of the metal-metal bond; however, the cyclopentadienyl and bromide ligands rearrange from bridging to terminal positions. A similar rearrangement also occurs in the addition of allene to **1b**, but with cleavage of the Pd–Pd bond.[5]

The reactivity of methyl isocyanide and SO_2 towards **1b** and **1a**, respectively, is similar to that of CO. The reaction of **1b** with $CNCH_3$ occurs rapidly in toluene even below 0 °C to give **3b** in high yield.[3] The spectroscopic data for **3b** are consistent with a structure similar to that of the CO-bridged complexes **2a,b** and **2b**, Cl instead of Br.[6] According to the ^1H- and ^{13}C-NMR spectra of **2a,b** and **3b**

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(as well as of **4a**),[3b] the phosphane ligands are non-equivalent. Compound **4a** is formed quantitatively by bubbling SO_2 into a solution of **1a** in toluene. The chemical properties of **4a** and the carbonyl complex **2a** are similar; owing to the oxidation state +1 of the palladium, the most noteworthy feature of these compounds seems to be their stability in air.



The differing nature of the two fragments $[Pd(PR_3)Br]$ and $[Pd(PR_3)C_5H_5]$ present in **2a,b**, **3b**, and **4a**, whose anionic ligand is a *two*-electron and a *six*-electron donor, respectively, should be reflected in the structure of the bridging unit. On the basis of a comparison with binuclear cobalt and rhodium complexes in which one of the metals formally has 16 and the other 18 electrons in the valence shell,[7,8] we expected the bridging ligand in **2a,b**, **3b**, and **4a** to be more firmly bonded to the electron-deficient part of the molecule. This is confirmed by the results of the X-ray structural analysis of **4a** (Fig. 1).[9] The SO_2 ligand

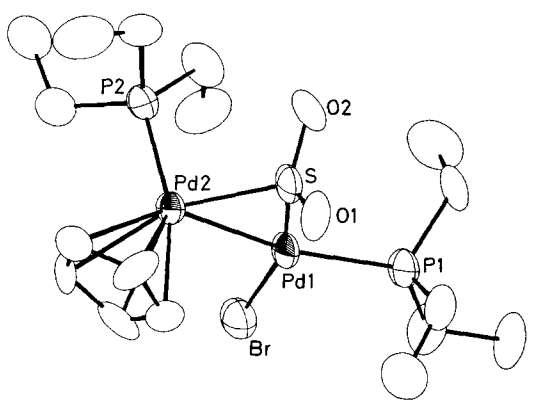
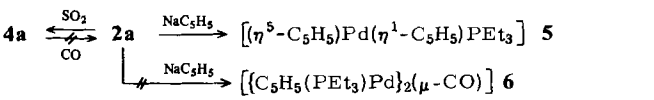


Fig. 1. Structure of **4a** in the crystal. Selected bond lengths [pm] and bond angles [°]: Pd1–Pd2 274.7(2), Pd1–Br 247.8(3), Pd1–P1 225.1(6), Pd1–S 215.6(6), Pd2–S 227.9(6), Pd2–P2 226.7(5), S–O1 144(2), S–O2 148(2), Pd2-midpoint of the C_5H_5 ring 196.6(2); Pd2–Pd1–P1 149.4(2), Pd2–Pd1–Br 107.3(1), P1–Pd1–Br 102.0(1), Pd1–Pd2–P2 101.7(2), Pd1–S–Pd2 76.5(2), Pd2–Pd1–S 53.8(2), P1–Pd1–S 97.2(2), O1–S–O2 116.0(1).

bridges the Pd–Pd bond in an unsymmetrical fashion, the Pd–S bond lengths differing by 12.3 pm. The bond angle Pd1–S–Pd2 is relatively small and similar to that in $[\{C_5H_5(CO)Rh\}_2(\mu\text{-}SO_2)]$, which contains a symmetrical $Rh–SO_2–Rh$ bridge.[10] Owing to the size of the sulfur atom, the Pd–Pd distance in **4a** (274.7(2) pm) is significantly larger than that in **1b** (260.9(1) pm)[11] and comparable to the Pd–Pd distance in palladium metal (274 pm). To the best of our knowledge, there is only one other known example of a polynuclear metal complex, having an unsymmetrical SO_2 bridge, namely, $[(\mu\text{-}C_6H_5)(\mu\text{-}PPh_2)(\mu\text{-}SO_2)Pt_3(PPh_3)_3]$; in this case, the Pt–S distances are 217.0(6) and 227.2(6) pm.[12]

The preference of SO_2 to form the $Pd(\mu\text{-}SO_2)Pd$ unit is also manifested in the reaction of **2a** with SO_2 to produce **4a** which is complete in benzene at 25 °C in a few minutes. Ligand exchange in the reverse direction is not detectable under the same conditions. Treatment of **2a** with NaC_5H_5



in toluene at −78 °C does not lead to the formation of the symmetrical binuclear compound **6**, but gives instead the complex **5**[13] by cleavage of the metal-metal bond.

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CAS Registry numbers:
1a, 96445-58-8; **1b**, 57622-82-9; **2a**, 96445-59-9; **2b**, 96445-60-2; **3b**, 96453-14-4; **4a**, 96453-15-5; **5**, 72244-78-1; Pd, 7440-05-3.

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[3] a) **2a**: CO is bubbled into a solution of 275 mg (0.50 mmol) **1a** in 5 mL toluene at room temperature. After concentration to ca. 1 mL, addition of 10 mL pentane, and cooling to −30 °C, ruby-red crystals are obtained which are recrystallized from toluene/pentane; m.p. 71 °C (decomp.); yield 263 mg (91%). The synthesis of **2b** (m.p. 89 °C (decomp.); yield 90%) from **1b** and of **4a** (red-violet crystals, m.p. 82 °C (decomp.); yield 82%) from **1a** is carried out analogously. For the preparation of **3b**, a solution of **1b** in toluene is treated dropwise at −78 °C with $CNCH_3$ and then warmed to room temperature; brick-red crystals, m.p. 85 °C (decomp.); yield 82%. Correct elemental analysis for all compounds.—b) IR in KBr, all NMR spectra in C_6D_6, δ-values.—**2a**: IR: ν(CO) = 1804 cm^{-1}; ^{1}H-NMR: 5.85 (dd, J(PH) = 1.9 and 1.6 Hz, C_5H_5), 1.65 (m, CH_2 on P1), 1.52 (m, CH_2 on P2), 1.10 (dt, J(PH) = 17.0, J(HH) = 7.0 Hz, CH_3 on P1), 0.89 (dt, J(PH) = 17.2, J(HH) = 7.2 Hz, CH_3 on P2); ^{31}P-NMR: 33.1 (d, J(PP) = 14.6 Hz, P1), 23.3 (d, J(PP) = 14.6 Hz, P2).—**2b**: IR: ν(CO) = 1828 cm^{-1}; ^{1}H-NMR: 6.02 (dd, J(PH) = 1.7 and 1.5 Hz, C_5H_5), 2.31 (m, CH on P1), 1.70 (m, CH on P2), 1.27 (dd, J(PH) = 14.6, J(HH) = 7.4 Hz, CH_3 on P1), 1.10 (dd, J(PH) = 14.8, J(HH) = 7.4 Hz, CH_3 on P2); ^{31}P-NMR: 70.2 (d, J(PP) = 7.4 Hz, P1), 51.9 (d, J(PP) = 7.4 Hz, P2).—**3b**: IR: ν(CN) = 1791 cm^{-1}; ^{1}H-NMR: 6.02 (dd, J(PH) = 2.0 and 1.4 Hz, C_5H_5), 2.94 (s, $CNCH_3$), 2.60 (m, CH on P1), 1.86 (m, CH on P2), 1.32 (dd, J(PH) = 13.8, J(HH) = 6.8 Hz, CH_3 on P1), 1.02 (dd, J(PH) = 15.0, J(HH) = 7.2 Hz, CH_3 on P2); ^{31}P-NMR: 69.9 (d, J(PP) = 11.9 Hz, P1), 49.5 (d, J(PP) = 11.9 Hz, P2); ^{13}C-NMR: 196.8 (d, J(PC) ≈ 10 Hz, $CNCH_3$), 97.5 (dd, J(PC) = 7.4 and 6.0 Hz, C_5H_5), 42.4 (d, J(PC) ≈ 8 Hz, $CNCH_3$), 25.9 (d, J(PC) = 20.7 Hz, CH on P1), 24.1 (d, J(PC) = 16.5 Hz, CH on P2), 20.2 (d, J(PC) = 5.7 Hz, CH_3 on P1), 20.0 (d, J(PC) = 5.2 Hz, CH_3 on P2).—**4a**: IR: ν(SO) = 1205, 1067, 1030 cm^{-1}; ^{1}H-NMR: 5.78 (dd, J(PH) = 2.3 and 2.1 Hz, C_5H_5), 1.72 (m, CH_2 on P1), 1.62 (m, CH_2 on P2), 1.13 (dt, J(PH) = 17.0, J(HH) = 7.3 Hz, CH_3 on P1), 0.90 (dt, J(PH) = 17.5, J(HH) = 7.5 Hz, CH_3 on P2); ^{31}P-NMR: 40.8 (d, J(PP) = 6.0 Hz, P1), 26.8 (d, J(PP) = 6.0 Hz, P2); ^{13}C-NMR: 100.6 (dd, J(PC) = 6.7 and 6.5 Hz, C_5H_5), 18.9 (d, J(PC) = 27.7 Hz, CH_2 on P1), 17.0 (d, J(PC) = 24.8 Hz, CH_2 on P2), 8.5 (d, J(PC) = 4.3 Hz, CH_3 on P1), 8.2 (d, J(PC) = 4.1 Hz, CH_3 on P2).

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[7] $[C_5H_5(PMe_3)Co(\mu\text{-}CS)_2CoC_5H_5]$: H. Werner, O. Kolb, U. Schubert, K. Ackermann, *J. Organomet. Chem. 240* (1982) 421; $[MeC_5H_4(PMe_2Ph)Co(\mu\text{-}CO)_2CoC_5H_4Me]$: W. H. Hersh, F. J. Hollander, R. G. Bergman, *J. Am. Chem. Soc. 105* (1983) 5834.

[8] $[C_5H_5(PPh_3)Rh(\mu\text{-}CO)_2RhC_5H_5]$: F. Faraone, G. Bruno, S. L. Shiavo, P. Piraino, G. Bombieri, *J. Chem. Soc. Dalton Trans. 1983*, 1819; $[C_5Me_5\{P(OMe)_3\}Rh(\mu\text{-}CO)_2RhC_5Me_5]$: H. Werner, B. Klingert, R. Zolk, P. Thometzek, *J. Organomet. Chem. 266* (1984) 97.

[9] Triclinic, space group P1, $Z=2$; $a=845.1(10)$, $b=945.6(15)$, $c=1537.1(21)$ pm, $\alpha=85.89(12)$, $\beta=85.31(10)$, $\gamma=84.12(12)°$, $V=1215\cdot10^6$ pm^3, $\rho_{calcd.}=1.80$ g/cm^3, $\rho_{exp.}=1.78$ g/cm^3; $5°\leq2\theta\leq45°$ ($Mo_{K\alpha}$, $\lambda=71.069$ pm, ω-scan); 3168 independent reflections, Lorentz and polarization corrections, Multan (Pd, Br) and Fourier methods (S, P, O, C); $R_1=0.089$, $R_2=0.106$ for 2538 structure factors ($F_0\geq2.96\sigma(F_0)$). Further details of the crystal structure analysis are available on request from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2, by quoting the depository number CSD 51354, the names of the authors, and the journal citation.

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[11] A. Ducruix, C. Pascard, *Acta Crystallogr. B33* (1977) 3688.

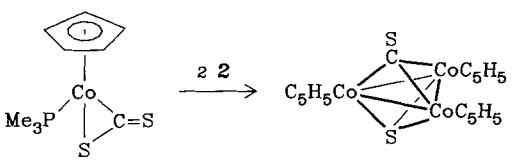
[12] D. J. Evans, G. R. Hughes, D. M. P. Mingos, J. M. Bassett, A. J. Welch, *J. Chem. Soc. Chem. Commun. 1980*, 1255.

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Fragmentation and Recombination of CS_2 and CSSe in the Coordination Sphere of Platinum Metals**

By *Martin Ebner, Heiko Otto,* and *Helmut Werner**

Whereas drastic reaction conditions are needed to split CS_2 into CS and sulfur,[2] such a process occurs readily in the coordination sphere of transition metals. A striking example is the formation of the Co_3 cluster **3** from **1** and the 16-electron fragment $[C_5H_5Co(PMe_3)]$ generated from **2**, which proceeds in benzene at ca. 80 °C in 82% yield.[3]

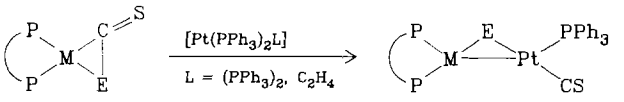


1 **3**

$[C_5H_5(PMe_3)Co(\mu\text{-}CO)_2Mn(CO)C_5H_4Me]$ **2**

We have now observed that it is possible to reverse the metal-initiated fragmentation of CS_2 (or of CSSe) into CS and S (or CS and Se). Two platinum atoms or one platinum and one palladium atom are involved in this process.

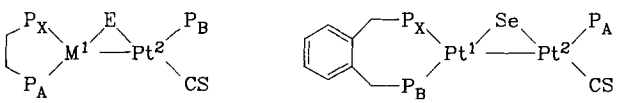
The chelate complexes **4**—**7**[4] react with $[Pt(PPh_3)_4]$ and with $[Pt(C_2H_4)(PPh_3)_2]$ in acetone at room temperature by displacement of triphenylphosphane and ethylene, respectively, to produce the binuclear μ-sulfido or μ-selenido compounds **8**—**11**.[5] The addition of $[Pt(PPh_3)_2]$ to the exocyclic sulfur atom, which was originally expected to occur (see [6]), does not take place. *Walker* et al. have independently described the synthesis of the Pt_2 complex **8**.[7] A similar cleavage of CS_2 by phosphane-platinum compounds has recently been reported by *Scherer* et al.[8] who isolated the complex $[\{PtL(CS)\}_2(\mu\text{-}S)_2]$ ($L=tBuN{=}P{-}N(SiMe_3)tBu$) on reaction of PtL_3 with CS_2. In this product, however, platinum is in the +2 oxidation state and thus the two metal atoms are *not* linked by a metal-metal bond.



4–7 **8–11**

Comp.	M	E	P⌒P
4, **8**	Pt	S	diphos = $Ph_2P{-}CH_2CH_2{-}PPh_2$
5, **9**	Pt	Se	diphos
6, **10**	Pt	Se	dpmb = $Ph_2P{-}CH_2{-}o{-}C_6H_4{-}CH_2{-}PPh_2$
7, **11**	Pd	Se	diphos

The evidence for the proposed structures of complexes **8**—**11** was obtained from the ^{31}P-NMR spectra which confirm the presence of ABX spin systems.[5b] The assignment is based on reference data which allow for the size of the chelate ring.[9]



8, 9, 11 **10**

The molecular structure of compound **10** is shown in Figure 1.[10] The selenium and platinum atoms form an isosceles triangle to which the CS ligand is coordinated in *trans* position to Se. The metal atoms and the non-metal atoms bonded to them are nearly coplanar, the dihedral angles formed between the planes [Pt1, Pt2, Se] and [Pt2, P1, C1] and between [Pt1, Pt2, Se] and [Pt1, P2, P3] being 5.5 and 4.5°, respectively. The Pt–Pt distance is nearly the same as in other platinum(I) complexes.[11]

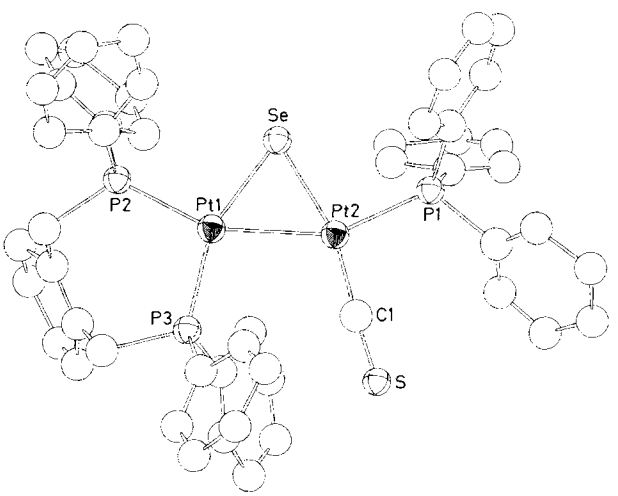
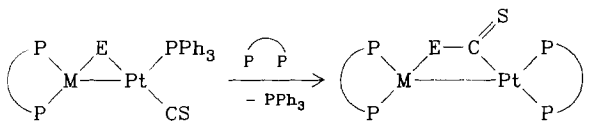


Fig. 1. Structure of **10** in the crystal; only one of the two independent molecules present in the asymmetric unit is shown. Selected bond lengths [pm] and angles [°] of the molecule illustrated in the figure (the values of the second molecule are the same within the standard deviations): Pt1–Pt2 266.1(3), Pt1–Se 238.5(7), Pt2–Se 238.0(7), Pt1–P2 229(2), Pt1–P3 223(2), Pt2–P1 230(2), Pt2–C1 183(4), C1–S 152(4); Pt1–Pt2–Se 56.1(2), Pt2–Pt1–Se 56.0(2), Pt1–Se–Pt2 67.9(2), Se–Pt2–P1 95.8(5), Se–Pt2–C1 163(1), Se–Pt1–P2 99.2(4), Se–Pt1–P3 156.6(4), Pt2–C1–S 177(3), Pt1–Pt2–P1 151.5(4), P2–Pt1–Pt2 155.1(4), P3–Pt1–Pt2 101.0(4), P2–Pt1–P3 103.8(6), Pt1–Pt2–C1 107(1), P1–Pt2–C1 102(1).

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An attempt to displace the two monodentate ligands at the platinum atom Pt^2 in **8**—**11** by a second chelating diphosphane led to an unexpected result. On treatment of **8**, **10**, and **11** with diphos or dpmb, the complexes **12**—**14** are formed, which, according to the IR spectra, contain a bridging CS_2 or CSSe ligand.[12] The position of the CS stretching frequency at ca. 900 cm^{-1} is very similar to that of the compound $[Pt_2Cl_2(\mu\text{-}Ph_2P\text{-}CH_2\text{-}PPh_2)_2(\mu\text{-}CS_2)]$, the structure of which has been determined by X-ray structural analysis.[13] The ^{31}P-NMR spectrum of **13** consists of two AB pairs which correspond to two pairs of phosphorus atoms (P_A, P_B and P_X, P_Y) located in a similar chemical environment.[12b]



8, 10, 11 **12–14**

	M	E	P⌒P
8, **12**	Pt	S	diphos
10, **13**	Pt	Se	dpmb
11, **14**	Pd	Se	diphos

The reaction of **9** with diphos does not lead to the formation of a product comparable to **12**—**14**. Although displacement of PPh_3 by the chelating ligand occurs, a band at 1055 cm^{-1} in the IR spectrum corresponding to a ν(CS) stretching frequency points to the presence of a CS bridge in the binuclear complex. Thus, the tendency of the two fragments CS and S or CS and Se to reform the corresponding heteroallene depends both on the metals and on the ligands.

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4, 96482-93-8; **5**, 89606-43-9; **6**, 89606-44-0; **7**, 85318-47-4; **8**, 85897-25-2; **9**, 96482-94-9; **10**, 96482-95-0; **11**, 96482-96-1; **12**, 85698-24-4; **13**, 96502-47-5; **14**, 96482-97-2; $[Pt(PPh_3)_4]$, 14221-02-4; $[Pt(PPh_3)_2C_2H_4]$, 12120-15-9; SeCS, 5951-19-9; CS_2, 75-15-0; S^{2-}, 18496-25-8; Se^{2-}, 22541-48-6; CS, 2944-05-0; Pt, 7440-06-4; Pd, 7440-05-3.

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[2] I. S. Butler, *Acc. Chem. Res. 10* (1977) 359, and references therein.
[3] a) H. Werner, K. Leonhard, *Angew. Chem. 91* (1979) 663; *Angew. Chem. Int. Ed. Engl. 18* (1979) 627; b) H. Werner, K. Leonhard, O. Kolb, E. Röttinger, H. Vahrenkamp, *Chem. Ber. 113* (1980) 1654.
[4] Preparation from $[M(\eta^2\text{-}CSE)(PPh_3)_2]$ (E = S, Se) and diphos or dpmb. **4**: M. Ebner, *Dissertation*, Universität Würzburg 1985; **5**, **6**: H. Werner, M. Ebner, *J. Organomet. Chem. 258* (1983) C 52; **7**: H. Werner, M. Ebner, W. Bertleff, U. Schubert, *Organometallics 2* (1983) 891.
[5] a) **8**—**11** are prepared by stirring a suspension of 0.4 mmol **4**—**7** with a molar equivalent amount of $[Pt(PPh_3)_4]$ or $[Pt(C_2H_4)(PPh_3)_2]$ in 20 mL of acetone for 60—90 min. The orange precipitate is filtered off, washed with acetone and ether, dissolved in 5 mL of CH_2Cl_2, and chromatographed on alumina (Woelm, activity III) with CH_2Cl_2 (**8**, **9**, **11**) or benzene (**10**). Removal of the solvent gives a fairly air-stable solid which is washed with hexane and dried in vacuo. Yield 70—90%; correct C, H, Pt, Pd analyses.—b) Decomposition temperature determined by differential thermal analysis; IR in Nujol; ^{31}P-NMR (90 MHz, ext. 85% H_3PO_4) in CH_2Cl_2/C_6D_6 (1 : 10) with 1% Cr(acac)$_3$, all signals dd.—**8**: Decomp. temp. 197°C; IR: ν(CS) = 1305 cm^{-1}; ^{31}P-NMR: $\delta(P_A) = 58.79$, $\delta(P_B) = 27.56$, $\delta(P_X) = 47.83$, $J(P_AP_B) = 147$, $J(P_AP_X) = 3$, $J(P_BP_X) = 27$, $J(Pt^1P_A) = 3200$, $J(Pt^1P_X) = 3160$, $J(Pt^2P_B) = 2330$ Hz.—**9**: Decomp. temp. 178°C; IR: ν(CS) = 1305 cm^{-1}; ^{31}P-NMR: $\delta(P_A) = 59.87$, $\delta(P_B) = 28.13$, $\delta(P_X) = 42.97$, $J(P_AP_B) = 148$, $J(P_AP_X) = 5$, $J(P_BP_X) = 25$, $J(Pt^1P_A) = 3180$, $J(Pt^1P_X) = 3280$, $J(Pt^2P_B) = 2400$ Hz.—**10**: Decomp. temp. 162°C; IR: ν(CS) = 1305 cm^{-1}; ^{31}P-NMR: $\delta(P_A) = 22.47$, $\delta(P_B) = 7.18$, $\delta(P_X) = 1.22$, $J(P_AP_B) = 184$, $J(P_AP_X) = 24$, $J(P_BP_X) = 18$, $J(Pt^1P_B) = 3100$, $J(Pt^1P_X) = 3640$, $J(Pt^2P_A) = 2060$ Hz.—**11**: Decomp. temp. 135°C; IR: ν(CS) = 1300 cm^{-1}; ^{31}P-NMR: $\delta(P_A) = 59.14$, $\delta(P_B) = 28.32$, $\delta(P_X) = 42.03$, $J(P_AP_B) = 148$, $J(P_AP_X) = 5$, $J(P_BP_X) = 26$, $J(Pt^2P_B) = 2360$ Hz.
[6] W. P. Fehlhammer, H. Stolzenberg, *Inorg. Chim. Acta 44* (1980) L 151.
[7] W. M. Hawling, A. Walker, M. A. Woitzik, *J. Chem. Soc. Chem. Commun. 1983*, 11.
[8] O. J. Scherer, R. Konrad, E. Guggolz, M. L. Ziegler, *Chem. Ber. 116* (1983) 2676.
[9] P. E. Garrou, *Chem. Rev. 81* (1981) 229.
[10] Crystals from acetone. Triclinic, space group $P\bar{1}$, $Z = 4$; $a = 1434.7(3)$, $b = 1452.8(1)$, $c = 2522.3(3)$ pm, $\alpha = 89.0(2)$, $\beta = 88.8(1)$, $\gamma = 70.8(2)°$, $V = 5257 \cdot 10^6$ pm^3; $\rho_{calcd} = 1.67$ g/cm^3; $5° \leq 2\theta \leq 32°$ ($Mo_{K\alpha}$, $\lambda = 71.069$ pm); 5038 independent reflections; position of the platinum atoms by Multan-80, position of the other atoms from difference Fourier synthesis; $R_1 = 0.098$, $R_2 = 0.113$ for 4228 structure factors ($F_0 \geq 2.96\sigma(F_0)$). Further details of the crystal structure analysis can be obtained from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2, by quoting the depository number CSD 51355, the names of the authors, and the journal citation.
[11] Example: $[Cl(PPh_3)Pt(\mu\text{-}CO)Pt(PPh_3)_2Cl]$: 264.3 pm; R. Bender, P. Braunstein, A. Tiripicchio, M. Tiripicchio-Camellini, *J. Chem. Soc. Chem. Commun. 1984*, 42; $[(PPh_3)_2Pt(\mu\text{-}S)Pt(CO)PPh_3]$: 264.7 pm; A. Skapski, P. Traughton, *J. Chem. Soc. Chem. Commun. 1969*, 170.
[12] a) Complexes **12**—**14** are prepared by stirring a suspension of 0.15 mmol **8**, **10**, **11** with a molar equivalent amount of diphos or dpmb in 10 mL of acetone for 60—90 min. The yellow precipitate is filtered off, washed repeatedly with ether, and dried in vacuo. Yield 92% (**12**), 65% (**13**), 77% (**14**); correct C, H, Pt, Pd analyses.—b) Decomposition temperature, IR, and ^{31}P-NMR as for **8**—**11** [5].—**12**: Decomp. temp. 251°C; IR: ν(CS) = 885 cm^{-1}; ^{31}P-NMR could not be completely analyzed; the spectrum consists of two AB parts which overlap.—**13**: Decomp. temp. 226°C; IR: ν(CS) = 920 cm^{-1}; ^{31}P-NMR: $\delta(P_A) = 39.78$, $\delta(P_B) = 37.73$, $\delta(P_X) = 33.47$, $\delta(P_Y) = 32.83$, $J(P_AP_B) = 46$, $J(P_XP_Y) = 16$, $J(P_AP_X) = 7$, $J(P_BP_Y) = 6$, $J(PtP_A) = 4120$, $J(PtP_B) = 2600$, $J(PtP_X) = 4400$, $J(PtP_Y) = 2380$ Hz.—**14**: Decomp. temp. 198°C; IR: ν(CS) = 905 cm^{-1}.
[13] T. S. Cameron, P. A. Gardner, K. R. Grundy, *J. Organomet. Chem. 212* (1981) C 19.

Catalyzed Acetal Reduction with >BH Boranes — 1-*O*-Alkyl(aryl)alditols, Anhydroalditols, and 1-*O*-Alditylalditols from *O*-Glycopyranosides**

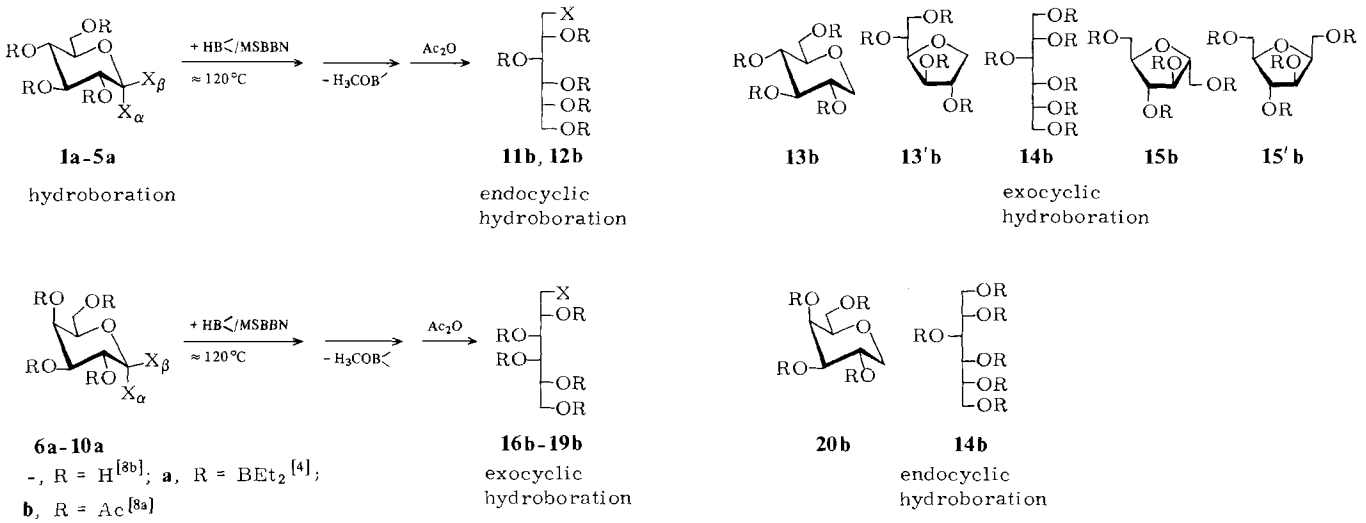
By *Roland Köster,** *Soledad Penadés-Ullate,* and *Wilhelm Volker Dahlhoff*

In contrast to semiacetals, acetals are completely stable towards >BH-boranes and ≥BH-borates up to ≳130°C. In the course of our investigations on the analytical uses of organoboron reagents we found that open-chain and cyclic *O,O*-acetals can be quantitatively reduced with aliphatic-substituted >BH boranes in the presence of certain electrophiles, e.g. ether-trifluoroboranes or alkane- and arenesulfonyloxy(diorgano)boranes, respectively.[1] We report here on the preparation of open-chain and cyclic polyhydroxyethers from *O*-gluco- and *O*-galactopyranosides[2] with alkyldiboranes(6) in the presence of the activator 9-methanesulfonyloxy-9-borabicyclo[3.3.1]nonane (MSBBN).[3] Apart from 1-*O*-methylalditols, 1-*O*-phenylgalactitol and various anhydroalditols, also 1-*O*-alditylalditols can now be prepared from disaccharides.

The per-*O*-diethylboryl derivatives **1a** to **10a**[4] of the *O*-glycopyranosides **1** to **10** (cf. Scheme 1 and Table 1) are especially suitable for the reduction with alkyldiboranes(6) (alkyl = ethyl, propyl)[5a] in the presence of MSBBN[3] at

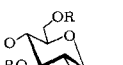
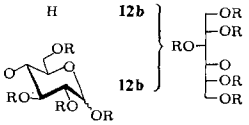
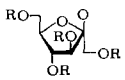
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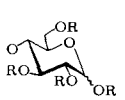
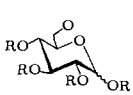
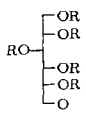
[**] Boron Compounds, Part 66.—Part 65: R. Köster, G. Seidel, B. Wrackmeyer, *Angew. Chem. 97* (1985) 317; *Angew. Chem. Int. Ed. Engl. 24* (1985) 326.



Scheme 1. Catalytic hydroboration of per-*O*-diethylboryl-substituted α- and β-glucopyranosides **1a**—**5a** and α- and β-galactopyranosides **6a**—**10a** (see Table 1).

Table 1. Products **11b**—**20b** of the catalytic hydroboration after deborylation and subsequent acetylation of the pyranosides **1a**—**10a** (see Scheme 1) [a, b]. Products: Per-*O*-acetylated 1-*O*-methyl-D-glucitol **11b** and 1-*O*-(4-D-glucityl)-D-glucitol **12b**; per-*O*-acetylated 1,5-anhydro-D-glucitol **13b**, 1,4-anhydro-D-glucitol **13'b**, D-glucitol **14b**, 2,5-anhydro-D-mannitol **15b** and 2,5-anhydro-D-glucitol **15'b**; per-*O*-acetylated 1-*O*-methyl-D-galactitol **16b**, 1-*O*-phenyl-D-galactitol **17b**, 1-*O*-(4-D-glucityl)-D-galactitol **18b**, 1-*O*-(D-glucityl)-D-galactitol **18'b** and 1-*O*-(6-D-glucityl)-D-galactitol **19b**; per-*O*-acetylated 1,5-anhydro-D-galactitol **20b**.

Per-*O*-(diethylboryl)-D-glucopyranoside	X_α	X_β	X	M.p. [°C]	$[\alpha]_D^{20}$ (*c*, $CHCl_3$)	Yield [%]	Yield [%] 13b	13'b	14b	15b	15'b
1a Methyl α-D-glucopyranoside	OCH_3	H	**11b** OCH_3	53–55 [11]	23.7 [11]	55	45	0	—	—	—
2a Methyl α-D-glucopyranoside	H	OCH_3	**11b** OCH_3		(1.2)	90	10	0	—	—	—
3a Maltose		H	**12b** 	47	38.2 (0.4)	50	24	1	25	—	—
4a Cellobiose	H		**12b**			76	6	6	12	—	—
5a Sucrose		H		—	—	0	6	0	50	6	38

Per-*O*-(diethylboryl)-D-galactopyranoside	X_α	X_β	X	M.p. [°C]	$[\alpha]_D^{20}$ (*c*, $CHCl_3$)	Yield [%]	Yield [%] 20b	14b
6a Methyl α-D-galactopyranoside	OCH_3	H	**16b** OCH_3	117–118 [11]	11.6 [11] (0.6)	56	44	—
7a Methyl β-D-galactopyranoside	H	OCH_3	**16b** OCH_3			90	10	—
8a Phenyl β-D-galactopyranoside	H	OC_6H_5	**17b** OC_6H_5	133	20 (0.3)	99	0	—
9a Lactose	H		**18b** 	82	18.2 (0.55)	70	7	7
			18'b [c]	[d]	[d]	≈ 16		
10a Melibiose		H	**19b** 	97–98	2 (1)	20	40	40

[a] Standard conditions: 5—6 h heating of **1a** to **10a** in boiling, neat ethyldiboranes(6) [12—15% $H^\ominus$] [5] with addition of MSBBN **3** in the ratio educt: >BH : MSBBN ≈ 1 : 4 : 0.1; in the case of **4a** and **9a**: 1 : 4 : 0.8. [b] The mixtures of **11b** to **20b** [8a] were separated gas-chromatographically; GC [12]: Siemens instrument glass capillary column (25—55 m, OV-1), He (1.5 bar), column 100—320 °C (10/min); injection block: 250 °C. [c] 1-, 2-, 3- or 5-D-glucityl-substituent. [d] Not determined.

100 °C. Hydroboration of the endocyclic acetalic C—O bond takes place, leading to open-chain *O*-ethylboron-protected[5b] polyhydroxy ethers, e.g. **11a**, **12a** and **16a** to **19a**.[6] Hydroboration of the exocyclic acetalic C—O bond leads to cyclic *O*-ethylboron-protected polyhydroxyether, e.g. **13a** and **20a**. *O*-Diethylboryl-, and the *O,O'*-ethylbo-

ranediyl-protective groups formed therefrom in the presence of ethyldiboranes(6) can readily be removed with methanol/glycol.[7] The per-*O*-acetyl derivatives[8a] **11b** to **20b** are prepared from the product mixture and can be separated chromatographically and characterized spectroscopically (MS, NMR).[8b]

The *O*-glycopyranosides **1a** to **10a** react with varying rates on reduction with ethyldiboranes(6); **4a** and **9a** are reduced especially slowly. By increasing the amount of MSBNN (cf. Table 1, footnote [a]), the formation of pyranosylalditols in the product mixture can be avoided. The composition of the polyhydroxyether mixtures is influenced by the anomeric configuration of the D-glucopyranosides **1** to **4** and the D-galactopyranosides **6** to **10**. The methyl β-pyranosides **2a** and **7a** and the phenyl β-D-galactopyranoside **8a** afford highly selectively, via endocyclic C–O hydroboration, 1-*O*-methyl-D-alditols (**11**, **16** with 80% selectivity) and 1-*O*-phenyl-D-galactitol (**17**, 98%), respectively. Octakis-*O*-(diethylboryl)cellobiose **4a** and octakis-*O*-(diethylboryl)lactose **9a** preferentially yield the 1-*O*-alditylalditols[9] **12** (52%) and **18** and **18'** (72%), respectively. In contrast, octakis-*O*-(diethylboryl)maltose **3a** affords **12** and **13** practically non-selectively, while octakis-*O*-(diethylboryl)melibiose **10a** gives only 20% **19**, and mainly 1,5-anhydro-D-galactitol **20** and D-glucitol **14**, both of which are formed as a result of exocyclic C–O bond cleavage (cf. Scheme 1 and Table 1).

The "trehalose" moiety of the octakis-*O*-(diethylboryl)sucrose **5a** is not reduced at the endocyclic acetal bonds. The quantitative reduction of **5a**, however, takes place regioselectively (88%), showing preference for the exocyclic C–O bond of the furanoside ring. In each case, 44% glucitol **14** and a ca. 1:6 mixture of the 2,5-anhydroalditols **15** and **15'** formed via an oxycarbenium intermediate are obtained. Reductive pyranoside-cleavage of **5a** affords a further 6% of D-glucitol **14** and 6% of 1,5-anhydro-D-glucitol **13** (cf. Scheme 1).

Experimental

Penta-*O*-acetyl-1-*O*-phenyl-D-glucitol **17b**: MSBBN [3] (0.1 g, 0.38 mmol) was added under protective gas at ≈20°C to 1.94 g (3.67 mmol) **8a** [prepared from 1 g (3.9 mmol) of phenyl β-D-galactopyranoside **8** and 4 mL (28.4 mmol) of activated triethylborane [4]] and 1.27 g ethyldiboranes(6) [5a] (11.86% $H^{\ominus}$, i.e. 15.1 mmol >BH-borane) and the mixture stirred for 4 h at 120°C. After evaporation of the colorless solution in vacuo (10^{-3} torr; bath: 70–80°C) the residue was treated with ≈7 mL methanol/1,2-ethanediol (≈5:2) and all volatile components were removed in vacuo (10^{-3} torr). The procedure was repeated. The boron-free residue was then treated at 20°C with 5 mL of acetic anhydride in 5 mL pyridine and, after stirring for 1 hour, the mixture was evaporated to dryness. The solid residue was washed with a little ethanol, then with diethyl ether. The colorless, solid product (m.p. 129–131°C) was recrystallized from 20 mL diethyl ether/5 mL ethanol: 1.6 g (93%) pure **17b**; m.p. 133°C; $[\alpha]_D^{20} = 20$ ($c = 0.3$, $CHCl_3$); HZ (Hydridzahl = hydride number) [8b, 10] = 9.9.

1-*O*-Phenyl-D-galactitol **17**: A mixture of **17b** (404.4 mg, 0.86 mmol) and ethyldiboranes(6) (952.9 mg, 11.96 mmol >BH-borane) was heated for 2 h at ≈120°C. The excess >BH-borane was destroyed by addition of 20 mL of methanol (>BH-borane consumed: 8.53 mmol). After removal of volatile components by distillation in vacuo the residue was treated with a further 20 mL of methanol and the resulting solution evaporated to dryness, giving 225 mg (≈100%) **17**; m.p. 202°C; $[\alpha]_D^{20} = 7.2$ ($c = 0.4$, $(H_3C)_2SO$).

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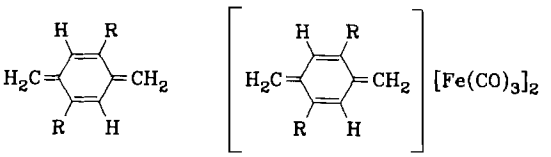
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[1] R. Köster, W. Schüssler, unpublished.
[2] Cf. W. V. Dahlhoff, S. Penadés-Ullate, R. Köster, 2nd European Symp. on Carbohydrates and Glycoconjugates, Budapest, August 1983, Abstract S. A-32.
[3] Cf. Houben-Weyl: *Methoden der organischen Chemie*, 4th edit., Vol. XIII/3a, Thieme, Stuttgart 1982, p. 590.
[4] R. Köster, K.-L. Amen, W. V. Dahlhoff, *Liebigs Ann. Chem. 1975*, 752.
[5] a) Ethyldiboranes(6) is a collective expression for mixtures of variously highly ethylated boranes and diboranes(6); R. Köster, P. Binger, *Inorg. Synth. 15* (1974) 141; b) here, "*O*-ethylboron-protected" signifies the presence of Et_2B- and EtB< groups; for clarity, only the Et_2B groups are shown in the formulas.
[6] Ethyldiboranes(6)-catalyzed reduction of the per-*O*-methyl-*O*-glycopyranosides of **1** and **2** leads predominantly (≳90%) to per-*O*-methyl-1,5-anhydro-D-glucitol of **13** with R = CH_3 (cf. Scheme 1).
[7] R. Köster, P. Idelmann, W. V. Dahlhoff, *Synthesis 1982*, 650.
[8] a) Elemental analyses and spectroscopic data (MS, ^{1}H-NMR, ^{13}C-NMR) of per-*O*-acetyl derivatives **11b** to **20b** are consistent with the calculated compositions and proposed structures. b) The polyhydroxy ethers **11** to **13** and **15**–**20**, free of protective groups, are obtained from **11b** to **13b** and **15b** to **20b** by reaction with alkyldiboranes(6) at ≳100°C [cf. W. V. Dahlhoff, R. Köster, *J. Org. Chem. 42* (1977) 3151] or by Zemplén saponification.
[9] In analogy to the trivial names of the 1-*O*-glycosidalditols (e.g. maltitol, cellobiitol), for the new 1-*O*-alditylalditols we propose the abbreviations maltdiitol ≡ cellobidiitol, lactdiitol, melibidiitol etc., which are formed by adding the syllables "diitol" to the parent names.
[10] R. Köster, L. Synoradzki, *Chem. Ber. 117* (1984) 2850.
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Bis(tricarbonyliron)-*para*-quinodimethanes: Preparation and Molecular Structure

By *Ali R. Koray, Claus Krieger,* and *Heinz A. Staab**

The stabilization of highly unstable organic molecules as tricarbonyliron complexes is well-known in several cases including cyclobutadiene, trimethylenemethane, and *ortho*-quinodimethane.[1] Other highly unstable molecules are *para*-quinodimethanes like **1** and **2** which have attracted a great deal of interest as intermediates in chemical reactions[2] and have been studied spectroscopically at low temperatures.[3] In this paper we would like to report on bis(tricarbonyliron) complexes of **1** and **2**, which, to our knowledge, are the first examples of *para*-quinodimethanes stabilized as ligands in transition metal complexes.



1: R = H **3**: R = H
2: R = CH_3 **4**: R = CH_3

3 and **4** were obtained by rapid dropwise addition of solutions of 1,4-bis(bromomethyl)benzene and 1,4-bis(bromomethyl)-2,5-dimethylbenzene, respectively, in benzene (≈0.01 mol/250 mL) into a suspension of $Fe_2(CO)_9$ in benzene (≈0.05 mol/250 mL) at 40–45°C. Evaporation of the solution, rapid chromatography (silica/cyclohexane), sublimation and recrystallization from hexane yielded **3**[4] (orange microcrystals, dec. >150°; 1.1% yield) and **4**[4]

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(red crystals, dec. > 160°C; 3.4% yield). All spectroscopic data of **3** and **4** agree well with the assumption of bis(tricarbonyliron) complexes of **1** and **2**, respectively.[4]

With regard to the bonding sites of the two tricarbonyliron units the molecular structure obtained for **4** by X-ray analysis was of special interest. Figure 1a shows a side-view of the C_i structure of the complex, from which the positions of the tricarbonyliron groups above and below the *para*-quinodimethane unit and the deformation from planarity of the latter can be seen. The complex consists of two trimethylenemethane-like sections with short distances between Fe and C(1), C(4), C(3i) and C(2) [195.2(1), 209.7(1), 220.5(1) and 230.8(1) pm, resp.]. This type of bonding is also supported by the carbon-carbon bond-lengths of the quinodimethane moiety which shows equal distances for C(1)···C(4), C(1)···C(2) and C(1)···C(3i) (Fig. 1b). Furthermore, the subdivision into two trimethylenemethane parts is impressively demonstrated by the long bond length of 146.2(1) pm found for the bonds C(2)···C(3) which are the formal double bonds of the *para*-quinodimethane ligand. Theoretical calculations (EHT-MO) agree well with the complex structure found.[6]

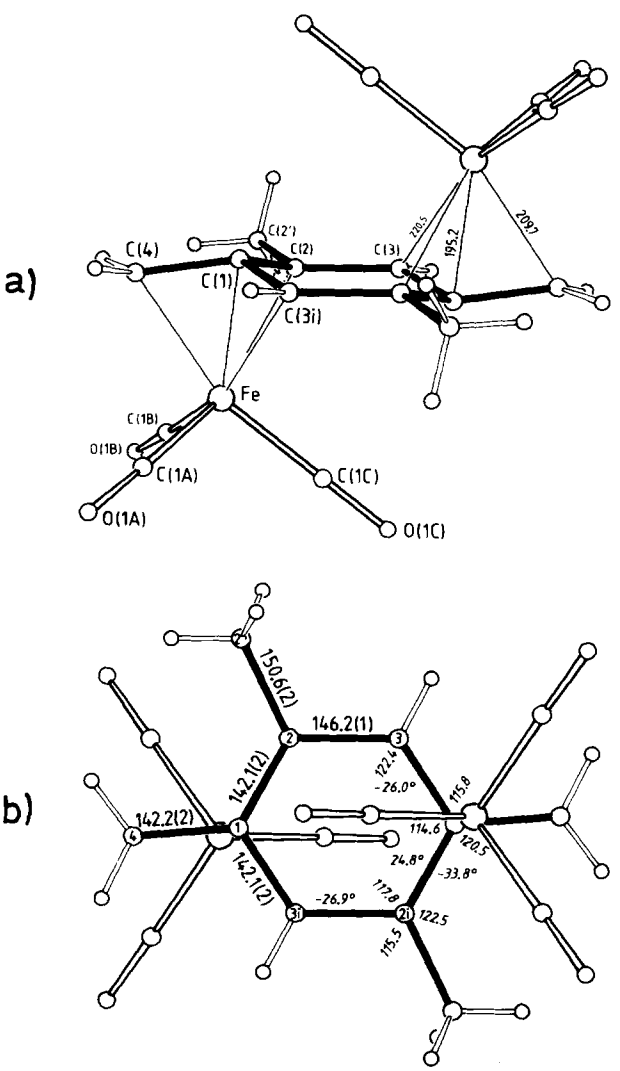


Fig. 1. Side-view (a) and top-view (b) of **4** with bond lengths [pm] and bond angles [°]. $a = 643.6(1)$, $b = 746.6(1)$, $c = 919.6(1)$ pm, $\alpha = 103.31(2)$, $\beta = 108.77(2)$, $\gamma = 91.42(2)°$; space group $P\bar{1}$, $Z = 1$; number of reflections measured 2061, number of reflections with $I \geq 1.96\sigma(I)$ 1827; $R = 0.021$. Further details of the X-ray structure analysis of **4** are available on request from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2, on quoting the registry number CSD 51246, the names of the authors, and the full citation of this journal.

As was to be expected on the basis of structures **3** and **4** both compounds react readily with bromine (tetrachloromethane, 0°C) to yield 1,4-bis(bromomethyl)benzene (67%) and 1,4-bis(bromomethyl)-2,5-dimethylbenzene (63%), respectively. Further reactions which can be rationalized as 'in-situ' generation of the *para*-quinodimethanes from bis(tricarbonyliron) complexes are under investigation.

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CAS Registry numbers:
3, 96453-09-7; **4**, 96453-10-0; 1,4-bis(bromomethyl)benzene, 623-24-5; 1,4-bis(bromomethyl)-2,5-dimethylbenzene.

[1] Cf. J. M. Landesberg in E. A. Koerner von Gustorf, F.-W. Grevels, I. Fischler (Eds.): *The Organic Chemistry of Iron, Vol. 1*. Academic Press, London 1978, p. 627.

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[4] Correct elemental analyses (C, H, Fe) were obtained for **3** and **4**.—**3**: IR (hexane): ν(CO) = 1984, 2040 cm^{-1}; ^{1}H-NMR (80 MHz, CD_2Cl_2): $\delta = 1.76$ (s, 4H), 4.27 (s, 4H); ^{13}C-NMR (90.5 MHz, CD_2Cl_2): $\delta = 38.76$, 80.31, 103.47, 211.03; MS: $m/z = 384$ (30%, M^+), 356 (7), 328 (40), 300 (16), 272 (40), 244 (100), 216 (80), 160 (37), 112 (21), 104 (18), 56 (13) [5].—**4**: IR (hexane): ν(CO) = 1980, 2038 cm^{-1}; ^{1}H-NMR (360 MHz, CD_2Cl_2): $\delta = 1.75$ (s, 6H), 1.79 (d, $J = 1.6$ Hz, 2H), 2.16 (d, $J = 1.6$ Hz, 2H), 3.74 (s, 2H); ^{13}C-NMR (90.5 MHz, CD_2Cl_2): $\delta = 19.44$, 37.43, 78.39, 102.88, 102.94, 211.34; MS: $m/z = 412$ (32%, M^+), 384 (8), 356 (37), 328 (16), 300 (37), 272 (100), 244 (73), 216 (3), 188 (72), 160 (20), 132 (54), 112 (24), 56 (35) [5].

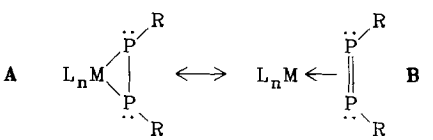
[5] Details about the mass spectrometric fragmentation of **3** and **4**: M. Rentzea, A. R. Koray, H. A. Staab, *Tetrahedron Lett.* **26** (1985) 2563.

[6] H. Vogler, unpublished results.

Chelate-Stabilized Diphosphene and Diphosphorus Complexes of Nickel**

By *Hans Schäfer,* Dieter Binder,* and *Dieter Fenske*

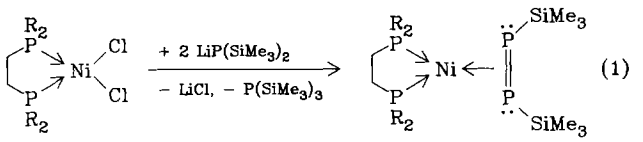
Diphosphenes R–P̈=P̈–R have two lone pairs of electrons and a double bond and can therefore coordinate in different ways to transition metals.[1] We are interested in complexes of the η^2-type in which only the double bond is formally bonded to a metal center.[2] This coordination pattern corresponds to the bonding of olefins to transition metals.



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[**] Transition-Metal Phosphido Complexes, Part 10. This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie. The crystal data were collected at the Institut für Kristallographie der Universität.—Part 9: H. Schäfer, J. Zipfel, B. Gutekunst, U. Lemmert, *Z. Anorg. Allg. Chem.*, in press.

The use of two resonance structures, **A** and **B**, to describe such complexes is supported by the P–P distances (212–215 pm)[1a-d,2] and the ^{31}P-NMR spectra (see below). We are interested exclusively in complexes which formally contain diphosphene ligands that are not stable as free species. We obtained the first P-functional compounds of this kind from *trans*-$(R_3P)_2NiCl_2$ (R = alkyl) and $LiP(SiMe_3)_2$.[2] This method can be extended to the synthesis of the chelate-stabilized diphosphene complexes **2a** and **2b** [Reaction (1)].

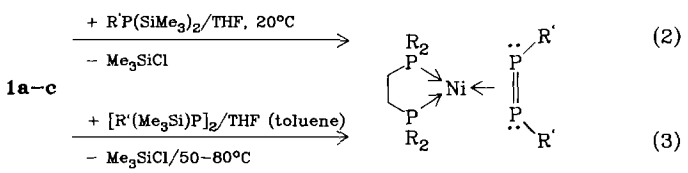


(1)

1a–c **2a, 2b**

a, R = Et; **b**, R = c-C_6H_{11}; **c**, R = Ph

In these reactions, some of the intermediates were shown by NMR spectroscopy to be nickel complexes containing terminal $P(SiMe_3)_2$ groups. For **1c**, however, redox reactions predominate, forming $(Me_3Si)_2P-P(SiMe_3)_2$ and $(chelate)_2Ni$. When **1a–c** are reacted with $LiP(R')SiMe_3$ (R' = Me, *t*Bu, Ph), redox reactions are also mainly observed, yielding diphosphanes and $(chelate)_2Ni$. Complexes containing diphosphene $(PR')_2$ ligands are accessible, however, via the simple reaction (2) and, in some cases, even better, starting from silylated diphosphanes [Reaction (3)].

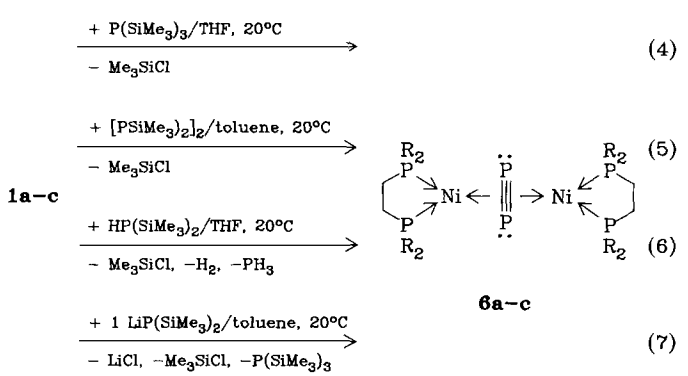


(2)

(3)

3, R' = Me; **4**, R' = *t*Bu;
5, R' = Ph

Surprisingly, attempts to synthesize complexes containing $(PSiMe_3)_2$ ligands in an analogous way from **1a–c** and $P(SiMe_3)_3$ or $(Me_3Si)_2P-P(SiMe_3)_2$ or complexes containing (PH_2) ligands from **1a–c** and $HP(SiMe_3)_2$ yielded the P_2 complexes **6a–c**.



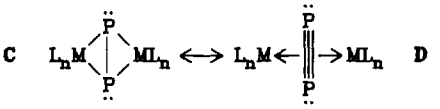
6a and **6b** can also be identified by NMR spectroscopy for Reaction (1) when a 1:1 stoichiometry is used. Even the cleavage of the Me_3Si groups in **2a** and **2b** with methanol leads to **6a** and **6b**, presumably via $(PH)_2$ complexes.



(8)

In Reactions (1)–(8), variable amounts of $(chelate)_2Ni$ are always formed, making the isolation of the diphosphene or diphosphorus complexes somewhat difficult. Reaction (6) proved to be the preparatively most convenient synthetic method for **6a–c**.

According to *Hoffmann*,[3] the (chelate)Ni group, viewed as a 14-electron fragment, is isolobal with the CH_2 group. The complexes **6a–c** are therefore formally bicyclobutane derivatives according to the resonance structure **C** and thus represent a new class of P_2 complexes, analogous to the As_2 complexe $[(C_2Me_5)(CO)_2Mn]_2As_2$ of *Herrmann* et al.[4]



In all P_2 complexes known so far, the P_2 group is bonded to two 15-electron fragments, which, as units isolobal to the CH group, are connected by a metal-metal bond, resulting in a closed tetrahedron.[5] **6a** crystallizes with two crystallographically independent molecules in the asymmetric unit.[6] The two molecules primarily differ only in the fold angle between the (NiP_2) planes (95.4 and 98.3°, see Fig. 1). This is presumably due to packing effects and causes a marked difference in the Ni–Ni distances (291 and 296 pm, respectively; no Ni–Ni bonding). Comparison of the structure of **6a** (see Fig. 1) with the tetraphosphabicyclobutane derivative $P_4[N(SiMe_3)_2]_2$[7] reveals the analogy to main-group chemistry. Both the P–P distance and the fold angle are very similar to those in the P_4 derivative (P–P = 213 pm, fold angle 95.2°). The Ni–Ni distance in **6a** corresponds to the transannular P–P distance (281 pm) of the open P_4 tetrahedron. The P–P distance of the P_2 group of **6a** (212 pm) lies, as in other P_2 complexes,[5] between the typical values for a single bond

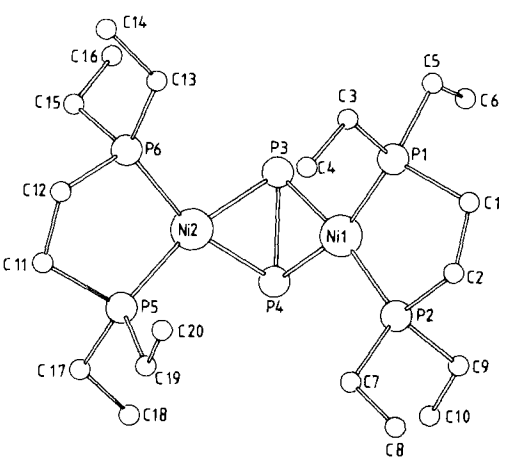


Fig. 1. Molecular structure of **6a** (molecule 1). The Ni atoms are surrounded by a nearly planar array of four P atoms and lie 9 pm below the mean plane. Fold angle (Ni1-P3-P4–Ni2-P3-P4) 95.4°. Important distances [pm] and bond angles [°]: Ni1–P1 212.5(5), Ni1–P2 213.1(4), Ni1–P3 223.8(5), Ni1–P4 223.1(5), Ni1–Ni2 290.8(3), P3–P4 212.1(6), Ni2–P3 223.3(3), Ni2–P4 223.3(3), Ni2–P5 213.4(4), Ni2–P6 214.9(5), P–C 182–186(1); Ni1–P3–P4 61.5(2), P3–P4–Ni1 61.8(2), P3–Ni1–P4 56.7(2), P1–Ni1–P2 91.5(2), P3–Ni1–P1 101.9(3), P4–Ni1–P2 109.6(2), P3–Ni1–P2 165.7(2), P4–Ni1–P1 158.3(2), Ni1–P3–Ni2 81.1(2), Ni1–P4–Ni2 81.3(2). The distances in molecule 2 correspond to the values given above within the standard deviation.

(220—225 pm) and the values for a P—P double bond in sterically protected free diphosphenes (200—205 pm).[8] This is analogous to the C—C bond in alkyne complexes such as $[(cod)Ni]_2(CPh)_2$[9] and supports the resonance structure **D**.[10]

Table 1. $^{31}P\{^1H\}$-NMR data for the diphosphene and phosphorus complexes. Standard: 85% H_3PO_4, high-field signals have negative signs, $\delta \pm 1$ ppm; $J \pm 1$ Hz.

	Solvent [a]	$\delta(^{31}P)$ (chelate)	$\delta(^{31}P)$ (P_2R_2)	J(PNiP) [b]
2a	Tol	+58 (t)	−101 (t)	28
2b	Tol	+76 (t)	−103 (t)	24
3b	THF	+72 (t)	− 30 (t)	28
4a	Tol	+53 (t)	+ 55 (t)	25.5
4b	THF	+68 (t)	+ 39 (t)	20
4c	THF	+52 (t)	+ 66 (t)	21
5a	Tol	+58 (t)	− 19 (t)	30
5b	Tol	+75 (t)	− 34 (t)	27
		$\delta(^{31}P)$ (chelate)	$\delta(^{31}P)$ (P_2)	J(PNiP) [c]
6a	Tol	+55 (t)	+133 (q)	33
6b	Tol	+67 (t)	+135 (q)	27.5
6c	Tol	+48 (t)	+161 (q)	28

[a] Tol = toluene, THF = tetrahydrofuran. [b] AA'XX' spectra, $J(PNiP) = 1/2|cis\text{-}^2J(AX) + trans\text{-}^2J(AX')|$; since $^1J(PP) \gg$ all $^2J(PNiP)$, two pseudo triplets result, which do not allow a further calculation of the coupling constants. [c] $A_2A'_2XX'$ spectra, J(PNiP) as for [a], pseudo triplet and pseudo quintet; further calculation of the coupling constants not possible.

The $^{31}P\{^1H\}$-NMR spectra are most useful for the characterization of the diphosphene and diphosphorus complexes.[11] As shown in Table 1, **2**—**6** exhibit simple splitting patterns. The signals of the diphosphene ligands show significant downfield shifts relative to those of P-containing three-membered rings,[12] which correspond to the resonance structure **A**. However, the signals of the diphosphene ligands lie at much higher field than those of free diphosphenes.[8] The signals of the P_2 ligands (see Table 1) exhibit a downfield shift of 350—450 ppm relative to those of $P_4[N(SiMe_3)_2]_2$.[7] Thus, the resonance structure **D** should not be neglected.

Experimental Procedures

2a [Reaction (1)]: A solution containing 4.7 g (15 mmol) of $LiP(SiMe_3)_2 \cdot 1.8\,THF$ (THF = tetrahydrofuran) is slowly added under argon to a stirred suspension of **1a** (2.5 g, 7.5 mmol) in 50 mL of toluene at −30°C. After 2 d at −20°C, the reaction mixture is slowly warmed to 20°C and filtered, and the solvent is removed *in vacuo*. Fractional crystallization from pentane at −78 and −20°C affords reddish brown crystals of **2a** (1.31 g, 37%). **2b** is synthesized analogously from **1b** (2 g, 3.6 mmol) and $LiP(SiMe_3)_2 \cdot 1.8\,THF$ (2.26 g, 7.2 mmol). After evaporation of the solvent, the residue is washed with pentane until a yellow powder remains. Recrystallization from toluene at −20°C gives yellow crystals of **2b** (0.69 g, 28%).

4c [Reaction (3)]: A suspension of **1c** (2 g, 3.8 mmol) in 20 mL of THF and $[(t\text{Bu})(Me_3Si)P]_2$ (1.22 g, 3.8 mmol) is heated under argon to 50°C for 20 h. After removal of the solvent in vacuo at 20°C, the residue is recrystallized from toluene at −20°C. Yield: 1.45 g **4c** (60%), orange crystals.

5b [Reaction (2)]: A suspension of **1b** (2 g, 3.6 mmol) in 60 mL of THF and $PhP(SiMe_3)_2$ (1.83 g, 7.2 mmol) is stirred under argon for 10 d at 20°C. The solvent of the suspension (green solid, greenish yellow solution) is evaporated in vacuo at 20°C. Recrystallization of the residue from CH_2Cl_2 at −20°C affords **5b** (1.12 g, 44%), yellow crystals.

6a [Reaction (6)]: A suspension of **1a** (2 g, 6 mmol) in 60 mL of THF and $HP(SiMe_3)_2$ (2.13 g, 12 mmol) is stirred under argon for 2 h. After removal of the solvent in vacuo at 20°C, the residue is recrystallized from pentane at −20°C. Yield: **6a** (1.04 g, 59%), brown crystals.—**6c** is obtained analogously from **1c** (5 g, 9.5 mmol) and $HP(SiMe_3)_2$ (3.37 g, 19 mmol) in 130 mL of THF. The reaction mixture is concentrated to half of its volume in vacuo at 20°C, cooled to −78°C for 2 d, and filtered. The mother liquor is evaporated in vacuo at 20°C and the residue recrystallized from toluene at −20°C. Yield: 1.86 g **6c**·**3toluene** (31%), brown crystals.

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CAS Registry numbers:
1a, 37504-45-3; **1b**, 96555-88-3; **1c**, 14647-23-5; **2a**, 96555-89-4; **2b**, 96555-90-7; **3b**, 96555-96-3; **4a**, 96555-97-4; **4b**, 96575-43-8; **4c**, 96555-91-8; **5a**, 96555-98-5; **5b**, 96555-92-9; **6a**, 96555-93-0; **6b**, 96555-95-2; **6c**, 96555-94-1; $LiP(SiMe_3)_2$, 59624-91-8; *t*-$BuP(SiMe_3)_2$, 55793-25-4; $PhP(SiMe_3)_2$, 24103-44-4; $HP(SiMe_3)_2$, 15573-39-4; $LiP(Me)SiMe_3$, 96555-99-6.

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[6] **6a**: acentric space group $Pna2_1$, $Z = 8$, $a = 1791.4(11)$, $b = 1201.0(6)$, $c = 2691.5(15)$ pm (180 K). $\mu(Mo_{K\alpha}) = 15.1\ cm^{-1}$. Syntex R3, to $2\theta = 50°$, 5043 reflections, 3440 of these with $I > 2\sigma(I)$, empirical absorption correction. Structure solution: Patterson method, Ni and P anisotropic, C isotropic, H positions calculated and refined as rigid groups. $R_1 = 0.064$, $R_2 = 0.069$. Further details of the crystal structure investigation are available on request from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen, by quoting the depository number CSD 51389, the names of the authors, and the journal citation.

[7] E. Niecke, R. Rüger, B. Krebs, *Angew. Chem. 94* (1982) 553; *Angew. Chem. Int. Ed. Engl. 21* (1982) 544.

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[10] The Ni—Ni distance in **6a** is appreciably longer than in $[(cod)Ni]_2(CPh)_2$ (262 pm),[9] since the fold angle in **6a** is larger and the Ni—P bond is longer than the Ni—C bond in $[(cod)Ni]_2(CPh)_2$. Thus, no direct Ni—Ni interaction needs to be assumed in **6a**.

[11] All diphosphene complexes isolated so far can be evaporated in vacuo without noticeable decomposition, so that the molecular peaks in the mass spectra show reasonable relative intensities. The P_2 complexes **6a**—**c** exhibit the molecular peaks with only minor intensities, if at all.

[12] M. Baudler, *Angew. Chem. 94* (1982) 520; *Angew. Chem. Int. Ed. Engl. 21* (1982) 492.

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Chelate Ligand-Controlled η^1-η^2 Change of Coordination in Amino(imino)phosphane Ligands and Their Conversion into a Nickelaazadiphosphetidine

By *Otto J. Scherer*,* *Richard Walter* and *William S. Sheldrick*

Amino(imino)phosphanes, compounds containing triply bonding phosphorus of coordination number two, are versatile ligands.[1,2]

Reaction of the nickel complex **1** and the amino(imino)phosphane **2** (molar ratio 1:3) affords the synthetic building block **3** with terminal P-coordination of the ligand **2**. The tridentate ligand **7** reacts with **3** such that the η^1-type coordination of the amino(imino)phosphane ligand is retained in **4**, whereas in the reaction of **3** with dppe to give **5**, a change of coordination from the η^1- to the η^2-type of coordination takes place.[3] **5** is the first example of a compound containing a classical side-on coordinated P=N ligand.[4,12] The reaction is steered in a completely different fashion by bpy. Two P=N functions form, via coupling of a P–N bond, the nickelaazadiphosphetidine **6**, the first P_2N_2 four-membered ring[5] in which a nitrogen atom is replaced by a metal atom (Ni). **3**, **4**, and **6** form dark red to brownish-black crystals, while **5** forms yellowish-orange crystals;[6] in each case the crystals are readily soluble in benzene, moderately (**3** and **4** readily) soluble in pentane, and only very sparingly soluble in acetonitrile.

The $^{31}P\{^1H\}$-NMR signal (Table 1) of the π-bonded –P=N– ligand in **5** is shifted upfield by about 260 ppm compared to that of free **2** ($\delta = 327$), the largest shift so far observed in the case of coordinated amino(imino)phosphane ligands (cf. the upfield shift of ca. 155 pm in the case of μ_3-η^2 coordination[2]). One of the two R_2N groups of **6** exhibits hindered P–N rotation at room temperature.

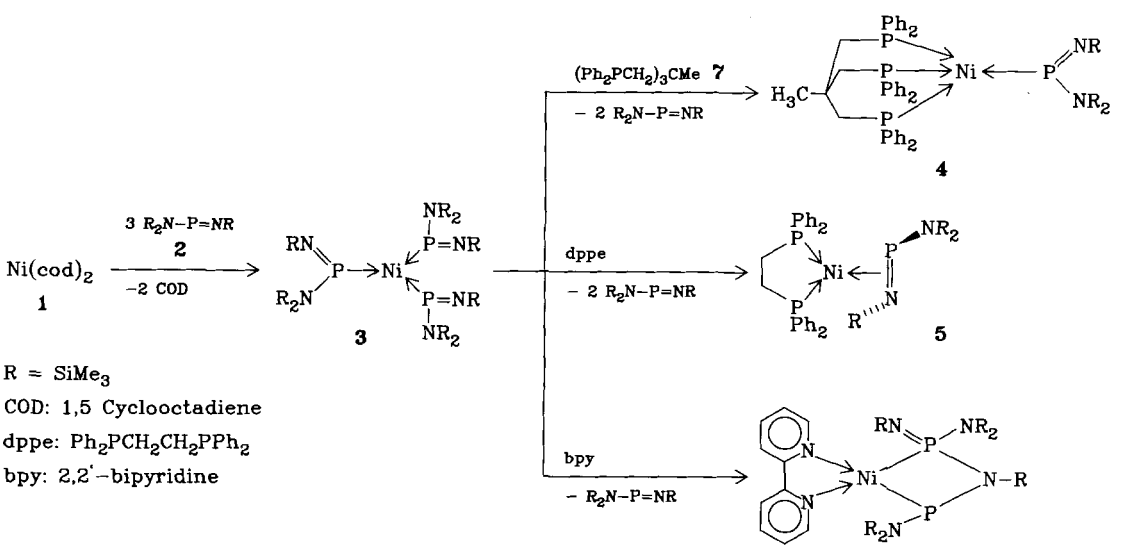
The crystal structure analysis[7] shows that **2** is side-on coordinated in **5** (Fig. 1) and that its *trans* arrangement at the P=N-bond is retained. The characteristic structural data of the free ligand **2** (P=N 1.545(2), P–N 1.674(1) Å, NPN 108.4(1), PNSi 129.9(1)°[8]) are changed by the coordination as follows: P=N(P1–N2) is about 0.101 Å longer, P–N(P1–N1) about 0.063 Å longer. The N1–P1–N2 angle, with a value of 109.1(1)°, remains virtually unchanged; P1–N2–Si2 (125.2(2)°) is ca. 5° smaller. The Ni–P distance differs only very slightly from that of the side-on coordinated R–P=P–R ligand to the Ni.[9] The bending angles between P1,N2 and the planes Si2,N2,P1 and N1,P1,N2 away from the nickel atom are 42.3° and 12.3°, respectively. Ni is almost planar coordinated (dihedral angle P1,Ni1,N2/P3,Ni1,P4 3.4°).

In the case of **6** (Fig. 2) the crystal structure data[7] indicate a somewhat more pronounced tetrahedral distortion (P1,Ni1,P2/N5,Ni1,N6 8.8°). The ring-P–N distances and angles are comparable with those of *trans*-$(R_2N-PN-R)_2$,[10] the dimer of **2**, whereas the corresponding exocyclic distances and angles lie in the normal range found for diazadiphosphetidines.[5] The N2–Si2

Table 1. NMR data of **3**–**6** (δ, J [Hz]).

	^1H [a]	$^{31}P\{^1H\}$ [b]
3	0.40 (s, 81 H)	262.4 (s)
4	0.43 (s, 18 H) 0.58 (s, 9 H)	245.2 (q), 6.2 (d), $^2J(PP) = 30.0$
5	0.54 (d, 18 H) [c] $^4J(PH) = 1.0$ 0.49 (s, 9 H)	ABC spin system P_A(dppe) 42.3 (dd), P_B(dppe) 51.6 (dd) P_C(PN) 65.8 (d, br.) assumption: $^2J(PP_C\ trans) > {}^2J(PP_C\ cis)$, $^2J(P_AP_B) = 55.6$, $^2J(P_AP_C) = 25.9$, $^2J(P_BP_C) = 8.3$
6	0.36 (s, 9 H), 0.54 (d, 9 H) $^4J(PH) = 2.8$, 0.57 (s, 9 H), 0.62 (s, 9 H), 0.76 (s, 18 H)	180.5 (s, λ^3-P), –4.8 (s, λ^5-P)

[a] 200 MHz, 293 K, C_7D_8, TMS int., only the signals of PN ligand(s) are quoted. [b] 81.01 MHz, 293 K, C_6D_6, 85% H_3PO_4 ext. [c] Dynamic NMR spectroscopy: $T_c = 213$ K, $\Delta\nu = 58.3$, $\Delta G^{\neq}(T_c) = 43.0$ kJ·mol^{-1}.



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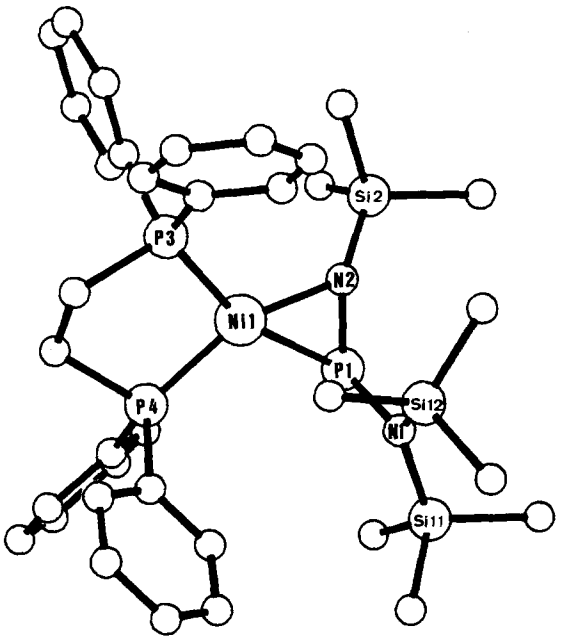


Fig. 1. Structure of **5** in the crystal. Selected bond lengths [Å] and angles [°] (see also text): Ni1–P1 2.231(1), Ni1–P3 2.192(1), Ni1–P4 2.126(1), Ni1–N2 1.908(2), P1–N1 1.737(2), P1–N2 1.646(2), N2–Si2 1.705(2), N1–Si11 1.756(2), N1–Si12 1.759(2); P1–Ni1–P4 108.66(4), P1–Ni1–N2 46.05(7), P1–N2–Ni1 77.4(1), Ni1–P1–N2 56.58(9), N2–Ni1–P3 114.43(7), P3–Ni1–P4 90.80(4), P1–N2–Si2 125.2(2), N2–P1–N1 109.1(1), sum of angles at N1 360.0.

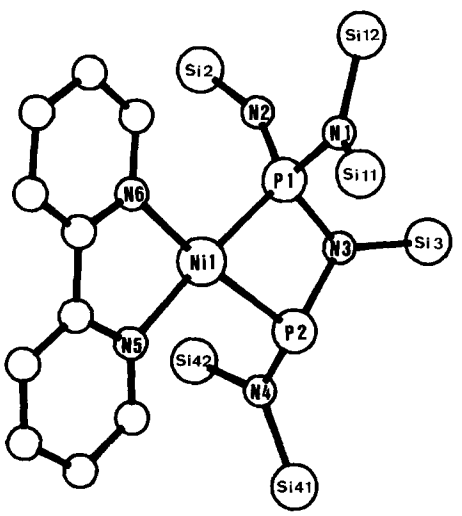


Fig. 2. Structure of **6** in the crystal (methyl groups are omitted for clarity). Selected bond lengths [Å] and angles [°] (see also text): Ni1–P1 2.160(1), Ni1–P2 2.201(1), Ni1–N5 1.978(3), Ni1–N6 1.976(3), P1–N1 1.738(3), P1–N2 1.556(3), P1–N3 1.700(3), P2–N3 1.772(3), P2–N4 1.759(3), Si2–N2 1.677(3), Si–N (average value, amine N-atoms) 1.759; P1–Ni1–P2 73.75(2), P1–Ni1–N6 102.7(1), P2–Ni1–N5 102.3(1), N5–Ni1–N6 81.2(2), P1–N3–P2 97.8(2), Ni1–P1–N3 95.4(1), Ni1–P2–N3 92.0(1), N1–P1–N2 102.9(2), P1–N2–Si2 154.8. Sum of angles at N1 359.8, N3 358.0, N4 360.0.

bond with a length of 1.677(3) Å, is distinctly shorter than the other Si–N bonds (average length 1.759 Å).

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CAS Registry numbers:
1, 1295-35-8; **2**, 50732-21-3; **3**, 96502-46-4; **4**, 96482-91-6; **5**, 96482-92-7; **6**, 96532-15-9.

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[6] Preparation of **3**–**6**; **3**: A solution of **2** [11] (1178 mg, 4.23 mmol) in toluene (1 mL) was added dropwise at room temperature to a stirred suspension of **1** (388 mg, 1.41 mmol) in toluene (4 mL) and the mixture stirred for a further 20 min. Such solutions were then used for further reactions. **3** crystallizes out (sometimes difficult) in 8 d at –78 °C in the form of red crystals. These were washed with 2 mL of cold toluene and dried under vacuum (oil-pump). Yield 416 mg (33%). **4**: **1** (262 mg, 0.95 mmol) was allowed to react with **2** (796 mg, 2.85 mmol) in benzene—under the same conditions as for **3**—and then the solution was treated with 594 mg (0.95 mmol) of 7 at room temperature. The reaction mixture was stirred for a further 20 min, the solvent and COD removed in vacuo, and the residue recrystallized from 4 mL acetonitrile/1 mL toluene at ca. –20 °C (2 d). The reddish-black crystals thus obtained were washed twice with 4 mL CH_3CN and dried in vacuo. Yield 705 mg (77%). **5**: **1** (280 mg, 1.02 mmol) and **2** (853 mg, 3.06 mmol) were allowed to react under the conditions described for **3** and the reaction mixture was then treated with a solution of 406 mg (1.02 mmol) of dppe in benzene (3 mL) at room temperature. The work-up procedure was the same as in the case of **4**. The residue was treated with 10 mL pentane, with stirring, whereupon **5** precipitated as a yellow powder. Subsequent washing of the precipitate with ca. 20 mL pentane and recrystallization from CH_2Cl_2/CH_3CN (1:1, ca. –20 °C, 2 d) furnished 532 mg of **5** (71%). **6**: **1** (215 mg, 0.78 mmol) and **2** (653 mg, 2.34 mmol) were allowed to react, as described for **3**, and then treated with 123 mg (0.78 mmol) bpy at room temperature. After work-up—in the same way as for **4**—the brownish-black residue was taken up in 5 mL pentane and allowed to stand for 1 d at –78 °C. The brownish-black crystals that separated out (yield 512 mg (85%) of **6**) were recrystallized from toluene/acetonitrile (5:2, 3 d, ca. –20 °C).
[7] **5**: $P2_1/n$, $a = 11.543(3)$, $b = 10.655(2)$, $c = 32.074(4)$ Å, $\beta = 91.87(2)°$, $Z = 4$, $\rho_{calc} = 1.24$ g cm^{-3}. 5141 independent reflections, 3960 observed ($Mo_{K\alpha}$, $F_0^2 \geq 2.0\sigma(F_0^2)$, $2\theta \leq 45°$); $R = 0.049$, $R_w = 0.042$. **6**: $P\bar{1}$, $a = 13.270(2)$, $b = 14.185(2)$, $c = 11.599(2)$ Å, $\alpha = 92.55(1)$, $\beta = 91.61(1)$, $\gamma = 96.99(1)°$, $Z = 2$, $\rho_{calc} = 1.18$ g cm^{-3}. 5843 independent reflections, 3754 observed ($Mo_{K\alpha}$, $F_0^2 \geq 2.0\sigma(F_0^2)$, $2\theta \leq 45°$); $R = 0.053$, $R_w = 0.041$. Further details of the crystal structure investigations are available on request from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2 on quoting the depository number CSD 51282, the names of the authors, and the full citation of the journal.
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[11] O. J. Scherer, N. Kuhn, *Chem. Ber. 107* (1974) 2123.
[12] *Note added in proof:* The oxidation of **5** with RN_3 and selenium, respectively, affords (dppe)Ni[η^2-(X=)P(=NR)(NR$_2$)], X=Se, NR, R=SiMe$_3$ with side-on coordination of the P=X moiety.

Wood Chemistry, Ultrastructure, Reactions. By *D. Fengel* and *G. Wegener*. de Gruyter, Berlin 1984. xiii, 613 p., bound, DM 245.00.–ISBN 3-11-008481-:

This book by the Munich wood researchers fills a gap. Since the appearance of *Wenzl*'s "The Chemical Technology of Wood" in 1970 and of *Sjöstrom*'s short "Wood Chemistry" in 1981 no competent author has produced a comprehensive treatment of the chemistry and ultrastructure of wood.

This work by *Fengel* and *Wegener*—without any other coauthors—consists of a presentation of the latest state of the subject area named in the title. This effort alone, backed up by many references (up to 1983), commands respect. The English text is clear and understandable. The numerous tables, diagrams and excellent electron micrographs increase the vividness.

The content and emphasis of the work can be seen from its division into 18 chapters: 1. Introduction (5 p.), 2. Structure and ultrastructure (20 p.), 3. Chemical composition and analysis of wood (40 p.), 4. Cellulose (40 p.), 5. Polyoses (hemicelluloses) (26 p.), 6. Lignin (50 p.), 7. Extractives (45 p.), 8. Distribution of the components within the wood cell wall (13 p.), 9. Constituents of bark (28 p.), 10. Reactions in acidic medium (28 p.), 11. Reactions in alkaline medium (23 p.), 12. Influence of temperature (26 p.), 13. Degradation by light and ionizing rays (28 p.), 14. Microbial and enzymatic degradation (28 p.), 15. Aging and fossilization (7 p.), 16. Pulping processes (68 p.), 17. Derivatives of cellulose (44 p.), 18. Utilization of wood and wood components for chemicals and energy (41 p.). The very comprehensive index (19 p.) is completed by a compilation of wood types categorized according to the properties treated in the text (26 p.) and a list of the bacteria and fungi described (2 p.).

The size of the book is just sufficient to cover the topics adequately according to their importance. Students of wood science are presented with sufficient information for graduation and the specialist is aided by an almost complete reference list of the newer literature. The clear division of the material allows a rapid familiarization with specialist areas and makes the book of utility to non-specialists who wish to inform themselves about an area of wood chemistry. The treatment is deliberately not historical, that is, most of the references cited come from the years after 1960. The interested reader must come indirectly to earlier pioneering publications. The authors are very sparing in their evaluations and occasionally leave the beginner in some confusion, as for instance when the various models of the organization of cell wall components (Figs. 8-5 to 8-7) or the gas yields on pyrolysis (Figs. 12-20 and 12-21) are presented without commentary. In general it would have been of advantage to differentiate the fundamental somewhat more emphatically from the preliminary and speculative.

This book contains an astonishingly small number of printing errors and few mistakes and deficiencies: Thus it would have been preferable to reproduce the structural formulas of all the compounds mentioned. The formation of condensed tannins (p. 209/211) and the peeling-off reaction (p. 297) remain unclear to non-chemists. The role of B_2O_3 in the modified sulphate process (p. 446) and the importance of crosslinking reactions for the textile industry (Chapter 17) are worthy of a more comprehensive treatment. Individual mistakes (particularly confusing "preceded" instead of "succeeded" on p. 430) should be corrected in a later edition.

The above remarks apply only to a small fraction of the book. All in all this work is greatly to be recommended and should be included in every specialist library. It is to be hoped that, despite its high price, it also comes into the hands of all who are interested in wood and wood chemistry.

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Principles of Peptide Synthesis. By *M. Bodanszky*. Springer-Verlag, Berlin 1984. xvi, 308 pp., bound, DM 148.00.—ISBN 3-540-12395-4

It should be said right from the start—this book is a welcome enhancement of the literature available in the highly topical field of peptide chemistry. This enhancement can best be substantiated by a comparison:

The chemistry student learns to estimate the reactivity of molecules by formulating the mesomeric structures from which the reactions can be deduced. But, at the same time, he learns that every mesomeric structure is of itself only a formalism—the molecular reality lies somewhere between all these mesomeric forms.

This collection of principles from the field of peptide synthesis represents such a mesomeric form for the presentation of the topic—important and admissible alongside many other more topical reviews which for their part mostly only describe the newest advances or one single aspect, e.g. the Merrifield Synthesis. It is all these contributions taken together which yield a proper picture of the state of the art in the field of peptide chemistry.

Judging by the method of presentation "Principle Problems of Peptide Synthesis" would have been an apt title for the book. The author describes a wealth of beautiful organic chemistry, side reactions and the limits of peptide synthesis, not only in the chapters intended for this but scattered throughout most of the specialist sections. The experienced peptide chemist finds an excellent collection of information about the problems, plentifully supplied with mostly older references in which a certain egocentricity and one-sidedness in the choice is unmistakable. However, a novice coming to this book will be turned away from peptide chemistry rather than drawn to it because of the numerous, certainly technically correct discussions of problems. It would certainly have been more useful to have clearly emphasized a few essential principles, perhaps furnished with short, quantitative experimental details. For the rest the text is precise and the discussions comprehensive. The fact that the mechanistic arrows have occasionally been omitted from the formulas even though they are necessary for instructional purposes (e.g. p. 14) does not do justice to the clarity of the rest of the book. In addition, a whole range of typographical errors, and that not just in the text, ought to have been removed from the monograph.

Finally, it must be said that this work should be included in the libraries covering the sphere of activity which includes peptide synthesis if only because this book emphasizes the often misunderstood, delicate and easily rearranged nature of peptides—a facet to which at the moment only cursory attention is paid by many molecular biologists.

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Advances in Polymer Science. Edited by *H.-J. Cantow, G. Dall'Asta, K. Dušek, J. D. Ferry, H. Fujita, M. Gordon, G. Henrici-Olivé, H.-H. Kausch, J. P. Kennedy, W. Kern, S. Okamura, S. Olivé, C. G. Overberger, T. Saegusa, G. V. Schulz, W. P. Slichter,* and *J. K. Stille*. Springer-Verlag, Berlin 1984. **Vol. 59: Liquid Crystal Polymers I.** Edited by *M. Gordon* and *N. A. Plate*. 1984. ix, 158 pp., bound, DM 98.00.—ISBN 3-540-12818-2; **Vol. 60/61: Liquid Crystal Polymers II/III.** Edited by *M. Gordon* and *N. A. Plate*. 1984. x, 266 pp., bound, DM 138.00.—ISBN 3-540-12994-4

Solid State Chemistry and its Applications. By *A. R. West*. John Wiley, Chichester 1984. 734 pp., bound, £ 37.00.—ISBN 0-471-90377-9

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Specialist Periodical Reports. Organometallic Chemistry, Vol. 12. A Review of the Literature Published during 1982. Edited by *F. G. A. Stone* and *E. W. Abel*. The Royal Society of Chemistry, London 1984. xviii, 498 pp., bound, £ 83.00 (price reduction for members of the Royal Society of Chemistry).—ISBN 0-85186-601-8

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Serono Symposia Publications from Raven Press. Vol. 12: Neuroimmunology. Edited by *P. O. Behan* and *F. Spreafico*. Raven Press, New York 1984. xvi, 484 pp., bound, $ 105.50.—ISBN 0-89004-963-7

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Consequences of Strain for the Structure of Aliphatic Molecules

By Christoph Rüchardt* and Hans-Dieter Beckhaus

Dedicated to Professor Rolf Huisgen on the occasion of his 65th birthday

The chemist is accustomed to deriving structures and preferred conformations of organic compounds from rigid molecular models and standard values for bond lengths, bond angles, and torsional profiles. In the case of strained compounds, this rigid structural model has to be abandoned and replaced by a flexible one which takes individual conditions of strain into consideration. It is shown, on the basis of new experimental structural data, that the force field method is suitable and highly reliable for the calculation of structural parameters and preferred conformations of strained compounds. It is, therefore, capable of replacing the rigid molecular model. Furthermore, the systematic analysis of strain induced angle and bond deformation gives a new pivot for the development of a qualitative discussion of deformation in strained molecules and hence for improved conformational analysis.—In the course of this work we were able to isolate two rotamers of D,L-3,4-di(1-adamantyl)-2,2,5,5-tetramethylhexane; this is the first isolation of a rotamer pair of an aliphatic hydrocarbon.

1. Introduction

Probably the most important concept in the whole of chemistry is that of molecular structure. The properties of matter are connected with it, and discussions of reactivity are based on the molecular structures of the reaction partners.[1, 2] Hence, the development of structural models is of central importance.

Additivity rules have been developed for a uniform description of the structural data[3] and thermodynamic quantities of numerous organic compounds.[4, 5] These enable a calculation of molecular properties from increments for the atoms and groups involved. In this context, standard bond lengths and bond angles are used, and ideal conformations with a staggered arrangement of the groups on neighboring tetracoordinated carbon atoms with a 60° torsional angle are assumed. Individual deviations from the standard values caused by conjugational effects can be taken into account with the aid of correction factors[5] as regards both geometry and thermodynamic properties.

Structural models based on this simple concept allow the discussion of reactivity without having to analyze experimentally the structures of whole series of compounds. However, this simple additive and hence rigid structural model rapidly reaches its limits when used to explain steric effects on reactivity.[6–8] The deliberately pragmatic concept "steric effects" incorporates phenomena arising from individual structural properties of the reactants and the activated complexes. If the result of a steric effect is a change in the activation enthalpy,[9] it can be described by the model quantity "strain enthalpy H_s".[10] This is defined as the difference between the enthalpy of formation of a real

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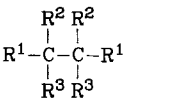
molecule, ΔH_f° (g), and a norm or standard value ΔH_f^N calculated from group increments.[10]

Strain can result, for example, from ring formation or repulsion between non-bonded atoms and is associated with changes in the geometric parameters of a molecule, i.e. bond lengths, bond angles, and torsional angles, with respect to the standard values.[11,12] Therefore, the rigid structural model breaks down in the treatment of steric effects,[13] and the question is posed as to the alteration of bond lengths and bond angles under the influence of strain.[6-8,11,12] Consequences for the conformational behavior can also be expected as a result of the deformability of the molecular framework; the fundamental rules of conformational analysis are based on the rigid structural model.

The study of steric influences is of increasing importance not only in organic chemistry. Studies of the relationships between structure and activity of drugs attest to intermolecular effects as one of the reasons for the high selectivity of biochemical recognition processes, which have been described, inter alia, as docking processes between an active substance and its receptor.[14,15] As another example, special material properties of polymers resulting from preferred conformations in a polymer chain should be mentioned. These in turn are determined by steric effects.[16] In these and many other cases only a flexible structural model which requires variation of the structural parameters as well as knowledge of the dynamic behavior of organic molecules subjected to internal or external strain, is applicable.

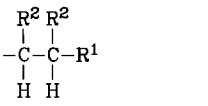
Hitherto, the investigation of highly strained compounds has largely been confined to monocyclic and polycyclic small ring compounds,[11] the rigid skeletons of which permit the evaluation of angle deformations and preferred conformations. In this review we summarize the structural investigations of highly branched open chain carbon skeletons, which are in part characterized by very high strain enthalpies. Therefore, the extent and consequences of the deformability of these molecular structures are particularly readily perceived.[17-31] Because of the inherent flexibility of the open chain framework, predictions about the extent and nature of the deformation can hardly be made in the realm of classical conformational analysis.[13]

In order to answer the question posed, experimentally derived structural parameters of strained compounds are required. These also permit an extension of the parameter basis of empirical force field methods[32-34a] to include strongly deformed and highly strained compounds. Their application to strongly deformed molecules permits an evaluation of the usefulness of the various empirical force fields as regards dynamic behavior and deformability of molecular structures under the influence of strain. Therefore, these evaluations will also answer the question whether the rigid structural and thermodynamical increment model for aliphatic molecules can be replaced. In this context *Mislow*'s comparison of the X-ray structure of the propeller-like molecules trimesitylmethane and the result of a force field calculation was a pioneer work[34b]. The increasing use of empirical force field (EFF) calculations in the quantitative analysis of structure reactivity relationships[35] makes a demanding test all the more essential. We will use the experimental structural data of strained representatives of the classes of compounds **1**—**8** (Table 1) as test cases.



C_q–C_q skeleton

1–4, 8



C_t–C_t skeleton

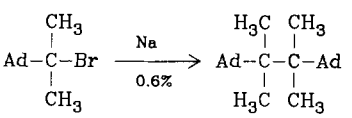
5–7

1, R^1, R^2, R^3 = alkyl
2, R^1, R^2 = alkyl; R^3 = phenyl
3, R^1, R^2 = alkyl; R^3 = CN
4, R^1 = alkyl; R^2 = alkyl or phenyl; R^3 = $COOCH_3$

5, R^1, R^2 = alkyl
6, R^1 = alkyl; R^2 = aryl
7, R^1 = alkyl; R^2 = 1-cyclohexenyl
8, R^1 = phenyl; R^2 = OCH_3; R^3 = CN

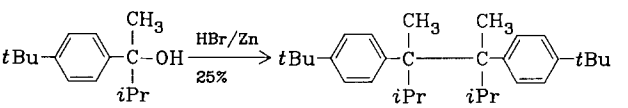
2. Synthesis

The sixfold (C_q–C_q) and fourfold (C_t–C_t) symmetrically substituted ethanes **1**—**8** were mostly synthesized by dimerization of the "half" molecules. These were obtainable either by Wurtz type reactions[26,36-39] [e.g. Reaction (a),[26] (b),[19]] or by dimerization of thermally or photochemically



(a)

1d

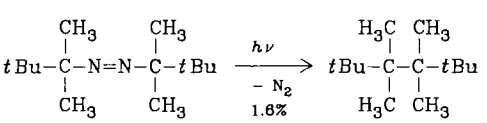


(b)

Ad = 1-adamantyl

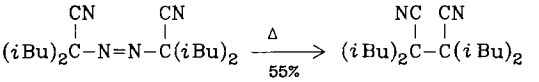
meso/D,L

generated radicals from azoalkanes[20,28,36] [Reaction (c),[36] (d),[28] (e),[40]], or dimerization of radicals generated by hydrogen abstraction [Reaction (f)[41]].



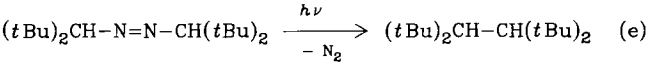
(c)

10



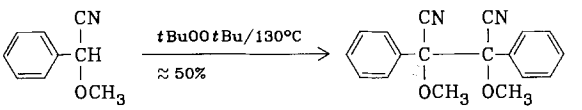
(d)

3b



(e)

5g

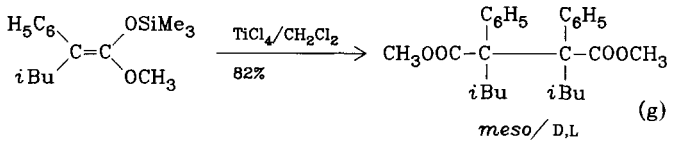


(f)

meso/D,L

8

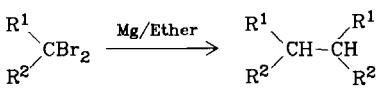
Moreover, oxidative coupling reactions have been used [Reaction (g)[29,42]].



(g)

4b

In general, the yields were higher for phenyl-[19,39] or cyano-substituted[28] compounds than for unsubstituted alkanes[36] because in the latter case radical disproportionation often predominated. The highest yields were obtained when β-hydrogen atoms were absent in the radicals concerned, because in these cases disproportionation was no longer possible.[20,40] The peroxide-induced oxidative dimerization gave, as expected, particularly good yields of dimers when capto-datively substituted radicals were involved.[43] The *oxidative* dimerization of enolates or enol ethers proved less broadly applicable than expected.[29] The reductive dimerization of geminal dibromides [Reaction (h)[44]] proved to be an excellent strategy for the synthesis of the highly strained molecules tetra-*tert*-butylethane (3,4-di-*tert*-butyl-2,2,5,5-tetramethylhexane), **5g**,[44] [H_s(exp) = 66.3 kcal/mol] and 1,2-diadamantyl-1,2-di-*tert*-butylethane (3,4-di(1-adamantyl)-2,2,5,5-tetramethylhexane) [**5**, R^1 = 1-adamantyl, R^2 = *t*Bu; H_s(MM2) = 72.9 (*meso*) or 73.3 (D,L) kcal/mol].[40]



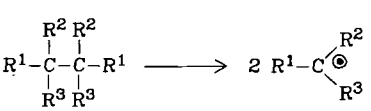
(h)

5g, $R^1 = R^2 = t$Bu (13%)

5e, f, R^1 = 1-adamantyl, $R^2 = t$Bu, *meso*/D,L (21%)

3. Force Field Calculations of Strained Molecules

Strain enthalpies of interest for the discussion of strain effects on structure were obtained by force field calculations[7b] on numerous representatives of compound classes **1**–**8** and compared with experimental values derived from combustion calorimetry.[7b] In general, the agreement between calculated and experimental values was excellent; only in the case of the most highly strained compounds, e.g. tetra-*tert*-butylethane **5g**,[44] was a discrepancy of a few kcal/mol found. The validity of the calculated strain enthalpies was also seen in the successful quantitative analysis of the thermal decomposition of the compound classes **1**–**8**.[6,7] Here, radical formation is associated with a decrease in strain and a gain in conjugational energy. These results have been reported elsewhere.[7]



Force field calculations not only give heats of formation, ΔH_f°(g), but also predict structural data for organic compounds.[32] The reliability of the computational results is well documented within the range of parametrization, not however for compounds which, because of high strain, fall outside this range. This is the case for most of the compounds given in Table 1.[7]

The potential of the force field method in structure determination can be evaluated by comparison of its predictions with the experimental structural data for highly strained compounds; these have been worked out in recent years by crystal structure analyses. In Table 1, only selected characteristic structural parameters are given from which the influence of strain on the structure can be derived. These are, on the one hand, the bond lengths from the central carbon atom in the ethane skeleton (C_e), and, on the other, the bond angles at the central atoms C_e and the carbon atoms in the α position C_α. The bond lengths C_e–C_e and C_e–C_α are lengthened to up to 164 pm—in the record case, 2,3-di(1-adamantyl)-2,3-dimethylbutane **1d**, there are three neighboring bonds of this length. The bond angles at the tetracoordinated carbon atoms in these positions are also increased to a maximum of 123°. These are clear signs of significant molecular strain.

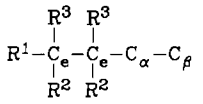
We have carried out calculations of the strain and structures for all compounds in Table 1 using the MM2 force field of *Allinger*.[45] Of the several force fields tried for **1b**, this one gave results in closest agreement with the experimental data.[22] We have extended the force field with the necessary parameters to include alkyl benzenes,[46] nitriles,[28] and carboxylic acid esters,[29] and correspondingly modified the MM2 program for alkylcyclopropanes.[18]

The structural data obtained with the extended MM2 force field just described are given in Table 1 together with the experimental results. Furthermore, for each compound the calculated strain enthalpy H_s is given.[7b] A comparison shows that even pronounced molecular deformations created through high molecular strain are well reproduced by the calculation. Only the values calculated for extremely elongated bonds are somewhat too short (see e.g. **2d**, **4a**, **4b**, **5c**). If packing effects on the crystal structure are also taken into account (this, of course, not being possible in the force field calculations on isolated molecules) the data in Table 1 demonstrate the high reliability of the EFF calculations for the structural types investigated here. This could not have been predicted, since up until now highly strained compounds such as those given in Table 1 had not been used in the parametrization of the MM2 force field.[32,45] The reliability of the MM2 force field in calculating structures of sterically strongly deformed compounds justifies the use of computational structural data in the discussion of the relationships between structure and strain.

4. The Breakdown of the Additive Structural Model through Strain Induced Deformation

The results in Table 1 clearly show that in the case of strained compounds whose heats of formation no longer can be verified by simple increment calculations, also the

Table 1. Selected structural data for highly branched ethanes **1**–**8** from crystal structure analysis and force field calculations [a].



	R^1	R^2	R^3	Configuration	H_s [b] [kcal/mol]	Bond lengths [pm] $d(C_e-C_e)$	Bond lengths [pm] $d(C_e-C_\alpha)$ [c]	Bond angles [°] $(C_e-C_e-C_\alpha)$ [c]	Bond angles [°] $(C_e-C_\alpha-C_\beta)$ [c]	Torsional angles [°] $(C_\alpha-C_e-C_e-C_\alpha)$ [c]	Ref.
1a [d]	Me	Me	Me	—	6.9 (6.9)	158.2 (157.7)	154.2 (154.3)	111.0 (111.8)	— —	175 ± 7 (164)	[47]
1b	*c*Hex	Et	Me	*meso*	34.8 (34.8)	162.6 (163.0)	160.2 (159.2)	112.1 [e] (112.0)	117.5 (117.3)	180 (180)	[22]
1c	*c*Pr	*c*Pr	*c*Pr	—	17.9 [f] (23.4)	163.6 (161.5)	153.2 (155.2)	108.9 (109.9)	124.6 (123.7)	180 (180)	[18]
1d	1-Ad	Me	Me	—	— [f] (42.1)	163.9 (164.0)	164.7/164.0 (164.5)	117.6 (120.9)	— —	162 (162)	[26]
2a	Ph	Me	Me	—	11.1 (12.0)	158.5 (157.4)	154.5 [e] (155.5)	110.8 (110.6)	— —	180 (180)	[19]
2b [g]	Ph	Et	Et	—	24.9 [h] (27.4)	162.2/163.5 (162.1)	153.6–157.1 [e] (156.8)	109.0–109.6 (107.9)	113.9–119.9 [e] (119.0)	164/180 (180)	[19]
2c	Ph	$-(CH_2)_7-$		—	45.0 (42.1)	162.2 (161.8)	155.2 (154.1)	109.0 (108.9)	118.5/119.0 [e] (118.5)	180 (180)	[20]
2d	Ph	*n*Bu	*n*Bu	—	22.7 [h] (22.3)	163.8 (161.2)	155.4 (154.6)	108.7 (108.2)	119.1 [e] (120.9)	180 (180)	[27]
3a	*i*Bu	Me	CN	*meso*	— (12.9)	155 (158)	153 (156)	114.2 (112.0)	122.9 (119.8)	180 (180)	[28]
3b	*i*Bu	*i*Bu	CN	—	25.9 (23.8)	160 (160)	155/156 (156)	112.7 (107.5)	117.8/118.9 (119.5)	180 (180)	[28]
4a	Ph	Et	CO_2Me	D,L	— (21.0)	163.5 (160.4)	156.2 (154.6)	108.1 (109.4)	116.2 [e] (119.6)	175 (176)	[29, 30]
4b	*i*Bu	Ph	CO_2Me	*meso*	— (24.9)	163.7 (161.2)	156.3 (156.8)	111.2 (112.2)	121.1 (122.8)	44 (48)	[29, 30]
4c	*i*Pr	Et	CO_2Me	D,L	— (36.4)	162.0 (161.8)	157.8 (158.8)	115.3 —	119.5 [e] —	172 (164)	[31]
5a [d]	Me	Me	H	—	2.7 (2.7)	154.6 (154.9)	153.9 (153.8)	111.3 (113.9/109.2)	— —	— (70)	[46, 48]
5b	*c*Hex	*c*Hex	H	—	— (20.1)	157.7 (158.1)	156.8 (156.7	113.1 (115.8)	— —	69 (58)	[21, 37]
5c	*t*Bu	*c*Hex	H	*meso*	— (34.5)	160.2 (158.5)	159.4/158.9 (158.3/158.6)	123.5/115.1 (123.7/118.8)	119.6/121.3 [e]	129 (117)	[22, 37]
5d	*t*Bu	*c*Hex	H	D,L	— (28.1)	158.9 (158.0)	154.8/156.2 (157.5)	113.3/113.9 (115.8)	120.4/120.9	139 (147)	[22, 37]
5e	1-Ad	*t*Bu	H	D,L [i]	— [f] (57.5)	162.1 (161.5)	162.9 (162.3)	120.0 [e] (119.1)	— —	115 (113)	[30, 40]
5f	1-Ad	*t*Bu	H	D,L [i]	— [f] (58.1)	163.1 (162.1)	162.8/163.5 [e] (160.8/161.2)	120.8/120.6 (119.3/120.9)	—	52 (52)	[30, 40]
5g	*t*Bu	*t*Bu	H	—	66.3 (57.7)	— (161.4)	— (15.1/161.2)	— (117.6/119.8)	— —	— (65)	— [37, 44]
6a [g]	*t*Bu	Ph	H	*meso*	— (14.7)	157.7/157.3 (156.1)	159.9/158.2 (157.2)	116.0(116.8 (118.7)	—	180 (180)	[23]
6b	*t*Bu	Ph	H	D,L	— (18.4)	158.9 (155.9)	156.9/158.3 (156.8)	114.0/115.2 (117.1)	—		[23]
6c [g]	*t*Bu	Mesityl	H	*meso*	— (31.7)	155.2/151 (157.2)	161.1/163 (157.9)	111.8/111.2 (121.2)	—	180 (180)	[24]
6d	*t*Bu	Mesityl	H	D,L	— (35.1)	158 (158.2)	161 (158.4)	116.6 (121.0)	—	138	[24]
7 [k]	*t*Bu	1-*c*-Hexenyl	H	*meso*	— (20.1)	157.0 (156.2)	160.0 (156.2)	115.6 (120.5)	—	180 (180)	[25]
8	Ph	OCH_3	CN	*meso*	— (12.8)	157.8 (157.3)	152.7 (152.8)	111.9 (109.6)	—	180 (180)	[30, 41]

[a] Computational value using the MM2 force field according to *Allinger* et al. [45] with extensions [28, 29, 46]. [b] Experimental values from enthalpies of combustion and sublimation (MM2 computational values in parentheses) [49]. [c] C_α belongs to the group R^1 unless otherwise indicated. [d] Electron diffraction experiments. [e] C_α belongs to the group R^2. [f] Ring strain is subtracted: H_s(cyclopropane) = 28.12, H_s(adamantane) = 7.9 kcal/mol. [g] Two independent molecules are present in the crystal. [h] Derived from the *p-tert*-butyl derivate. [i] See Figures 4 and 5 for a designation of the rotamers **5e** and **5f**. [k] Calculated using the force field described in reference [49].

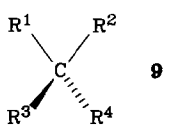
structural parameters strongly deviate from the norm, i.e. bond angles, bond lengths, and torsional angles. However, common traits can be perceived from the structures of the strained four- and six-fold substituted ethanes. These can be used as guidelines in the interpretation of the structures of other branched molecules. The generalizations reached

in the rigid structure model by the standardization of bond lengths and bond angles have been lost again in favor of individual structural parameters for each molecule. Such phenomena are successfully taken into account by the force field method, which therefore pragmatically becomes the basis for a flexible structural model. The realization that molecular strain can be spread over large areas rather than localized in individual bond lengths or angles, is almost trivial but extremely important in this context. Many internal coordinates change in order to evade repulsive van der Waals interactions between neighboring atoms within the molecule. Each individual deformation is compensating for only a small part in the total strain. For example, the elongation of a C–C bond to 160 pm is calculated as requiring an energy of less than 2 kcal/mol.[50]

4.1. Angle Deformation

From vibrational spectroscopy it is known that angle deformation is energetically more favorable than bond elongation: the stretching vibrations have larger force constants. Furthermore, and more importantly, a bending vibration is more effective in separating two groups than is simple bond stretching. *The preference for angle deformation over bond stretching* is impressively demonstrated in Table 1 by comparison of the fourfold substituted ethanes (C_t–C_t series **5**–**7**), with the sixfold substituted ethanes (C_q–C_q series **1**–**4**). In the first series the four residues evade mutual repulsion by increasing the C_e–C_e–C_α angle at the central tertiary carbon atom and simultaneously decreasing the C_e–C_e–H angle. This is much more difficult to achieve for the six residues in the C_q–C_q systems **1**–**4** because each C–C–C angle enlargement results in compression of another C–C–C angle in the center of the molecule (see however **1d**). The C_q–C_q systems, therefore, evade repulsion by more pronounced bond extension.

Table 2. Strain and angle opening caused by geminal repulsion in methanes **9** with two, three or four substituents (EFF calculations) [a].



9

	R^1	R^2	R^3	R^4	α [°]	H_s [kcal/mol]
9a	Me	Me	Me	Me	109	0.0
9b	Me	Me	H	H	113	0.0
9c	Ph	*t*Bu	H	H	114	0.7
9d	Et	*t*Bu	H	H	117	1.6
9e	*t*Bu	*t*Bu	H	H	125	7.4
9f	*t*Bu	*t*Bu	Me	H	121	13.9
9g	*t*Bu	*t*Bu	Me	Me	118	21.6

[a] Calculated according to the MM2 force field [45, 53, 54] extended to include alkyl benzenes [46].

The interplay between the relative space-filling property of the four residues at a four-coordinated carbon atom and the deformation of its geminal bond angles is seen in the case of the alkylated methanes **9** in Table 2. It is noteworthy that the central carbon atom in neopentane, **9a**, having four identical residues (R^1–R^4 = CH_3), adopts the ideal tetrahedral structure. The central C–C–C angle in propane, **9b**, is increased to 113° by the small repulsion between the two methyl groups. Thus, the C–C–C angle deformation in **9** depends less on the total strain and more on the difference in size between the four residues R^1–R^4. Di-*tert*-butylmethane (2,2,4,4-tetramethylpentane), **9e**, has a relatively small strain energy of 7 kcal/mol and has a C–C–C angle of 125° (according to crystal structure analysis: 124–126°).[51, 52] **9e** represents a rare case of a single internal coordinate carrying a high proportion (ca. 40%) of the total strain; according to MM2 ca. 3 kcal/mol is required for this degree of angle deformation.[45b]

The space-filling property of a group, which is decisive in geminal repulsion, is strongly dependent on shape, as seen in the comparison between ethyl and phenyl groups in **9c** and **9d** (Table 2). The larger and heavier phenyl group leads to less strain and a smaller C–C–C angle than does the smaller ethyl group in the presence of a geminal *tert*-butyl group.

The result is that the bond angles of the tetravalent carbon atom easily adapt to the space-filling requirements of the four substituents.

If the angle deformations of the highly branched ethanes shown in Table 1 are considered in this context, then again a clear correspondence with size and shape of the substituents R^1, R^2, and R^3 is seen. The large difference in size between H and an alkyl group results in the particularly large angle deformations already mentioned in the C_t–C_t-ethanes. It is somewhat smaller in the diarylethanes **6** and in dicyclohexenylethane **7**. Thus, the 1-cyclohexenyl residue, which is joined through a trigonal carbon atom, is more similar to the planar phenyl group than to the cyclohexyl ring as regards geminal repulsion. The quaternary centers in the C_q–C_q series **1**–**4** are, in general, less distorted, but here, too, differences in size determine the distortion pattern. In the most strongly strained compound **1d** the central bond angle is increased to almost 120°.

As shown for di-*tert*-butylmethane **9e** in Table 2, a secondary CH_2 center is particularly easily deformed as a result of steric pressure from geminal groups. The large C–C–C angles at the α-carbon atoms in the alkyl side chains of **1** are also a consequence of this phenomenon.

Increased angles caused by geminal repulsion decisively determine the conformational behavior of branched hydrocarbons. This will be further elaborated in depth in Section 5.

4.2. Bond Elongation

The steric repulsion in compounds **1**–**7** leads not only to angle deformation but also to bond lengthening. As expected from the preceding discussion, bonds between more highly alkylated, e.g. quaternary, carbon atoms are more strongly affected than those between tertiary or even secondary carbon atoms. This is shown in the graph in Figure 1. The correlation between central C–C bond length and strain enthalpy shows a steeper slope for C_q–C_q than

for C_q-C_t alkanes, and the smallest slope is found for the C_t-C_t series.

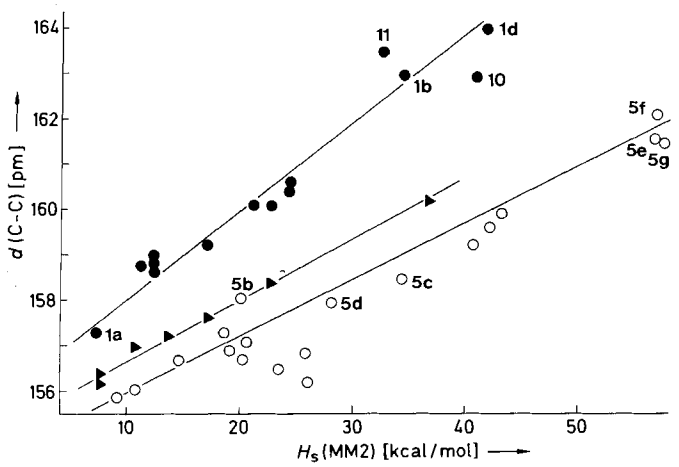
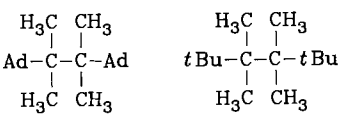


Fig. 1. Dependence of C–C bond length, d(C–C), on molecular strain, H_s(MM2), in various alkanes. ○ $R^1R^2CH-CHR^1R^2$ (C_t-C_t) [37, 40], ● $R^1R^2R^3C-CR^1R^2R^3$ (C_q-C_q) [36, 40], ▲ $(CH_3)_3C-CHR^1R^2$ (C_q-C_t) [53].

In the first two of these series, the length of the central C–C bond is surprisingly linearly dependent on the total strain of the system. Apparently, the two molecular halves constitute approximately equal steric domains and lead to qualitatively similar and only quantitatively different deformation of the molecules within each series. The proportion of the total strain manifested in the form of bond elongation is either constant or linearly related to the total strain within each series. Exceptions are found in the C_q-C_q series only for most highly strained compounds, viz. 2,2,3,3,4,4,5,5-octamethylhexane **10**, 3,3,4,4-tetraethylhexane **11**, and 2,3-di(1-adamantyl)-2,3-dimethylbutane **1d**. This is not surprising considering that in these C_q-C_q alkanes strongly deformed $C_q-C_q-C_\alpha$ or $C_q-C_\alpha-C_\beta$ bond angles are also present (see Table 1 and Section 4.1).



1d **10**

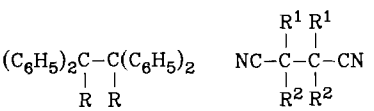
$(C_2H_5)_3C-C(C_2H_5)_3$ **11**

Ad = 1-adamantyl

The longest C–C bonds ever measured experimentally in acyclic systems are found in 2,3-di(1-adamantyl)-2,3-dimethylbutane **1d** (164.7, 164.0, and 163.9 pm).[12] Moreover, these bonds are immediate neighbors[26] (Table 1). The good agreement between experimental and calculated (MM2) values is noteworthy. The central C_q-C_q bond in the structurally related octamethylhexane **10**[36] is comparatively shorter (MM2 value 162.9 pm). Apparently, the more flexible *tert*-butyl group permits a stronger molecular deformation by means of angle opening than does the polycyclic adamantyl skeleton. The question as to the inherent limit of bond elongation has often been posed and finds a general answer here: the multifarious deformability of alkyl chains prevents further elongation of bonds in acyclic molecules. Of the total strain in **1d** (over 40 kcal/mol) only about 3 kcal/mol is manifested in the form of elongation of the central bond to a total of 164 pm.[45b,50] Thus, even in the C_q-C_q ethanes, only a very small part of the total strain is reflected in the lengthening of the central bond.

In contrast to the C_q-C_q and C_q-C_t series, a less direct relationship between central bond length and strain enthalpy is found in the C_t-C_t series[37] (Fig. 1). In particular, the compounds with linear side chains have shortened central bonds because strain is readily relieved through angle deformation at the methylene groups in the side chains (see Section 4.1).

As already shown in another connection, the linear correlation for the C_q-C_q series (Fig. 1) is also valid for phenyl, cyano, and otherwise substituted compounds,[7] although with a somewhat larger spread. In this context it is of interest that comparatively short central C–C bonds are found in the compound classes **3** and **12** with planar phenyl or linear nitrile groups. Apparently, these substituents increase the opportunities for angle deformation.

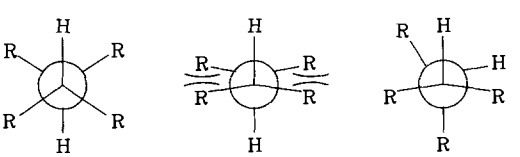


12 **3**

In view of these findings it is understandable that the length of a bond is no criterion for its strength.[7] The bond broken in a homolysis reaction is the one leading to the less strained and more stabilized radical, as evidenced by us in detailed kinetic studies. Also in compound **1d** the somewhat shorter central bond is clearly weaker than the longer neighboring C_e-C_α bond.[26]

5. Preferred Conformations

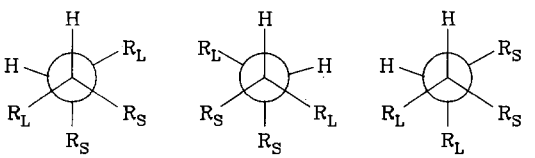
Angle deformation caused by repulsion between geminal groups has direct consequences for the preferred conformations.[6,37] Although the angle deformations typical for the C_t-C_t alkanes **5** (see Section 4.1) decrease geminal repulsion, they increase vicinal repulsion in the *anti* conformation as seen from the Newman projection of the en-



13 **14** **15**

vironment of the C_t-C_t bonds in **13** and **14**. In the conformation **15** with *gauche* hydrogens, the groups R can adopt positions minimizing both vicinal and geminal repulsion. Thus, according to force field calculations, the *anti* ro-

tamer of 1,2-di-*tert*-butyl-1,2-dicyclohexylethane (3,4-dicyclohexyl-2,2,5,5-tetramethylhexane) is 10 kcal/mol less stable than the preferred *gauche* conformation.[22,37] This difference is even more extreme in the case of tetra-*tert*-butylethane **5g**[33,44,55] or the isomeric 3,4-di(1-adamantyl)-2,2,5,5-tetramethylhexanes,[40] which prefer *gauche* conformations similar to **15** in which vicinal hydrogens and R-groups are almost eclipsed. It is still an open question why structures with non-alternating Newman projections have not been found so far. Their occurrence in tetra-*tert*-butylethane, **5g**, was suggested originally by *Mislow* et al. on the basis of earlier force field calculations.[55c] Even in 2,3-dimethylbutane, **5a**, the *gauche* conformation **15** ($R=CH_3$) is slightly preferred.[37,48] If the two residues in a C_t-C_t alkane **5** differ in the space-filling properties, the D,L diastereomer **16** turns out to be more stable than the *meso* form **17**.



16 (D,L) **17** (*meso*)

This is because in the preferred conformation of the D,L diastereomer **16** the two large substituents R_L are flanked by the steric vacancy caused by the small hydrogen atoms. In the *meso* compound **17** only one of the large groups R_L can adopt this preferred position, the other one being in a *gauche* relationship to two R residues. Accordingly, D,L-1,2-dicyclohexyl-1,2-di-*tert*-butylethane, **5d**, is thermodynamically more stable than the *meso* diastereomer **5c** by 6 kcal/mol.[22] These conformation-controlling factors, which have already been identified earlier for C_t-C_t alkanes and phenyl-substituted analogs,[6,37] are more generally applicable than hitherto believed.

With respect to the central bond, a total of five staggered, alternating rotamers are possible for a symmetrically substituted ethane[56] having three substituents of different steric requirement (R^1, R^2, and R^3, designated L, M, and S). Two of these rotamers (**I** and **II**) correspond to the *meso* form (*erythro*), and three (**III**—**V**) to the D,L (*threo*) form. These are shown in Newman projections with a schematic representation of the steric requirements in Figure 2. The expected increase of the L–C–M angle, and decrease of the L–C–S and M–C–S angles at the central carbon atoms (cf. Section 4.1) have been taken into account in these projections.

The consequences of this angle increase are readily seen in Figure 2. Judging from the repulsion between the groups, rotamer **I** in the *meso* series clearly appears less favorable than rotamer **II**. The deformation of the central carbon atom in **I** causes a closer approach of the medium-sized substituents, M, to the large ones, L. In **II**, however, the increased bond angle between the L and M substituents leads to relief of vicinal interaction between these groups.

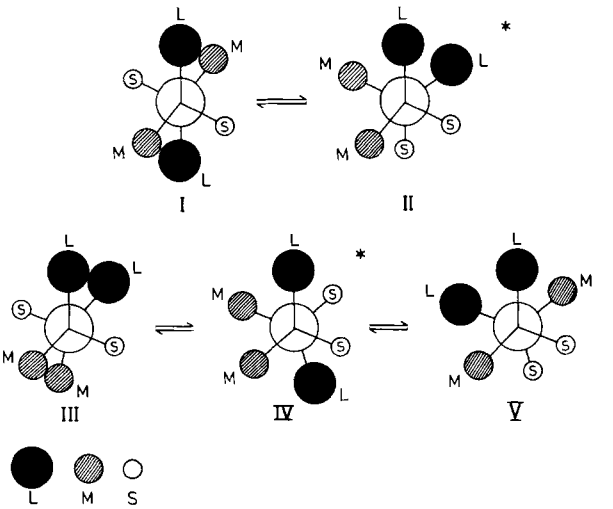


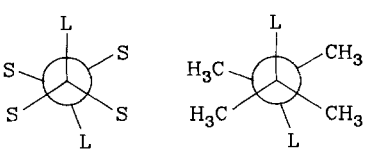
Fig. 2. Model for conformational analysis of C–C single bonds taking into account geminal repulsion between groups of different sizes (L = large, M = medium, S = small). **I**—**II**: *meso*; **III**—**V**: D,L. In each case, only one enantiomer of **III**—**V** is shown. * Denotes the preferred conformation.

Thus, although conformer **I** with the large substituents L *anti* to each other is slightly preferred as long as ideal tetrahedral geometry is maintained, this conformer becomes less favorable when increasing differences in size cause an increased deformation of the central bond angles.

By analogy, **IV** is seen to be the preferred conformation in the lower row of Figure 2. Here, too, the two large substituents L profit from less vicinal repulsion of the smallest substituents as a result of opening of the L–C–M bond angle. Of all the rotamers shown, **IV** should be the most stable. Consequently, the D,L diastereomer becomes more stable than the *meso* form.

Further predictions can be made for particular combinations of groups. If two of the groups are identical or effectively identical, the differences between **II**, **IV**, and **V** vanish (see **5e** and **5f** in Table 1 and Fig. 2).

The differences between the conformers become less pronounced as the differences in size between the groups R diminish. This is particularly true for **IV** and **V**, the *meso*-2,3-diisobutyl-2,3-diphenylsuccinic ester **4b** (L = *i*Bu, M = Ph, S = COOMe) exists in the *gauche* conformation **II** in clear agreement with the model.[29,30] Also, with respect to the total strain, the methoxycarbonyl group proved to be "smaller" than the phenyl group.[29] Force field calculations indicate that the *anti* form **I** is less stable by 1.7 kcal/mol.[29]



18 **19**

Another special case obtains in the C_q-C_q series when two large substituents R^1 are combined with two small ones, R^2 and R^3. Here, conformation **18** is, of course, preferred, because the large groups L are *anti*, but the torsional angle between these groups is not 180° but signifi-

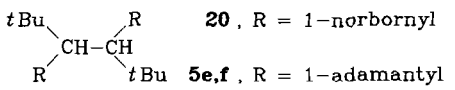
cantly less (165–175°; see Fig. 2). Thus, conformations corresponding to **IV** are present, and surprisingly enough this is also the case when R^2 and R^3 are methyl groups, as in **1a** and **1d** (cf. **19**). Apparently, the methyl groups in **19** differ as regards their vicinal repulsion. A sterically less demanding pair (Fig. 2) gets closer together and reduces the total strain, as shown earlier.[57] This is due to the fact that methyl groups do not behave as spheres; in contrast, their interlocking ability allow them to reduce repulsion pairwise.

Phenyl groups influence the conformations of substituted ethanes in a different manner. Their disk shape allows them to avoid geminal repulsion more easily, and hence the bond angles at the ethane carbons are much less deformed (see Table 2). In the C_q–C_q series the 1,2-diphenylethanes **2** with *n*-alkyl side chains adopt the *anti* conformations **I** or **III** with normal torsional angles of 180° between the phenyl groups. Similarly, in the C_t–C_t series, the diarylethanes **6** carrying smaller alkyl groups (methyl to isopropyl), follow the usual conformational rules: *meso* and D,L configurations prefer the conformations **I** and **III**, respectively, the hydrogen atoms being *anti*; the *meso* form is somewhat more stable than the D,L form.[13] Only *tert*-alkyl groups (**6a**–**6d**) increase the geminal repulsion to such an extent that the *gauche* conformation **IV** becomes preferred in the D,L series because of increased angle deformation. In contrast, the *meso* form maintains the *anti* conformation **I** and remains more stable than the D,L form.[13, 14]

6. Rotational Barriers and the Isolation of Stable Rotational Isomers

The height of the barrier toward rotation around the central bond of an ethane is not a simple function of the total strain or the sum of the volumes of the groups. Six-fold substituted C_q–C_q ethanes show rather uniform rotational profiles, and the rotational barriers are generally not high ($\Delta G^* \leq 13$ kcal/mol; see Fig. 3). Secondary groups can co-rotate (like cogwheels) in the course of a rotation around the central bond. This can result in a complex change of the enthalpy as a function of the inner movements during rotation.[58] This is very nicely illustrated by the rotation profile of the isopropyl derivative in Figure 3.

C_t–C_t ethanes with large substituents have very steep torsional profiles.[23, 24] In tetra-*tert*-butylethane, **5g**, the barrier toward rotation around the central bond is even higher than that for dissociation.



20, R = 1-norbornyl

5e,f, R = 1-adamantyl

Starting with this phenomenon and using a strategy based on orienting force field calculations, the compounds **20** and **5e**, **f** were synthesized[40] [see Reaction (h)]. NMR-spectroscopy demonstrated that in both cases three isomers were formed, assigned as the three rotamers **II** (*meso*), **IV**, and **V** (D,L) (Fig. 2). The two conformationally stable rotamers D,L-**5e** and D,L-**5f** could even be separated by manual crystal selection, and after purification by fractional crystallization were subjected to crystal structure analysis[30, 40] (see Fig. 4). **5e** corresponds to the *anti* conformation **IV** and **5f** to the *gauche* conformation **V** when L = 1-adamantyl, M = *tert*-butyl, and S = H.

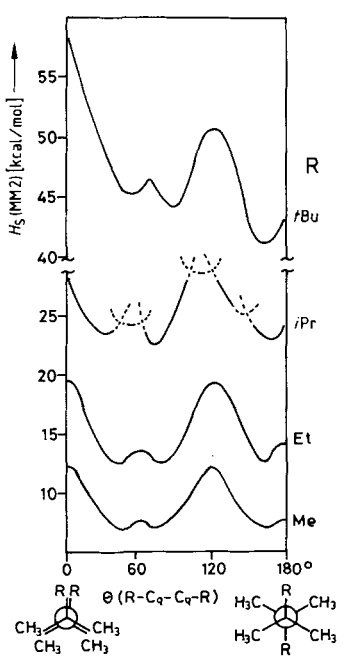


Fig. 3. Rotational potentials for the C_q–C_q bonds in hydrocarbons $R(CH_3)_2C$–$C(CH_3)_2R$ according to MM2 calculations [57].

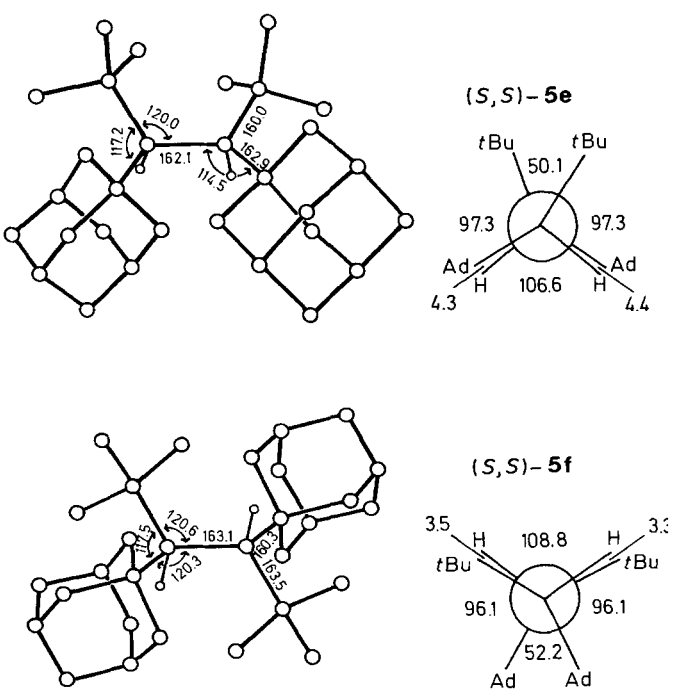
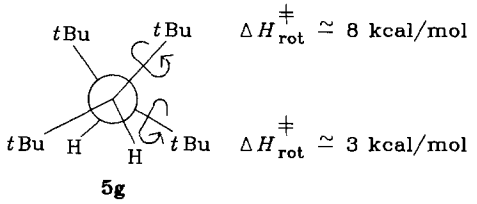
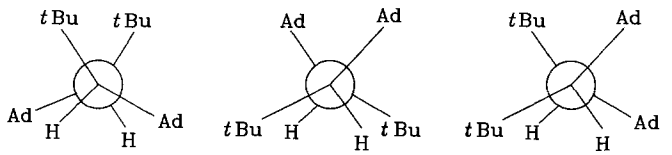


Fig. 4. Structures and Newman projections of the two rotamers of D,L-3,4-di(1-adamantyl)-2,2,5,5-tetramethylhexane with important bond lengths [pm] and angles [°] derived from crystal structure analysis [30, 40]. Ad = 1-adamantyl. The (*S*,*S*)-enantiomers are shown.

The assignment of the rotamers made previously by NMR was based on a characteristic difference between the *tert*-butyl groups *gauche* or *anti* to the methine C–H bond. The former possess lower rotational barriers ($H_{rot} = 3$ kcal/mol), as is also observed for tetra-*tert*-butylethane, **5g**; the latter have higher barriers ($H_{rot} = 8$ kcal/mol), both being MM2 calculated values[40, 44, 55] (Fig. 5).



5g



(*R*,*R*)-**5e** (*R*,*R*)-**5f** *meso*

Fig. 5. Newman projections of tetra-*tert*-butylethane (**5g**), the two rotamers of D,L-3,4-di(1-adamantyl)-2,2,5,5-tetramethylhexanes [40, 59] (illustrated: (*R*,*R*)-enantiomers) and the corresponding *meso*-compound. Ad = 1-adamantyl.

To the best of our knowledge, **5e** and **5f** are the first examples of stable rotameric aliphatic hydrocarbons.[60] Their strongly deformed structures, in particular the Newman projections, eminently confirm the rules for conformational analysis of C–C single bonds, derived for C_t–C_t hydrocarbons in the present work, and applicable also to other compounds.

7. Conclusion and Outlook

Starting with the work of *D. H. R. Barton*,[61] the development of general rules of conformational analysis with the aid of geometrically standardized molecular models has made possible a unifying description of an unusual wealth of questions relating to structure and reactivity. Strained molecular structures, however, are at the limit of applicability of simple conformational analysis, and standard bond lengths, bond angles, and torsional profiles are no longer valid. The conformational analysis of each strained molecule becomes an individual problem, in the solution of which the force field method has proved well suited.

The knowledge of structural data for a variety of strained compounds also makes it possible to give new and refined guidelines for qualitative conformational analysis. Here, the consequences of angle enlargement caused by geminal repulsion between large groups are particularly decisive for the conformation. If angle enlargement is energetically unfavorable, bond lengthening will be the dominating outcome of strain. However, strain is always distributed over many structural coordinates, so that the degree of distortion of individual bond angles and bond lengths is limited. The influence of a substituent on the conformation depends less on the size than on the shape of the substituent.

The possibility of calculating unusual molecular geometries using the force field method is of importance not only for the determination of intramolecular but also intermolecular interactions. After all, van der Waals interactions can influence the nature of the accessible reaction channels[62] and hence the selectivity, e.g. in radical recombination[63] or in asymmetric synthesis.[35] Their importance should be even more far reaching in biological recognition processes.[14, 15, 64–65]

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Chiral Compounds Synthesized by Biocatalytic Reductions

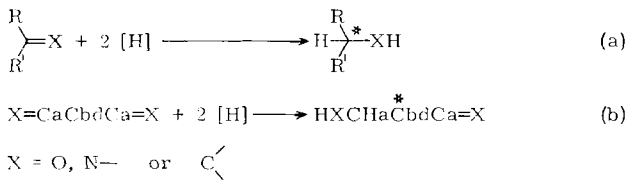
New Synthetic Methods (51)

By Helmut Simon,* Johann Bader, Helmut Günther, Stefan Neumann, and Jordanes Thanos

It has been known for many decades that chiral compounds can be obtained by stereospecific biocatalytic reduction. Further significant methodological developments in this field have, however, only been made during the past ten years; they include the application of previously unused microorganisms and electron donors, the discovery of additional substrates for the known reductases, the development of methods for regenerating reduced pyridine nucleotides, and the discovery of new reductases which were sought for specific preparative purposes. Many chiral compounds can now be synthesized by microbial hydrogenation using H_2 and hydrogenase-containing microorganisms as well as by electromicrobial or electroenzymatic reduction. In the two latter methods, anaerobic or aerobic organisms are supplied with electrons from electrochemically reduced, artificial mediators, e.g., methyl viologen. Reductases that do not require pyridine nucleotides and can accept electrons directly from reduced viologens are especially useful. Two examples of this type of enzyme are described which are of preparative interest. Many cells contain methyl viologen-dependent NAD(P) reductases, a large number of which have still not been characterized. A productivity number is proposed which allows different methods of bioconversion with microorganisms to be compared. The productivity numbers of compounds synthesized by the methods described in this review are often 10- to 100-fold higher than those of substances obtained by conventional techniques.

1. Introduction

A large number of chiral products can be obtained by stereospecific reduction of appropriately substituted unsaturated compounds according to Reaction (a) or (b):



(a)

(b)

In Reaction (a), the biocatalyst only has to differentiate between the *Re* and *Si* faces of a π system. Two alternatives are possible in Reaction (b). If the originally sp^2-hybridized C atom does not become chiral after reduction,



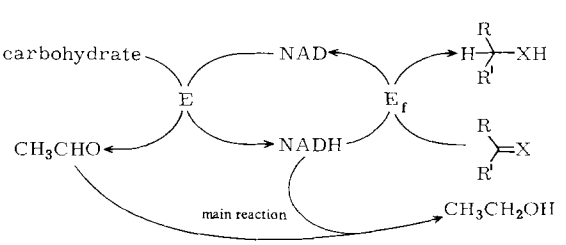
then only the pro-*R* or pro-*S* group ($-C=X$) has to be differentiated. If, however, substituent a is such that a chiral group is formed from the π system after hydrogenation, this raises the question of diastereomeric purity, since the *Re* and *Si* faces must be differentiated in addition to the pro-*R* and pro-*S* groups.

Reaction (a) is more important than (b). The reduction of carbonyl groups has been described much more frequently than that of CC double bonds. The reduction of CN double bonds has rarely been described but plays an important part in the reductive amination of oxo compounds (e.g., in the synthesis of amino acids). A review of the microbial enantioselective reduction of ketones has recently been published[1] (for reviews and literature surveys see ref. [2–8]).

The reduction of phenylglyoxylic acid to mandelic acid by fermenting yeast was reported more than 70 years ago.[9] The reduction of ketones to chiral alcohols was described in about 160 publications in the mid-1950s. Microbial reductions of systems of the type $-CH=C<$ were the subject of only about 20 studies.[2] Later, in addition to microorganisms, enzymes of various purities were used for the preparative reduction of unsaturated compounds.[4, 10, 11] The reductases that have so far been employed, however, require reduced pyridine nucleotides (nicotinamide adenine dinucleotide = NAD or nicotinamide adenine dinucleotide phosphate = NADP), which cost several thousand marks per mole. The nucleotides must therefore be regenerated if they are to be used in catalytic quantities.

Six different methods of biocatalytic reduction can be differentiated according to the nature of the donor and the route of electron transport from the donor to the substrate:

– Up to now carbohydrates have usually been employed as electron donors for the microbial reduction of unsaturated substrates. NADH and an electron acceptor such

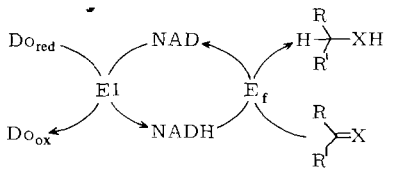


(I)

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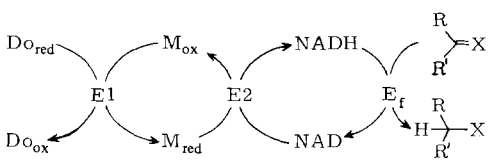
as acetaldehyde or pyruvate are formed from NAD and the carbohydrate in a series of enzyme-catalyzed steps (Route I). The desired reaction catalyzed by the "final" reductase E_f is usually a side reaction.

—It is better to have a system in which the electron donor Do_{red} converts NAD into NADH in a single, practically irreversible step, the NADH then being consumed in the reaction catalyzed by E_f (Route II). Two enzymes isolated from different sources can be combined for this route.



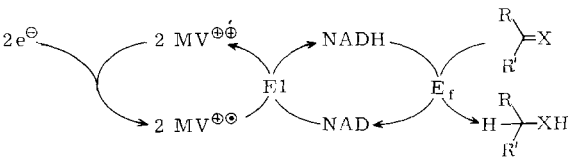
II

—Systems can also be very advantageous in which a natural electron mediator M_{red} (e.g., reduced ferredoxin) is formed from the primary electron donor (e.g., H_2 or formate); M_{red} then converts NAD into NADH in a reaction catalyzed by E2 (Route III.1). In this case, electron transport can often be accelerated if, instead of a natural mediator, an artificial mediator such as viologen can be used (Route III.2).



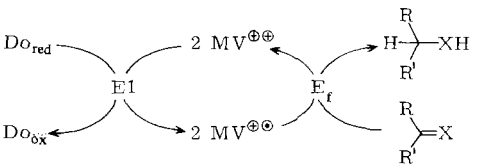
III. 1, III. 2

—Route IV has proved to be of value in many cases, because viologens (e.g., methyl viologen = $MV^{\oplus\ominus}$, 1,1'-dimethyl-4,4'-bipyridinium dication) can be electrochemically reduced in a defined manner and, according to our results, methyl viologen-dependent NAD reductases seem to be widely distributed.

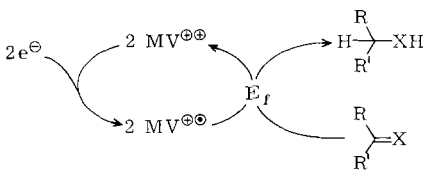


IV

—Further studies performed by our group have shown that preparatively useful reductases are available which can accept electrons directly from reduced viologens. Routes V and VI thus become accessible. In Route V, enzymatically reduced methyl viologen is produced with, for example, H_2 or formate as an electron donor. In Route VI, the shortest and simplest electron transport system, the enzyme E_f is supplied with electrons electrochemically (i.e., using electricity) via the mediator $MV^{\oplus\ominus}$.



V



VI

These six pathways are briefly described in Table 1 and will be discussed from a practical point of view in Section 2.2.

Table 1. Possible pathways of biological reductions.

Description	Electron donor	Catalyst(s) for NAD(P)H regeneration or reduction of the final reductase	Scheme of electron flow	Comments
NAD(P)H is produced after a series of enzyme-catalyzed steps and the formation of competing electron acceptors	Glucose or other carbohydrates	Whole cells, e.g., yeasts or bacteria	I	Used most often; productivity numbers are usually low
Direct NADH formation	HCOOH, H_2, CH_3CH_2OH	Whole cells, e.g., *Pseudomonas ovalis, Arthrobacter spec.*, or *Clostridium kluyveri*	II	Seldom used; cells are employed for NADH regeneration
Reduction of NAD(P) via natural or artificial mediators	H_2, HCOOH	Whole cells, e.g., clostridia or *Proteus vulgaris;* with or without mediators such as viologens	III.1; III.2 or V	Numerous α,β-unsaturated carboxylates and 2-oxocarboxylates are reduced to chiral compounds
Two-enzyme system	HCOOH or other substrates of an NAD-dependent dehydrogenase, e.g., isopropanol or cyclohexanol	Dehydrogenase and final reductase	II	In some cases successful on a pilot scale with NAD of increased molecular weight in membrane reactors
Electromicrobial	Cathode of an electrochemical cell	Cells with methyl viologen-dependent NAD(P)H reductase and pyridine nucleotide-dependent final reductase	IV	Examples are to be found in this review
Electroenzymatic or electromicrobial	Cathode of an electrochemical cell	Cells with final reductase that can accept electrons directly from mediators such as viologens or isolated final reductase	VI	Examples known so far are enoate reductase and 2-oxocarboxylate reductase. Both react with a wide range of substrates

As shown in this review, the methodology of biocatalytic reduction can be considerably extended by employing microorganisms that have not so far been generally applied together with the new types of enzymes found in them; a second approach is to utilize coenzyme regeneration methods which until now have been used either very rarely or not at all.

2. What Has Been and Can Be Improved by New Methods?

2.1. Criteria for Evaluating the Conversion of Substances Using Microorganisms

The efficiency of the conversion of substances using microorganisms can be characterized by a so-called productivity number (PN):[12, 13]

$$PN = \frac{\text{amount of product [mmol]}}{\text{dry weight of catalyst [kg]} \times \text{time [h]}}$$

High productivity numbers mean better volume-time yields and usually easier isolation of the product. If, for example, 500 mmol of a product is to be synthesized in 24 h, approximately 1000 g of catalyst is required for a productivity number of 20 (which is frequently the case), whereas only 10 g is needed if the productivity number is 2000. Moreover, it is much simpler to separate 100 g of a product from 10 g of a catalyst (i.e., microorganisms) than from 1000 g. If a microorganism consists of 50% protein, the productivity numbers and the enzyme units (U) customarily used in biochemistry are related as follows: if a crude extract of an organism contains the enzyme that is rate-limiting for the conversion with a specific activity of 1 U/mg protein (1 μmol substrate transformed per mg protein per min), a productivity number of 30000 can be attained. This assumes, however, that other factors, such as transport processes, concentration limits, and inhibition by the substrate and/or product, do not have any effect on the reaction. (So far, activities have seldom been expressed in SI units, according to which a quantity of an enzyme has an activity of 1 katal if it transforms 1 mol of substrate per second. 1 U $\triangleq 16.7 \times 10^{-9}$ katal.)

The following factors are also important for biocatalytic conversions in addition to satisfactory productivity numbers:

- —Availability of the cells. Are the cells or is the material for inoculation commercially available from a microorganism collection? Is cell culture simple and reproducible?
- —Reaction specificity. Is the substrate only converted into the desired product or do the substrate and/or product react further?
- —High stereospecificity of the enzyme (or the same high stereospecificity of each of the enzymes catalyzing the reaction). Many enzymes display a high degree of stereospecificity but there are a large number of exceptions.[14] Furthermore, a microorganism may possess two or more enzymes that react with the substrate in stereochemically different ways. For a discussion of this topic see ref. [1].
- —Michaelis-Menten constant (K_m) for the substrate and inhibition constants (K_i) for the substrate and product of the catalyzing enzyme. Low K_m values allow rapid conversion even of the last 5—10% of the substrate, i.e., the reaction does not end "gradually." Low K_i values for the substrate may mean that the substrate has to be added continuously, which is usually not difficult if the reaction rate and thus the actual substrate concentration is known. Low K_i values for the product require selective separation of the product, which is in most cases a complicated task.
- —Stability of the biocatalyst. Here, a distinction has to be made between whether resting or multiplying cells are used. In the former case, the activities of the required enzymes or the concentrations of the cosubstrates, such as NAD(P) or NAD(P)H, can decrease sharply (for example, within 24 h) before the substrate has been transformed. If growing cells are used, product isolation is usually impeded by the large quantities of biocatalyst, and, depending on the microorganism, the substrate and/or product may be converted further.
- —Suitability for immobilization. In order to facilitate product isolation and to stabilize (and eventually reuse) the biocatalyst (intact cells, crude extracts, or enzymes), it may be advantageous to immobilize it. The suitabilities of different biocatalysts for immobilization vary.
- —Storage stability. It is advantageous if the enzyme activities of a prepared biocatalyst remain stable for a long period of time (e.g., when frozen).

2.2. Evaluation of Older and More Recent Procedures

Bakers' yeast *(Saccharomyces cerevisiae)* is the biocatalyst most commonly used for reductions based on Route I (see Table 1); according to the criteria described above, however, it is not a very suitable catalyst even though it is readily accessible and stable. High productivity numbers cannot be achieved via Route I for fundamental reasons. Carbohydrates as electron donors must undergo five or six consecutive, enzyme-catalyzed reactions before NADH is formed. Also, the uptake of carbohydrate may be rate-limiting.[15] Furthermore, acetaldehyde is formed in alcoholic fermentation and competes for the reduction equivalents; formation of ethanol is usually the main reaction; it has been reported that for every mole of ketone produced 200—2000 moles of ethanol are formed.[16, 17]

The experimental data in many published studies do not allow the calculation or estimation of productivity numbers. Examples that permit calculation[17–25] show that the majority of reactions performed with microorganisms and carbohydrates have productivity numbers of 5—50, values of about 200 being very rare. To the best of our knowledge, the highest value, approximately 1000, has been reported for the reduction of 2,2,6-trimethyl-5-cyclohexene-1,4-dione to (6*R*)-2,2,6-trimethyl-1,4-cyclohexanedione with yeast.[24] The special problems associated with the use of non-standardized bakers' yeast or non-standardized methodology are illustrated by the studies published during the

past 50 years on the synthesis of chiral 3-hydroxybutyric acid esters.[22,25,26] Even if only studies reported during the last seven years are considered, *ee* (enantiomeric excess) values of between 80 and 97% have been reported for the synthesis of ethyl (*S*)-3-hydroxybutyrate with bakers' yeast.[22,25] Productivity numbers of about 100 were found. The *ee* values of 95–97% for the (*S*) enantiomer can, however, only be obtained if the concentration of the 3-oxo ester does not exceed 1 g/L; if the concentration is 5 g/L, the *ee* values only amount to 72%. Reductions with *Mucor javanicus*[27] and *Geotrichum candidum*[22] yield the (*R*) enantiomers. The investigations of *Sih* et al.[1,21,27] on the synthesis of esters of 4-chloro-3-hydroxybutyric acid, which is of interest as a precursor of carnitine, have helped to clarify the various factors involved in reductions with bakers' yeast (see Section 3.2).

Seldom and only recently have electron donors that are not carbohydrates (e.g., ethanol) been used for whole cells. Ethanol would also perhaps be a better electron donor than glucose for yeast. Furthermore, it has been suggested that ketones can be reduced by yeast without adding carbohydrates or another electron donor by the use of appropriately larger quantities of cell material.[17]

The different results obtained in a large number of investigations demonstrate that the biochemical fundamentals of reductions are not always well thought out and that the investigators are sometimes not aware of the fact that the bakers' yeast used is not always the same. Even if the same strain is used, the behavior of the yeast in reductions may depend strongly on the culture conditions (culture medium, temperature, stage of growth). An example is given by the reduction of the 5-oxo group of the monothioacetal of methyl 5,6-dioxocaproate. *Takaishi* et al.[29] found specific rotation values of between +5.4 and −21.1° for the products obtained with different strains of *Saccharomyces cerevisiae*. This applies of course to more or less all microorganisms.

According to our findings,[12,13,30–34] H_2 is an especially good electron donor (Routes III.1, III.2, or V) for reductions with organisms containing hydrogenases. In these cases, Do_{red} is H_2; this applies particularly if Route V is possible. Formate could presumably also be of advantage in cases in which the cells contain an NAD-dependent formate dehydrogenase. *Allais* et al.[35] found such an enzyme with a specific activity of 0.16 U/mg protein in a crude extract of *Pichia pastoris*. *Schütte* et al.[36] isolated a formate dehydrogenase from the yeast *Candida boidinii* which proved to be highly suitable for NADH regeneration in the enzyme membrane reactor of the groups led by *Kula* and *Wandrey* (see below). *Izumi* et al.[37] employed the NAD-dependent formate dehydrogenase from methanol-metabolizing bacteria to regenerate NADH with formate, whereby productivity numbers of up to about 6000 were obtained for regeneration.

Examples of the use of ethanol (Table 1) are given by the reductions of (+)- and (−)-carvone with *Pseudomonas ovalis* performed by *Noma* et al.[38] We have reduced various allyl alcohol derivatives with *Clostridium kluyveri* and ethanol to chiral alcohols such as (*R*)-2-methyl-1-butanol, (*R*)-3-methyl-1-pentanol, and (2*R*,3*S*)-2-methyl-3-phenyl[2,3-^{2}H]-1-propanol.[39] The advantages of ethanol over H_2 for this special case will be discussed in Section 3.1 (see also ref. [40]).

In the case of NAD(P)H-dependent reductases, if enzymes are utilized on a preparative scale instead of cells, NAD(P)H must be regenerated *enzymatically* (Table 1, Route II). It has not so far been possible to reduce NAD(P) chemically or electrochemically with practically useful recyclization numbers (for more recent experiments see *Wienkamp* and *Steckhan*[41,42]). The groups of *Kula* and *Wandrey* reported that NAD bound to polyethylene glycol in an enzyme membrane reactor could be used for the preparation of amino acids with the aid of formate dehydrogenase,[43] and could be recycled up to 80000 times. Numerous reports have appeared during the past few years on other possible ways of enzymatically regenerating NAD(P)H[44–47] (see also Section 4.2).

NADH regeneration, especially with formate dehydrogenase or one of the more recently described methods, is now a routine operation on a laboratory scale. Many chiral compounds have already become accessible by the use of this technique in combination with a small number of reductases. In the course of the past few years *Jones* et al.[11,48] and *Nakazaki* et al.[49] have, for example, found a large number of additional substrates for liver alcohol dehydrogenase, an enzyme that has been known for several decades. *Lamed* et al.[50] have drawn attention to some interesting applications of an alcohol/aldehyde/ketone oxidoreductase from the thermophilic bacterium *Thermoanaerobium brokii*. *May* and *Padgette*[51] have reported on the possible applications of oxidoreductases. It is likely that further preparatively or even industrially useful oxidoreductases will be discovered since an intensive search for these enzymes with a view to their possible applications only began a few years ago. (*S*)-Phenylalanine and (2*S*)-2-hydroxy-4-methylpentanoate dehydrogenase are recently discovered examples of such enzymes.[52,53]

Nonpolar compounds can also be enzymatically reduced in conjunction with NADH regenerating systems. *Hilhorst* et al.[54] regenerated NADH in reverse micelles with hydrogenase, methyl viologen, and lipoamide dehydrogenase. 20β-Hydroxysteroid dehydrogenase was used to reduce progesterone dissolved in hexanol/octane to 20β-hydroxy-4-pregnen-3-one at the boundary to the aqueous phase. Routes IV and VI can be utilized for the continuous reduction of catalytic quantities of artificial electron carriers by employing electrochemical cells; NAD(P)H can thus be regenerated with the NAD(P) reductases frequently encountered in microorganisms (Route IV) or electrons can be directly transferred to the final reductase E_f.

3. Hydrogenation with Microorganisms

3.1. Reduction of the CC Double Bond of α,β-Unsaturated Aldehydes and Carboxylic Acids

According to our studies, H_2 can be employed as an electron donor with some microorganisms.[12,13,30–34,55] This has the following advantages: 1) The equilibrium of Reaction (c) lies strongly to the right. 2) In resting cells the



(c)

electron donor can be used solely for the desired reaction. Side reactions, which can occur, for example, with acetaldehyde or other products that are formed from carbohydrates, do not take place. 3) The reaction can be monitored continuously by following the H_2 consumption. 4) The productivity numbers are often 10—100 times higher than those found for reductions with yeasts, which considerably simplifies isolation of the products. According to our findings, productivity numbers of 1000—3000 are often achieved, particularly if catalytic quantities (1—4 mM) of an artificial electron donor such as methyl viologen are added. The electron flow in reductions with clostridia can be described by Route III.1 or III.2.

Hydrogenation with *Clostridium spec. La1* (DSM 1460), *Clostridium kluyveri* (DSM 555), *Proteus mirabilis* (DSM 30115), and *Proteus vulgaris* (DSM 30118) will now be described. Many α,β-unsaturated carboxylic acids or aldehydes (Tables 2 and 3) can be hydrogenated with *C. La1*

Table 2. Enoates of the type $R^2R^3C{=}CR^1CO_2^{\ominus}$ that can be hydrogenated with *Clostridium La1* and H_2 [a]. The last five compounds are allene derivatives.

R^1	R^2	R^3	Relative rates [%] [b]
H	H	H	320
H	H	Me	170
Me	Me	H	150
Me	H	Me	30
H	Me	Me	20
Me	H	H	300
H	Et	H	100
H	Pr	H	90
H		H	100
H		H	130
H		H	100
H		H	20
CN	H	OEt [c]	20
Me	C_6H_5	H	40
OMe	*p*-ClC_6H_4	H	90
Br	C_6H_5	Br	90
Me	EtCH=		—
Et	MeCH=		—
Et	PhCH=		80
H	Ph(Et)C=		—
Et	Ph(Et)C=		—

[a] All the compounds listed in Table 3 can also be hydrogenated since they are substrates of enoate reductase. [b] A relative rate of 100 signifies that 100 mM solutions are hydrogenated at a rate of 150 μmol/h by 400 mg of wet cell sediment (≙80-mg dry weight) at 35° and pH 7.0. This corresponds to a productivity number of about 1900. [c] *E/Z* ratio unknown.

(Route V, Table 1). Do_{red} is H_2, E1 a hydrogenase, and E_f the enoate reductase that we have discovered (EC 1.3.1.31).[13, 56–60] The reactions catalyzed by this enzyme include Reactions (d) and (e).[12, 13, 60, 61]

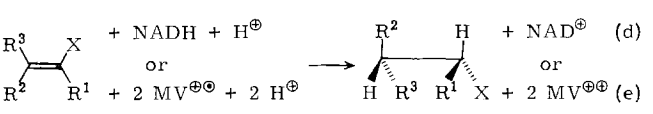
The reaction with $MV^{\oplus\ominus}$ proceeds 1.5 times faster than that with NADH. Enoate reductase can react with a very wide range of substrates. The following rules have been

Table 3. Substrates ($R^3R^2C{=}CR^1X$) of enoate reductase that are reduced according to Equations (d) or (e) [a] but can also be hydrogenated with H_2 and *C. La1* cells.

R^1	R^2	R^3	v_{max} [b]	K_m [c]
Me	Me	H	100	1.5
H	Me	H	280	0.8
H	Et	Me	11	—
H	Me	Et	11	—
H	*i*Pr	H	130	—
H	COOMe	H	9	—
H	$CH_3CH{=}CH_2$	H	18	[d]
H	C_6H_5	H	60	0.013
H	*p*-ClC_6H_4	H	88	—
H	*p*-$O_2NC_6H_4$	H	30	—
H	*p*-$MeOC_6H_4$	H	44	—
H	*p*-$Me_2NC_6H_4$	H	29	—
H	*o*-HOC_6H_4	H	35	—
NHCHO	C_6H_5	H	21	—
H	*o,m*-$(MeO)_2C_6H_3$	H	8	—
F	Me	H	150	6.2[f]
Cl	H	Me	180	5.2[f]
Br	Me	H	150[g]	28[f]
I	H	Me	180[h]	21[f]
F	C_6H_5	H	30	0.1
Br	C_6H_5	H	76	0.50
Cl	*p*-ClC_6H_4	H	20	0.1
Cl	H	*p*-ClC_6H_4	0.03	—
Me	$HOCH_2CH_2$	H	120	—
H	$HOCH_2CH_2$	Me	10	10
H	Me	$HOCH_2CH_2$	9	15
H	Me	$MeOCH_2CH_2$	5	14
H	HO	Me	6	3.3
H	$(CH_3)_2C{=}CHCH{=}CHCH_2$	H	7	—
H	$(CH_3)_2C{=}CH(CH_2)_3$	Me	19	0.014
H	Me	$(CH_3)_2C{=}CH(CH_2)_3$	1.1	0.19
H	$(CH_3)_2C{=}CH(CH_2)_3$	Me	60[e]	0.06
Me	PhCH=		20	—

[a] If not otherwise stated, $X = COO^{\ominus}$. [b] Relative rate with respect to (*E*)-2-methylbutenoate (100%). Purified enoate reductase displays a specific activity of 20 U/mg for this substrate with reduced methyl viologen at 25°C. [c] K_m values in mM. [d] Only the α,β double bond is hydrogenated. [e] X = CHO. [f] 90% *E* and 10% *Z* isomer. [g] Marked substrate inhibition above 40 mM. [h] Marked substrate inhibition above 10 mM.

found to apply: R^1 should not be too large; if R^2 is a phenyl ring, $NHCOCH_3$ and OC_2H_5 residues are not accepted in place of NHCHO and OCH_3, respectively. The halogens



(d)

(e)

X = $COO^{\ominus}$, $\overset{H}{\underset{|}{C}}{=}O$; R^1, R^2, R^3 see Tables 2 and 3

F, Cl, and Br are tolerated in the α position but are reductively eliminated in the β position.[62, 63] The choice of R^2 is subject to the least number of restrictions. Branching in the β position leads to reduced activities. If R^2 and R^3 are interchanged (i.e., if the *E* and *Z* isomers of substrates of the type $R^3R^2C{=}CHX$ are used), different enantiomers are produced. Therefore, *E/Z* mixtures of substrates in which the β-C atom becomes chiral on reduction cannot be employed. Complications can arise, however, if whole cells are used, as we observed in the hydrogenation of (*E*)- and (*Z*)-geraniate (**1a** and **2a**). As shown in Figure 1, **1a** yields

pure (*R*)-citronellate **1b**, but **2a** is largely isomerized to the thermodynamically more stable (*E*) isomer **1a** by clostridia (presumably enzymatically) and thus also converted into the (*R*) enantiomer. The *ee* value is lower because some of **2a** is also reduced directly. Isolated enoate reductase must be used in this case (see Section 3.6 and Fig. 1).

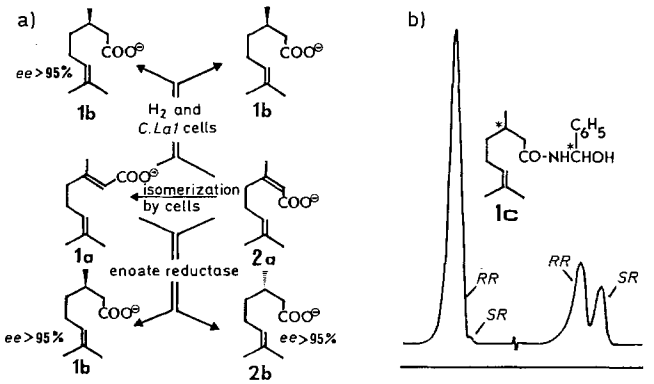
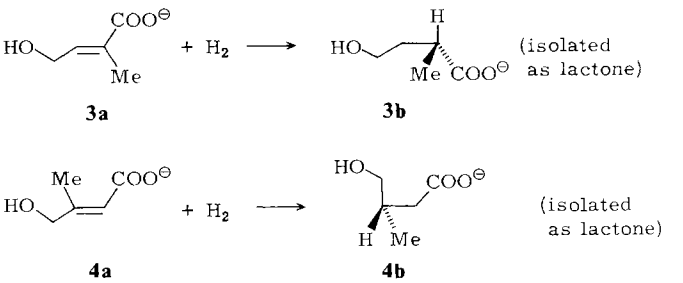


Fig. 1. Bioreduction of (*E*)- and (*Z*)-geraniate (**1a** and **2a**, respectively) to (*R*)- and (*S*)-citronellate (**1b** and **2b**, respectively). a) **1a** is hydrogenated to enantiomerically pure **1b** by *C. La1* cells with a productivity number of approximately 3000. The (*Z*) compound **2a** is reduced much more slowly and most of it is isomerized to **1a** prior to hydrogenation so that **1b** is formed with *ee* values between 60 and 85%. Pure **2b** can, however, be obtained if isolated enoate reductase is used for reduction. b) **1b** obtained after hydrogenation of **1a** with *C. La1* cells was derivatized to **1c** and then separated on 7-μ Lichrosorb columns by HPLC. (J. P. Lecomte et al., unpublished).

The high productivity numbers allow reactions to be carried out in small volumes. Products that are only chiral due to the stereospecific replacement of ^1H by ^2H on one or two methylene groups can therefore be obtained relatively easily by means of hydrogenation.[12,64] The cells are freeze-dried and then used in ^2H_2O buffer. H_2 can be used as an electron donor since 10^2—10^3 times more ^2H is present in the buffer than ^1H in the amount of hydrogen gas required. A preparative example has been described.[64]

Some of the hydrogenations that have so far been carried out are summarized in Tables 2 and 3. All compounds given in Table 3 had already been hydrogenated. It should be noted that nitro groups are reduced by whole cells but not by enoate reductase and NADH.[65] Figure 2 shows the time course of hydrogenation. Electron flow in the hydrogenation of α,β-unsaturated carboxylates and other carbonyl compounds with *C. La1* proceeds according to Route V (Table 1). (Hydrogenations without methyl viologen are possible but usually proceed slower.) There are two alternatives. If the rate at which the unsaturated substrate reacts with enoate reductase is greater than that at which the hydrogenase (E1) can reduce methyl viologen, the hydrogenation mixture is not initially blue. The solution only becomes blue due to reduced methyl viologen toward the end of the hydrogenation when the substrate concentration decreases and the enoate reductase is no longer saturated. If, however, the unsaturated substrate reacts relatively slowly so that the hydrogenase can reduce the methyl viologen rapidly enough, the solution remains blue throughout the entire reaction. Figure 2 shows that the hydrogenations of **3a** and **4a** with *C. La1* proceeded at about the same rates, although, according to Table 3, **3a** is reduced approximately twelve times more rapidly by enoate reductase than **4a**. Thus, the reduction of methyl viologen must be rate-limiting for the hydrogenation of **3a**. If **3a** is hydrogenated with a mixture of *C. La1* and *C. kluyveri* (the latter displays a considerably higher hydrogenase activity), the hydrogenation rate of **3a** can be increased by a factor of approximately 5. In the case of **4a**, this measure reduces the rate of hydrogenation because, although *C. kluyveri* has a higher hydrogenase activity than *C. La1*, its enoate reductase activity is lower. As will be demonstrated in Section 4.4, the conditions in an electrochemical cell are significantly different if the reduction of methyl viologen is not rate-limiting.



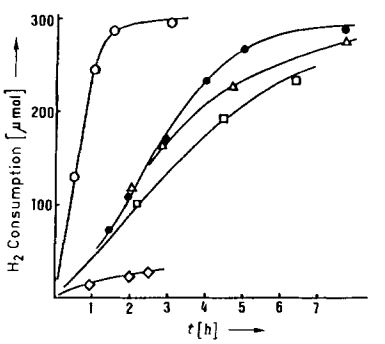
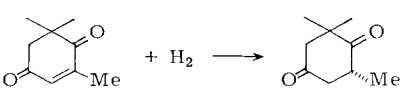


Fig. 2. Hydrogenation of a favorable (**3a**) and an unfavorable (**4a**) substrate of enoate reductase. 100 mM substrate was shaken at about 100 cycles per minute with 400 mg of cells (wet sediment) in 3.0 mL of phosphate buffer under 1 atm H_2 at 35 °C in a Warburg flask with a capacity of approximately 25 mL (manometer filled with Hg). ○—○ Hydrogenation of **3a** with 250 mg of *C. La1* and 150 mg of *C. kluyveri*; ●—● **3a** with only *C. La1*; △—△ **4a** with *C. La1*; □—□ **4a** with 250 mg of *C. La1* and 150 mg of *C. kluyveri*; ◇—◇ **4a** with only *C. kluyveri*. (The measurements were performed with *C. La1* cells that had been stored for 15 months and whose hydrogenase activity was about half of the normal value).

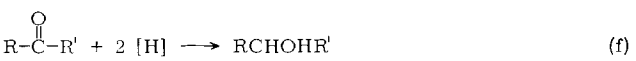
Although the pH maximum of Reaction (e) occurs at 5.2,[13] a pH of between 6.5 and 7.0 has proved to be optimal for the overall hydrogenation reaction. The hydrogenation of the diketone **5a** can also be carried out on a preparative scale—however, without methyl viologen (cf. Section 4.3).



In addition to α,β-unsaturated carboxylates and other carbonyl compounds, the CC double bonds of allyl alcohol derivatives can also be hydrogenated with *C. La1* or *C. kluyveri* cells. Enoate reductase does not, however, reduce allyl alcohol derivatives and the cells do not possess any other enzymes capable of catalyzing this reduction. It has been shown that the allyl alcohol derivatives are initially dehydrogenated to the corresponding aldehydes, and the CC double bonds of these compounds are then quickly reduced by enoate reductase. The aldehyde group is subsequently reduced back to an alcohol group. This is the reason why methyl viologen inhibits reduction in such cases; the entire NAD is rapidly reduced to NADH by H_2 and methyl viologen, and NAD is therefore not available for dehydrogenation of the allyl alcohol derivative. Ethanol is a more suitable electron donor in these cases.[39,40]

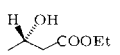
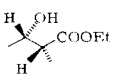
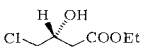
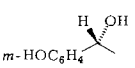
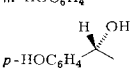
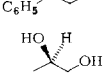
3.2. Hydrogenation of Ketones

Ketones can also be reduced to chiral secondary alcohols with clostridia such as *C. La1* or *C. kluyveri* [Reaction (f)]. Examples are given in Table 4. Excellent *ee* values can be obtained in a number of cases but low values are also encountered.



$$R{-}\overset{O}{\overset{\|}{C}}{-}R' + 2\,[H] \longrightarrow RCHOHR' \qquad (f)$$

Table 4. Reduction of ketones with clostridia. If not otherwise stated, H_2 was used as an electron donor.

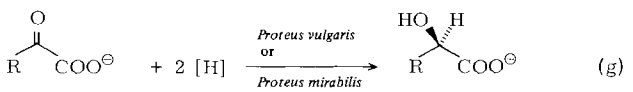
Microorganism	Product	*PN*	Enantiomer	*ee* [%]
C. kluyveri		1500	(*S*)	95[a]
C. kluyveri		80	(2*R*,3*S*)	81[b]
C. kluyveri		350	(*R*)	99[c]
C. kluyveri		6	(*R*)	94[c]
C. La1		4	(*R*)	96[c]
C. La1		22	(*R*)	94[c]
C. La1		11	(*R*)	91[c]
C. kluyveri		12	(*R*)	99[c,d]
C. kluyveri		3	(*R*)	98[c,d]
C. kluyveri and *Candida utilis*		3800	(*R*)	94
C. kluyveri and *Enterobacter agglomerans*		3300	(*S*)	—

[a] Determined by enzymatic analysis. [b] A racemic mixture of ethyl 2-methyl-3-oxobutyrate was used. The reaction mixture consisted of 81% ethyl (2*R*,3*S*)-3-hydroxy-2-methylbutyrate, 13% of the (2*R*,3*R*) form, 4% of the (2*S*,3*R*) form, and 2% of the (2*S*,3*S*) form. [c] Analysis: B. Koppenhöfer et al., unpublished. [d] 10% ethanol was used as an electron donor.

Sih et al.[1,21,27] have found that in the reduction of 4-chloro-3-oxobutyrate esters with bakers' yeast the *ee* value is a function of the size of the ester group. The methyl ester is hydrogenated to the (*S*) enantiomer with an *ee* value of 65%, whereas the octyl ester is converted to the (*R*) enantiomer with an *ee* value of 97%. For other alkyl residues of the type $(CH_2)_nH$ (n=2—7), the *ee* values lie between these two values. *C. kluyveri* hydrogenates the ethyl ester of 4-chloro-3-oxobutyrate to the (*R*) enantiomer with an *ee* value of >99% and an approximately 50-fold higher productivity number (*H. Simon* et al. and *B. Koppenhöfer* et al., unpublished). The enantiomeric purities of the phenylethyl and phenylpropyl alcohols obtained with *C. kluyveri* do not seem to have been reached yet by other means. In other cases (e.g., phenylglycol) the *ee* values are poor, but this has so far been seldom observed in clostridia. The very low productivity numbers also seem to be more of an exception.

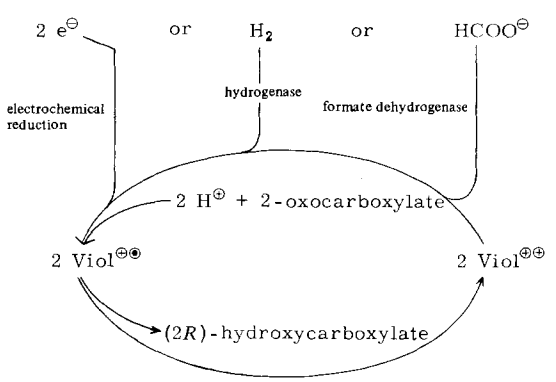
3.3. Hydrogenation of 2-Oxocarboxylates

A surprisingly wide range of 2-oxocarboxylate substrates can be reduced to (2*R*)-hydroxycarboxylates by *Proteus mirabilis* or *Proteus vulgaris* in the presence of methyl or benzyl viologen with very high enantiomeric purities.[47,66,67]



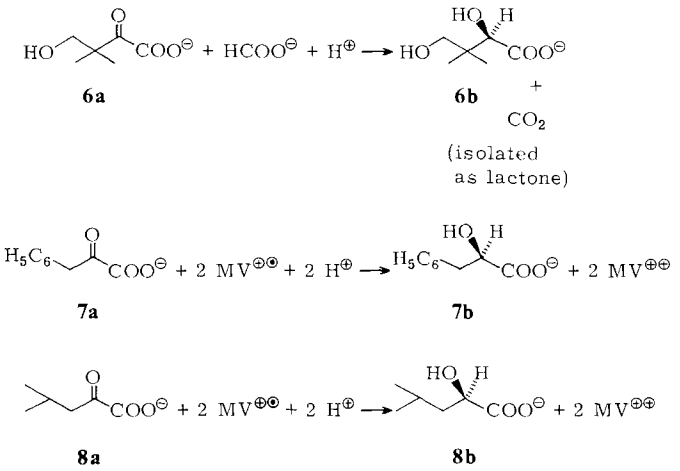
$$R{-}\overset{O}{\overset{\|}{C}}{-}COO^{\ominus} + 2\,[H] \xrightarrow[\text{or}]{\textit{Proteus vulgaris}} R{-}\overset{HO}{\overset{|}{C}}{-}H\ (COO^{\ominus}) \qquad (g)$$

This reaction is also based on an unknown type of enzyme which we have partially characterized (see Section 3.6). Instead of H_2, formate can be used as an electron donor in combination with a viologen. Since viologens (Section 4) can also be easily regenerated electrochemically, (2*R*)-hydroxycarboxylic acids may be obtained in three ways (Scheme 1), corresponding to Route V with



Scheme 1. *Proteus vulgaris* can be used with three different electron donors to synthesize (2*R*)-hydroxycarboxylic acids. $Viol^{\oplus\bullet}$ = oxidized methyl or benzyl viologen; $Viol^{\oplus\ominus}$ = reduced viologen. The mediator can be reduced either electrochemically or by H_2 gas and a hydrogenase present in the microorganism or by formate and a formate dehydrogenase also found in the microorganism.

$Do_{red} = H_2$ or $HCOO^{\ominus}$ and Route VI. Examples are the reductions of **6a**—**8a** to **6b**—**8b**.



6a **6b** **7a** **7b** **8a** **8b**

Figure 3 shows the time course of the reduction of 4-methyl-2-oxopentanoate **8a** to the corresponding (2*R*)-hydroxy acid **8b** with formate and H_2. As described in Section 4.4, productivity numbers of > 100000 can be obtained by determining and exploiting the kinetic parameters of the electrochemical reduction.

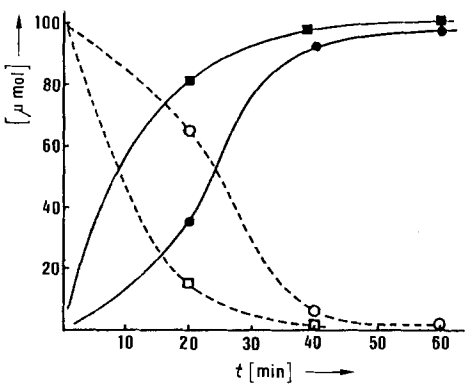


Fig. 3. Reduction of 4-methyl-2-oxopentanoate with *P. vulgaris* and H_2 or formate as an electron donor. Decrease in 4-methyl-2-oxopentanoate on reduction with H_2 ○--○--○ and with formate □--□--□ and formation of the product with H_2 ●—●—● and with formate ■—■—■.

Table 5. Relative rates for the reduction of 2-oxocarboxylates by a reductase found in *P. mirabilis* and *P. vulgaris*.

Substrate	Relative rate [%]	
	P. mirabilis	*P. vulgaris*
phenylpyruvate [a]	100	100
pyruvate [a]	92	85
2-oxobutanoate	40	65
indolylpyruvate	35	67
5-benzyloxyindolylpyruvate	30	—
3-fluoropyruvate	22	20
4-methyl-2-oxopentanoate	81	83
(*S*)-3-methyl-2-oxopentanoate	28	25
(*R,S*)-3-methyl-2-oxopentanoate	63	46
4-hydroxy-3,3-dimethyl-2-oxopentanoate [a]	7	4
phenylglyoxylate [a]	16	5
2-oxononanoate	83	93
2-oxododecanoate	27	46
2-oxotridecanoate	23	26
oxaloacetate [a]	73	50
2-oxoglutarate	78	62
2-oxoadipate	70	73
4-hydroxymethylphosphinyl(2-oxo)butanoate	24	6

[a] The enantiomeric purity of the products of these substrates was investigated by various methods. (*S*) enantiomers were not detected.

Table 5 provides a list of the substrates that can be reduced by *Proteus mirabilis* or *Proteus vulgaris* according to Scheme 1. Glyoxylic acid is so far the only 2-oxocarboxylate that does not react with this enzyme.

3.4. Hydrogenation with Two Microorganisms

As described in more detail in Section 4.2, crude extracts of *C. kluyveri* exhibit high activities for Reaction (h) in the presence of 1—2 mM methyl viologen. Reaction (h) corresponds to part of Route III.2 (Table 1). Yeasts, in particu-

$$H_2 + NAD(P)^{\oplus} \longrightarrow NAD(P)H + H^{\oplus} \qquad (h)$$

lar, demonstrate high reductase activities with certain carbonyl compounds, but the availability of NADH can be limiting. It therefore seemed reasonable to combine lysates from two species of cells; cell type 1 rapidly produces NADH using H_2 (or another electron donor): the NADH is then used by cell type 2 to reduce the unsaturated substrate. An example of this principle will be described in Section 4.4. 2(*R*)-Propanediol can, for example, be obtained in this way with a productivity number of up to 5700.[44] 3-Hydroxy-3-methyl-2-butanone can be hydrogenated to (*S*)-2,3-dihydroxy-2-methylbutane with a productivity number of 3300 (Table 4) by combining *C. kluyveri* and *Enterobacter agglomerans*. Aerobically cultured *Enterobacter agglomerans* cannot metabolize hydrogen, and *C. kluyveri* alone does not react with the ketone.

This method has the previously described advantages of high productivity numbers and simple control of the reaction (manometrically). In addition to *C. kluyveri*, *Alcaligenes eutrophus* can, for example, also be used for producing NADH according to Reaction (h). We found that crude extracts of cells that had been cultured according to *Schlegel* et al.[68] and then stored for 5 years at −15 °C still had a specific activity for NADH formation of 1 U/mg protein. Substrates for which the hydrogenase is rate-limiting (see Section 3.1) can also be more rapidly hydrogenated by employing a combination of *C. kluyveri* and *C. La1*.

3.5. Hydrogenations with Immobilized Cells

According to our experience,[69] clostridia can readily be immobilized with acrylic acid derivatives. These so-called photopolymerizable prepolymers introduced by *Tanaka* et al.[70] do not noticeably damage the cells. The observed decrease in activity can be accounted for solely by inhibition of diffusion. We have performed hydrogenations at room temperature for 63 d with immobilized *C. La1* cells in the presence of 2 mM methyl viologen. After 12 d the rate of H_2 uptake was still 50% of the starting rate. These immobilized preparations are highly suitable for storage. *C. kluyveri* stored in tris buffer with 50% glycerol did not show any decrease in activity after 150 d; under the same conditions *C. La1* cells lost 40% of their activity.[69] Purified enoate reductase can also be immobilized with photopolymerizable prepolymers. These substances are not, however, suitable for the immobilization of *Proteus mirabilis*, *Proteus vulgaris*, or the 2-oxocarboxylate reductases obtained from

these microorganisms. Ionotropic gels, such as alginates cross-linked with calcium ions, can be employed for these biocatalysts.[71] Since gels composed of photopolymerizable prepolymers are not very suitable for electrochemical cells in which rapid stirring is necessary, we have coated filter paper with alginate films containing immobilized enzymes. These systems have proved to be of value both for cells and for more or less purified enzymes. We have been able to increase the half-life of enoate reductase from approximately 6 h to 150 h in rapidly stirred electrochemical cells by using this approach.[61]

3.6. Kinetic Data for Enoate and 2-Oxocarboxylate Reductases

The pH optimum of enoate reductase with reduced methyl viologen is 5.2;[13] at pH 4.5 and 6.2 the rate is two-thirds that of the maximal value. A pH value of less than 5.2 should be avoided in an electrochemical cell. On the other hand, pH values of up to 8.0 do not seem to have a detrimental effect on the stability of the enzyme. A pH value of between 6.0 and 6.2 is recommended as a compromise between the stability of methyl viologen and the reaction rate of enoate reductase. A number of V_{max} and K_m values for substrates of enoate reductase are given in Table 3. The K_m values for reduced methyl viologen and NADH are 0.4 mM and 0.012 mM, respectively. A concentration of approximately 2 mM $MV^{\oplus\odot}$ thus seems appropriate for an optimal rate of Reaction (e). The K_i values for reduced and oxidized methyl viologen are so high that the rate is not affected when the total methyl viologen concentration is 3—4 mM. The K_m values for enoates vary over a range of two orders of magnitude. The smaller the K_m value, the later will the reaction rate be limited by the falling substrate concentration. The K_i values for aliphatic enoates and the reaction products are high (e.g., ca. 500 mM); hence, they are suitable for preparative purposes. The K_i values of aromatic products are, however, lower; the value for 3-phenylpropionate (15 mM) is the lowest that we have encountered so far. We have already reported in detail on the mechanisms and kinetics of the reductions of enoates with NADH.[58] The question arises, however, whether some of the values reported therein are different in the case of reduction with $MV^{\oplus\odot}$, as is found, for example, for the pH dependency of the reaction rate.

Table 6. Some typical K_m and K_i values for 2-oxocarboxylate reductase.

Substrate	K_m [mM]	Substrate/products	K_i [mM]
reduced methyl viologen	<0.05 [a]	reduced benzyl viologen	0.7 [b]
reduced benzyl viologen	0.1	benzyl viologen	10.0
phenylpyruvate	0.15	(*R*)-phenyllactate	100
4-methyl-2-oxopentanoate	2.1	(*R*)-2-hydroxy-4-methylpentanoate	100
4-hydroxy-3,3-dimethyl-2-oxobutanoate	7.5	4-hydroxy-3,3-dimethyl-2-oxobutanoate	50
2-oxoglutarate	2.5	phenylpyruvate	12
		4-methyl-2-oxopentanoate	70

[a] The hydrogenase of *Proteus vulgaris* has a K_m value of approximately 0.3 mM for reduced methyl viologen. [b] Concentration at which the reaction rate is half that found with 0.1 mM reduced viologen.

The 2-oxocarboxylate reductase from *Proteus vulgaris* displays a broad pH optimum with reduced methyl viologen. The maximum activity occurs at pH 7.0; the activity is still 80% of the maximal value at pH 6.0 and 8.0. Some typical K_m and K_i values are compiled in Table 6. The dependence of the reduction rate of 2-oxocarboxylates on the concentration of methyl viologen does not exhibit Michaelis-Menten behavior. The rate of reduction of a 2-oxocarboxylate increases with decreasing concentration of reduced methyl viologen until a concentration of <0.05 mM is reached! The behavior at lower concentrations cannot be followed due to experimental difficulties. Michaelis-Menten behavior was observed in the determination of the K_m values of various 2-oxocarboxylates. The K_m values vary greatly for different substrates but are suitable for preparative purposes. The K_i values of aliphatic substrates and products are favorable. The value for phenylpyruvate is relatively low but that of the product is again suitable. In practice this is of little importance. For instance, 100 mM solutions of phenylpyruvate can be reacted in the electrochemical cell with productivity numbers of >100000. The surprising behavior of 2-oxocarboxylate reductase toward oxidized methyl viologen plays an important part here. As shown in Table 7, oxidized methyl viologen is a positive effector—i.e., depending on the concentration of the reduced methyl viologen, the enzyme activity can be augmented by a factor of three to six by adding oxidized methyl viologen. The $MV^{\oplus\odot}/MV^{\oplus\oplus}$ ratio can easily be adjusted in an electrochemical cell by means of the cathode potential, thus allowing very high enzyme activities to be achieved.

Table 7. Influence of oxidized methyl viologen on the rate of reduction of a 2-oxocarboxylate.

0.14 mM $MV^{\oplus\odot}$ with increasing concentrations of $MV^{\oplus\oplus}$ [mM]	Ratio $MV^{\oplus\odot}/MV^{\oplus\oplus}$	Relative rate	1.6 mM $MV^{\oplus\odot}$ with increasing concentrations of $MV^{\oplus\oplus}$ [mM]	Ratio $MV^{\oplus\odot}/MV^{\odot\odot}$	Relative rate
0.02	7	18.1	0.02	80	10.2 [a]
0.07	2	41.9	0.8	2	29.3
0.14	1	46.0	1.6	1	33.7
0.7	0.2	62.0	8.0	0.2	53.1
			17.8	0.09	61.5

[a] The different rates obtained with the same $MV^{\oplus\odot}/MV^{\oplus\oplus}$ ratio are presumably due to the inhibitory effect of high $MV^{\odot\odot}$ concentrations.

4. Electromicrobial Reductions

4.1. Principles

The enoate reductase of *C. La1* and 2-oxocarboxylate reductase are enzymes that do not have to or cannot accept electrons from NADH or NADPH, but can accept them from reduced viologens. Since viologens can be reduced in electrochemical cells, unsaturated substrates can be stereospecifically reduced electrochemically with the aid of microorganisms containing enzymes such as enoate reductase or 2-oxocarboxylate reductase. Only one enzyme is

then required. The electron flow is described by Route VI.

We have also discovered that a large number of microorganisms catalyze Reactions (i) and (j) (see Section 4.2):[44,72]

$$2MV^{\oplus\ominus} + H^{\oplus} + NAD^{\oplus} \longrightarrow 2MV^{\oplus\oplus} + NADH \quad (i)$$

$$2MV^{\oplus\ominus} + H^{\oplus} + NADP^{\oplus} \longrightarrow 2MV^{\oplus\oplus} + NADPH \quad (j)$$

Reductions can thus be performed electrochemically with a variety of different microorganisms. Figure 4 shows a current-time curve for such a reaction. The reactions that occur are described by Equations (k), (i), and (l), which can be added together to give Equation (m):[72]

$$2MV^{\oplus\ominus} + 2e^{\ominus} \xrightarrow{\text{electrochemical}} 2MV^{\oplus\ominus} \quad (k)$$

$$H^{\ominus} + 2MV^{\oplus\ominus} + NAD^{\oplus} \xrightarrow[\text{other microorganisms}]{\text{yeast or}} 2MV^{\oplus\oplus} + NADH \quad (i)$$

$$H^{\oplus} + NADH + CH_3COCH_2OH \xrightarrow{\text{yeast}} NAD^{\oplus} + CH_3CHOHCH_2OH \quad (l)$$

$$CH_3COCH_2OH + 2H^{\oplus} + 2e^{\ominus} \longrightarrow CH_3CHOHCH_2OH \quad (m)$$

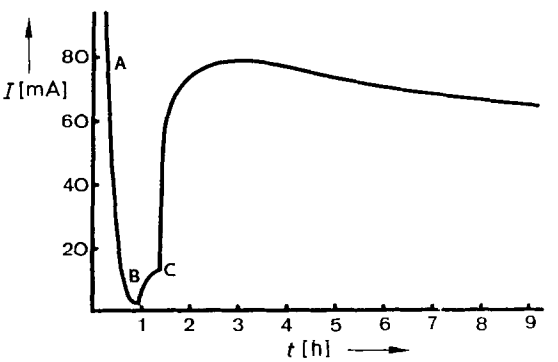


Fig. 4. Hydroxyacetone (40 mmol), methyl viologen (1.2 mmol), and NAD (0.1 mmol) were reduced in 200 mL of potassium phosphate buffer solution (0.1 M, pH 7.0). *Candida utilis* (175 mg, dry weight) was added at B and *C. kluyveri* (7.6 mg, dry weight) at C at -792 mV vs. the saturated calomel electrode. A current of 93 mA was obtained after adding a further 350 mg of *Candida utilis*, 3.8 mg of *C. kluyveri*, and 0.1 mmol of NAD. After a total of 140 h, 33 mmol of propanediol had formed and 2 mmol of hydroxyacetone was still present.

(2*R*)-1,2-Propanediol can be obtained by this method[47,72,73] with a 20- to 50-fold higher productivity number than that found for a procedure published in Organic Synthesis.[74]

4.2. Types, Sources, and Applications of Methyl Viologen-Dependent NAD and NADP Reductases for NAD(P)H Regeneration

Table 8 shows that many microorganisms catalyze Reactions (i) and (j).[44,47] These activities are of interest for the regeneration of NADH and NADPH, although their values vary by several orders of magnitude in different organisms. In order to evaluate these numbers it should be remembered that 0.1 U/mg protein corresponds to a productivity number of 3000 (see Section 2.1).

Table 8. Specific activities of methyl viologen-dependent NAD(P) reductases in crude extracts of various microorganisms (room temperature if not otherwise stated).

Microorganism	Source [a]	μmol / min × mg protein NAD	NADP
Anaerobic organisms			
Clostridium kluyveri	DSM 555	16.6	3.3
Clostridium La1	DSM 1460	2.4	0.31
Clostridium tyrobutyricum	DSM 663	3.3	0.55
Clostridium tyrobutyricum	ATCC 25755	1.2	0.79
Clostridium acetobutylicum	DSM 1731	0.77	0.81
Clostridium pasteurianum	DSM 525	0.17	0.05
Clostridium propionicum	ATCC 25522	1.02	0.04
Clostridium bifermentans	ATCC 638	1.56	1.1
Clostridium difficile	ATCC 9689	0.13	0.13
Clostridium ghoni	ATCC 25757	2.7	0.46
Clostridium hastiforme	ATCC 25772	1.2	0.25
Clostridium mangenoti	ATCC 25761	0.69	0.23
Clostridium oceanicum	ATCC 25647	1.03	0.38
Clostridium putrificum	ATCC 25784	0.55	0.60
Clostridium sordellii	ATCC 9714	1.96	1.5
Clostridium sporogenes	ATCC 3584	4.62	0.61
Clostridium sticklandi	DSM 519	0.29	0.79
Clostridium symbiosum	ATCC 14940	0.47	0.045
Peptococcus aerogenes	ATCC 14963	0.54	3.2
Peptostreptococcus anaerobius	DSM 20357	0.29	0.06
Acidaminococcus fermentans	ATCC 25085	1.3	0.24
Eubacterium limosum	DSM 20402	1.14	1.03
Methanobacterium thermoautotrophicum	DSM 2133 [b]	0.33	0.25
Desulfurococcus mobilis	DSM 2161 [c]	0.86	23.5
Thermoproteus tenax	DSM 2078 [c]	0.46	1.0
Thermococcus celer	DSM 2476 [c]	0.33	4.6
Aerobic organisms			
Candida utilis	DSM 70167	0.18	0.023
Candida boidinii	DSM 70026	0.066	0.013
Candida valida	DSM 70178	0.040	0.011
Rhodotorula glutinis	DSM 70389	0.10	0.007
Bakers' yeast		0.018	0.012
Geotrichum candidum	DSM 1240	0.16	0.10
Bacillus cereus	DSM 31	0.022	0.059
Bacillus macerans	DSM 24	0.016	0.076
Bacillus spec.	DSM 406	0.1	—
Alcaligenes eutrophus H 16	DSM 428	0.80	0.026
Aeromonas hydrophila	ATCC 13137	0.13	0.071
Enterobacter agglomerans	NCTC 9381	0.013	0.016
Escherichia coli	ATCC 10536	0.04	0.01
Klebsiella aerogenes	DSM 30102	0.12	0.07
Proteus mirabilis	DSM 30115	0.09	0.03
Pseudomonas fluorescens	DSM 50090	0.095	0.025
Pseudomonas aeruginosa	DSM 50071	0.086	0.010
Micrococcus luteus	DSM 20030	0.12	0.010
Staphylococcus aureus	DSM 20231	0.008	0.011
Staphylococcus carnosus	DSM 20501	0.011	0.015
Lactobacillus casei	ATCC 7469	0.001	0.001
Propionibacterium pentosaceum	DSM 20272	0.04	0.008
Sulfolobus solfataricus	DSM 1616	0.027	0.21

[a] DSM = Deutsche Sammlung Mikroorganismen, Göttingen. ATCC = American Type Culture Collection, Rockville, MD, USA. NCTC = National Collection of Type Cultures, London, England. [b] Determined manometrically by measuring the H_2 consumption. [c] Test at 80°C.

Four groups of microorganisms can be distinguished in Table 8:

1. Anaerobic eubacteria, in particular clostridia: These organisms contain NAD(P) reductases with high activities. If they contain a hydrogenase, the formation of hydrogen [Reaction (n)] may compete with Reactions (i) and/or (j).

$$2H^{\oplus} + 2MV^{\oplus\ominus} \xrightarrow{\text{hydrogenase}} 2MV^{\oplus\oplus} + H_2 \quad (n)$$

C. kluyveri is particularly advantageous at room temperature. This organism exhibits very high NAD(P) reductase

activities and the hydrogenase activity only amounts to about 10% of the value for the NAD reductases.

2. Archaebacteria: Methanogenic bacteria oxidize reduced methyl viologen mainly with production of H_2. The three thermophilic, sulfur-reducing archaebacteria that have so far been tested contain surprisingly high levels of NADP reductase activity. In two cases these activities are one order of magnitude higher than that for NADH formation.

3. Yeasts: They display lower NAD(P) reductase activities but do not contain any hydrogenases, which is of advantage for electromicrobial reductions.

4. Aerobic eubacteria: The majority of the aerobic eubacteria tested contain lower activities than the anaerobic bacteria.

The nature of the methyl viologen-dependent NAD(P) reductases is not always clear. A number of NAD(P)H-dependent flavoproteins catalyze these reactions. Diaphorase has already been used in practice.[54] In addition, Reactions (i) and (j) are known to take place with the hydrogenase from *Alcaligenes eutrophus*[76] and plant ferredoxin-NADP oxidoreductase,[77] respectively. Reactions (i) and (j) do not, however, seem to have been studied quantitatively so far. The measured activities of a series of enzymes for Reactions (i) and (j) are given in Table 9 and compared with the physiological activities of these enzymes. The following enzymes, which might have been expected to catalyze Reactions (i) and (j) on account of their structure, display low activities and are of little interest for practical purposes: glutathione reductase from yeast, NAD(P)H FMN reductase from *Photobacterium fisheri* and NADH dehydrogenase from the thermophilic bacterium *Bacillus spec* DSM 406. A very stable, methyl viologen-dependent NAD reductase can, however, be obtained from the latter microorganism; its activity as an NADH dehydrogenase with 2,6-dichlorophenolindophenol as an acceptor is low. This clearly shows that NADH dehydrogenase activity does not necessarily parallel the activity as a methyl viologen-dependent NAD reductase. The activity of the methyl viologen-dependent NAD reductase from *Bacillus spec.* DSM 406 remains practically constant over 50 d at 35 °C in a dilute solution.

In all entries in Table 9 in which the stereochemistry of [4-^{2}H]NAD(P)H formation is not accompanied by a literature reference, we prepared NADH or NADPH in an electrochemical cell using ^2H_2O buffer and determined which enantiomer was produced by means of NMR spectroscopy.[44] The method used to determine the stereochemistry has already been described.[78]

4.3. Construction of an Electrochemical Cell

Cathodes with a high overvoltage for hydrogen formation must be used for electrochemical reductions in water. Only the mediator and not the substrate must be electrochemically reduced; this can be checked by means of cyclovoltammetry.[81] Moreover, the mediator must not react spontaneously with the substrate. So far we have observed spontaneous reactions between reduced methyl viologen and the following substrates: phenylglyoxylate, ethyl 4-chloro-3-oxobutyrate, and **5a**. Phenylglyoxylate can be reacted in the presence of benzyl viologen; the two other compounds are reacted with H_2 and *C. kluyveri* without a mediator.

Gold, silver, carbon, and particularly mercury are suitable for use as cathode materials when working in the neu-

Table 9. Enzymes that have been tested for the reduction of NAD(P) with reduced methyl viologen. Initial rates for Reactions (i) and (j) and comparison of this activity with the physiological reduction or dehydrogenation of NAD(P)H in the presence of an artificial acceptor. All specific activities are for two electron transfers (μmol/mg protein × min). If not otherwise stated the tests were performed at pH 7.0 and room temperature in 0.1 M tris acetate buffer. The NAD(P) concentration was 2.5 mM, that of $MV^{\oplus\odot}$ was 1.8 mM. In order to determine the stereochemistry, NAD(P) was reacted with the relevant enzyme in an electrochemical cell (Fig. 5a) in ^2H_2O buffer [44].

Enzyme (EC number)	Physiol. reaction or NAD(P)H dehydrogenase reaction	Specific activity	$MV^{\oplus\odot}$/NAD	$MV^{\oplus\odot}$/NADP	Stereochemistry of [4-^{2}H]NAD(P)H [ref.]
lipoamide reductase (diaphorase) (1.6.4.3)	NADH/lipoamide	62	46	0.15	*S* [79]
diaphorase from microorganisms (Boehringer Mannheim)	NADH/*p*-iodonitrotetrazolium chloride	0.6	1.1	0.03	—
glutathione reductase from yeast (1.6.4.2)	NADPH/GSSG	98	0.02	0.06	—
NADPH-cytochrome P450 reductase from rat liver (1.6.2.4) [a]	NADPH/cytochrome c	6.5	1.2	15.2	*R*
hydrogenase from *Alcaligenes eutrophus* (1.12.1.2)	H_2/NAD	1.5 [b]	70	—	*S* [80]
NADH-cytochrome c reductase from porcine heart (1.6.99.3)	NADH/cytochrome c	0.16	0.22	0.001	*S*
NAD(P)H-FMN reductase from *Photobacterium fisheri* (1.6.8.1)	NADH/FMN	10	0.1	0.1	—
xanthine oxidase (1.2.3.2)	NADH/hypoxanthine	0.16	0.04	0.02	—
enoate reductase (1.3.1.31)	NADH/(E)-2-methylbutenoate	12	7	0.01	*S*
NADH dehydrogenase from *Bacillus spec.* DSM 406 (membrane-bound) [c]	NADH/dichlorophenolindophenol	61	1.5		—
NADH dehydrogenase from *Bacillus spec.* DSM 406 (soluble) [c]	NADH/dichlorophenolindophenol	8.8	44		*S*

[a] We are grateful to Prof. *V. Ulrich*, Constance, for this preparation. [b] The preparation had been stored for about 1 year. [c] Enzymes were isolated by *S. Nagata* in our laboratory (unpublished).

tral pH range and with potentials of approximately −450 mV versus the saturated calomel electrode (all potentials in this review are given versus this electrode). In the case of more negative potentials (e.g., −640 V), lead, bismuth, antimony, and tin cathodes are suitable. The potential is fixed in a standard three-electrode arrangement (Fig. 5). If cathode surface areas of <250 cm^2 are used, 200-mA potentiostats with a maximal terminal voltage of 15 volts are suitable.

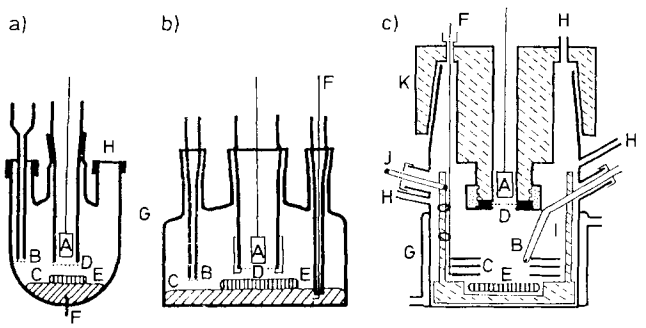


Fig. 5. Different electrochemical cells. a) 50-mL three-necked flask; b) 200-mL five-necked flask (two necks not shown); c) 70-mL cell with multiring carbon electrodes. A, platinum electrode; B, Luggin-Haber capillary for the reference electrode (saturated calomel electrode); C, mercury cathode in a) and b); D, diaphragm; E, stirring rod; F, cathode contact; G, glass vessel, in c) it can be thermostated; H, opening for taking samples and gassing with N_2; I, device for holding the cathode; J, device for preventing I from rotating; K, PVC lid and anode chamber.

Nafion membranes with a thickness of 0.5 mm have proved to be suitable for use as diaphragms in cells of over 50 mL. Vycor tips are also suitable for smaller cells (Fig. 5a). The diaphragm must satisfy the following requirements: it must allow proton transfer from the anolyte to the catholyte in which the protons are consumed (e.g., in Reaction (m)); it must be sufficiently conductive and prevent oxygen from passing from the anolyte to the catholyte. Oxygen reacts with reduced methyl viologen at a diffusion-limited rate. The superoxide radical anion formed[82,83] and its subsequent products can react with the enzymes, substrates, products, and mediator. Furthermore, the presence of oxygen results in an apparent rate of enzyme reaction that is too high. Potential differences of $> \pm 30$ mV should be avoided by means of proper design of the symmetry of the cathode.

Cells with mercury cathodes are especially easy to handle in the laboratory. A current of approximately 1 mA can be produced per cm^2 mercury surface area in solutions which contain 3 mM oxidized methyl viologen when the cell is in the stationary operational state. A current of 3.2 mA reduces 1 μmol of substrate per minute with two reduction equivalents.

Since it is easy to accomodate 10^2–10^4 U of enzyme activity in 100 mL of catholyte, especially if the enzyme is enriched, the preparative capacity of the operating cells is usually limited by the reduction of methyl viologen. The cells should therefore be operated under diffusion-controlled conditions. The diffusion layer on the cathode should be kept as thin as possible by, for example, efficient stirring (magnetic stirrer) or rotation of the cathode; this also results in thorough mixing of the reaction solution.

4.4. Practical Aspects of Performing Electromicrobial and Electroenzymatic Reductions

The optimal concentrations of oxidized and reduced methyl viologen, as well as the substrate concentration, depend on the kinetic parameters of the enzymes. For instance, enoate reductase and 2-oxocarboxylate reductase differ considerably in this respect (see Section 3.6). This also applies if cells or cell extracts are used that contain these enzymes. In the case of enoate reductase, 2–3 mM reduced methyl viologen should be present; the concentration of oxidized methyl viologen does not affect this enzyme.

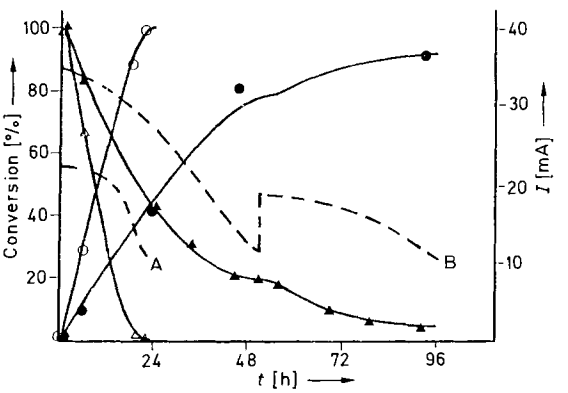


Fig. 6. Time course of the electromicrobial reduction of 30 mM (*Z*)-2-fluorocinnamate and 30 mM **4a** by 122 mg of *C. La1* and 184 mg of *C. La1*, respectively, in the cell shown in Figure 5c. Δ—Δ, Decrease in fluorocinnamate; O—O, formation of (2*R*)-2-fluoro-3-phenylpropionate; A, the observed current-time course in this reaction. ▲—▲, decrease in **4a**; ●—●, formation of **4b**; B, current-time course in this reaction. After 50 h, a further 70 mg of *C. La1* was added. The methyl viologen concentration was 3 mM, $T = 28$ °C, 36 mL of 100 mM phosphate buffer (pH 6.3), cell dry weights.

Figure 6 shows the reduction of (*Z*)-2-fluorocinnamate and of **4a** in an electrochemical cell (Fig. 5c) with *C. La1*. (*Z*)-2-Fluorocinnamate has a higher V_{max} value than **4a** and a much smaller K_m value (Table 3). This has the following consequences: (*Z*)-2-fluorocinnamate is reduced considerably faster than **4a** and the current yield is appreciably higher; this applies particularly to the reaction of the last third of the substrate and is mainly a result of the approximately 100-fold more favorable K_m value of fluorocinnamate. H_2 is produced from reduced methyl viologen (Reaction (n)) by the hydrogenase present and this reaction competes with the reduction of both substrates. Fluorocinnamate is reduced with a current yield of approximately 50%, whereas the current yield for the reduction of **4a** is ca. 10% during the first 5 h, ca. 7% after 24 h, and merely 4.5% after 72 h. The current is therefore mainly used for H_2 formation.

The current-time course during the reduction of phenylpyruvate with *Proteus vulgaris* is shown in Figure 7. The reaction is started by adding oxidized methyl viologen. The potential is adjusted in such a way that the optimal ratios given in Table 7 are obtained. A solution containing <0.1 mM reduced methyl viologen is sky blue. The subsequent current-time course can be qualitatively interpreted from the kinetic data given in Table 6. Phenylpyruvate causes substrate inhibition and has a low K_m value. As the

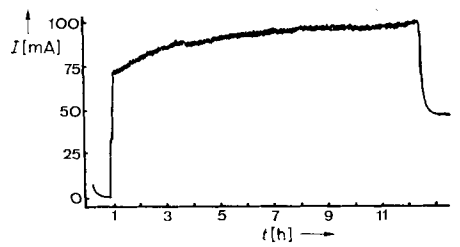


Fig. 7. Current-time course during the electromicrobial reduction of **7a** to **7b**. For further details see Experimental Procedure.

total concentration decreases, the enzyme activity and thus the current increase. Because of the K_m value, the reaction rate only begins to fall when substrate conversion is >98%, but then decreases very sharply. The solution becomes dark blue within one minute. The reason for this is that the steady state of the consecutive reaction sequence—the electrochemical reduction of methyl viologen and its reoxidation by the enzyme—collapses due to lack of substrate. The current does not fall to zero because *Proteus vulgaris* possesses hydrogenase. This reaction is of no importance until the phenylpyruvate is exhausted because the hydrogenase has the relatively large K_m value of 0.3 mM for reduced methyl viologen and up to this point the concentration of reduced methyl viologen is <0.05 mM. The product of current and time between the current increase and decrease shown in Figure 7 corresponds to the quantity of phenyllactate formed.

Typical Experimental Procedures

The cultivation of *C. La1*, *C. kluyveri*, *P. mirabilis*, and *P. vulgaris* has been described [57, 66, 67]. After the stationary growth phase has been reached, the cells are centrifuged off at ca. 5000 g and stored at approximately −15 °C under exclusion of air without being washed. The dry weight of the sediment amounts to about 20% of the wet weight. Hydrogenations are performed in 0.1 M potassium phosphate buffer (pH 7.0) under normal pressure in an H_2 atmosphere with shaking (approximately 200 cycles per min) at 35 °C and carried out in the presence of 0.4 mg tetracycline/10 mL buffer to prevent growth of other microorganisms. All experiments are performed under strict exclusion of oxygen. The H_2 consumption is read from a Warburg manometer that is filled with mercury and connected to the hydrogenation vessel. Quantities of cells are expressed as dry weights.

1. Hydrogenation of **1a** to **1b** with *C. La1*: The substrate (0.70 mmol) was completely hydrogenated in 4.5 h in 26 mL of buffer containing the cells (150 mg) and 1 mM methyl viologen (see Fig. 1).

2. Hydrogenation of **3a**, **4a**, and **5a**: *C. La1* cells (1.6 g), methyl viologen dihydrochloride (12 mg), and **3a** (6.0 mmol as the sodium salt) in 40 mL of buffer were hydrogenated for ca. 3—4 h in a shaking flask with a capacity of approximately 200 mL which was connected to a 2.5-L H_2 reservoir. **3b** was isolated in the form of a lactone; no contaminants could be detected by gas chromatography after distillation. **4b** was prepared from **4a** in an analogous fashion. The enantioselectivity of both reactions was >96%. **5a** (6 mmol) was hydrogenated with *C. kluyveri* cells (1.6 g) in 52 mL of buffer without methyl viologen in 3.5 h (*ee*>96%). (We are grateful to Dr. *H. G. Leuenberger* and Dr. *M. Schmid*, Hoffmann-La Roche, Basel, for the analyses.)

3. Reduction of **6a** to **6b** with *Proteus vulgaris* and formate: a mixture (90 mL) containing 85 mM phosphate buffer, 33.3 mM **6a** (as the sodium salt), 65 mM sodium formate, *Proteus vulgaris* (600 mg), and 1.0 mM benzyl viologen was shaken for 21 h at 35 °C under N_2. The resulting solution contained 32 mM **6b**; no **6a** could be detected. **6b** was isolated as the pantolactone. $[\alpha]_D^{25}$ −51.1 (H_2O, c=30 mg/mL). *ee*>99.5% (determined by gas chromatography). (We are grateful to BASF AG for this analysis).

4. Electromicrobial reduction of **7a** to **7b**: 0.1 M potassium phosphate buffer (200 mL, pH 7.0) containing 100 mM **7a** was flushed free of oxygen with N_2 in the cathode compartment of an electrochemical cell (Fig. 5b) and mixed with a suspension of *Proteus vulgaris* (15 mg dry weight). The cathode potential was set to −900 mV with respect to a saturated calomel electrode. A current of 70 mA flowed after addition of sufficient methyl viologen to give a 6 mM solution. The maximum current (100 mA) was obtained shortly before the end of the reaction, and the subsequent drop in current showed that the substrate was totally consumed (Fig. 7). The quantity of charge taken up at this point corresponded to a conversion of 99%. No remaining substrate could be detected by HPLC. The productivity number was 117000.

5. Electromicrobial reduction of **8b** to **8a**: The cathode compartment of the electrochemical cell contained 0.1 M potassium phosphate buffer (41 mL, pH 7.0) and 0.6 M **8a**. The diaphragm consisted of a 3.6-cm^2 Nafion cation exchange membrane; 10 mL of the above phosphate buffer served as an anolyte. Oxygen dissolved in the catholyte was removed by flushing with N_2. *Proteus vulgaris* (15.1 mg) was then added and the cathode potential set to −760 mV. After addition of sufficient methyl viologen to give a 6 mM solution and stirring at a rate of 400—500 rpm, a current of 120 mA was obtained. According to HPLC, 96% of the expected quantity of **8b** was formed after 12 h. $[\alpha]_D^{25}$ +11.1 (H_2O, c=20.7 mg/mL). If the concentration dependence is taken into consideration, this corresponds to the reported values [84, 85]. The productivity number was approximately 125000.

5. Outlook

The methodology of biocatalytic, enantioselective reductions of unsaturated compounds has undergone considerable development over the past few years. A number of efficient procedures for NADH regeneration are now available. The groups led by *Whitesides*[45] and *Jones*[48] have synthesized a variety of compounds on a laboratory scale using NADH regeneration. Amino acids can even be prepared on a commercial scale with kg prices of approximately 50 DM as a result of the studies performed by the groups of *Kula*, *Wandrey*, and *Leuchtenberger*.[43,86] This new battery of methods is, however, still used relatively seldom in preparative organic chemistry.

It can be assumed that further microorganisms and reductases will be found for reductions. These methods must, however, compete with other developments: namely, synthetic chiral hydrogenation catalysts and enzymes other than reductases. The latter include esterases that have recently often been employed to selectively cleave the esters of secondary alcohols;[87-89] also noteworthy are the syntheses of chiral secondary alcohols by biocatalytic condensation reactions.[90] Syntheses in which a center of chirality obtained by biocatalysis is utilized in subsequent sterically controlled reactions will probably also be developed further. For instance, *Reetz*[91] recently demonstrated the possibilities that are opened up by addition reactions with chiral α- and β-alkoxycarbonyl compounds.

We assume that many applications will also be found for the microbial hydrogenation and electromicrobial and electroenzymatic reductions that we have investigated during the past few years. It would also be interesting if other reductases such as enoate and 2-oxocarboxylate reductase could be discovered that are highly stereoselective, can react with a wide spectrum of substrates, and can also accept electrons from artificial mediators which can be electrochemically regenerated. We believe electrochemical regeneration, e.g., of reduced methyl viologen, to be superior in many respects to that obtained with the system light/[Ru(bpy)$_3$]/ethylenediaminetetraacetic acid.[92]

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Syntheses with Radicals—C-C Bond Formation via Organotin and Organomercury Compounds

New Synthetic Methods (52)

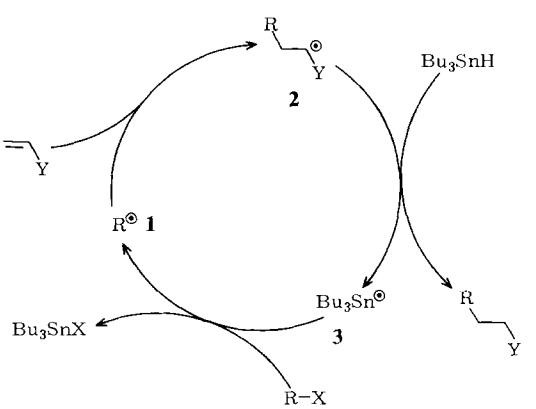
By Bernd Giese*

Dedicated to Professor Rolf Huisgen on the occasion of his 65th birthday

C–C bond formation is one of the most important synthetic steps in the construction of organic molecules. In the last few years it has been increasingly achieved by radical addition to alkenes. In such reactions the adduct radicals have to be trapped by an donor subsequent to the C–C bond formation in order to prevent polymerization. This task can be accomplished with organotin and organomercury hydrides, the use of which has led to new synthetic methods. The occurrence of radical chain reactions in which reactions take place between radicals and nonradicals is decisive for the success of the synthesis. In these cases small amounts of radical initiators suffice and numerous functional groups may be used in the C–C bond-forming reactions. The yields and selectivities of these radical reactions are often very high.

1. Introduction

Until a few years ago radicals were still a domain for mechanistically oriented research; a wealth of experimental data has led to a deeper understanding of their chemistry. Nowadays radical reactions are increasingly employed in synthesis, wherein the product is formed through reactions of radicals either with other radicals or with molecules whose electron spins are paired. In radical-radical reactions, the radicals must be continuously generated, so that at least equivalent amounts of radical initiators are required. Examples are the coupling reactions of electrochemically generated radicals[1] or the dimerization of capto-dative stabilized radicals developed by *Viehe* et al.[2] in recent years. Methods in which the products are produced in reactions between radicals and nonradicals are fundamentally different. These syntheses, occurring via radical chain reactions, require only small amounts of radical initiators, as shown, e.g., by the radical addition of alkyl halides to alkenes in the presence of tributyltin hydride.[3] The radicals **1**–**3** react with nonradicals (alkenes, tributyltin hydride, alkyl halides) with the formation of new radicals.



Radical chain reactions such as the $S_{RN}1$ reactions,[4] the additions of molecules with activated carbon-halogen[5] or carbon-hydrogen bonds,[6] the Minisci alkylations,[7] and the Meerwein arylations[8] have already been described in detail. The subject of this review is the C–C bond-forming reactions developed in recent years using organotin or organomercury compounds.

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2. Conditions for Radical Chain Reactions

In order that a radical chain reaction be synthetically useful, as little radical initiator as possible should be required and few side products should form. This is possible only if the chain propagating radicals meet certain conditions of reactivity and selectivity.

2.1. Reactivity Requirements

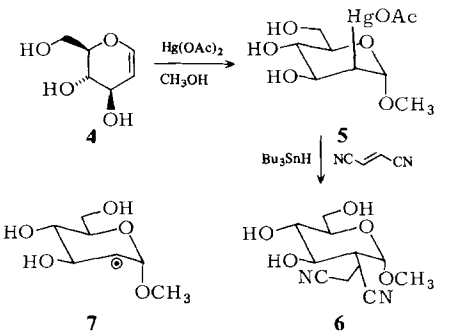
Chain reactions are terminated by combination or disproportionation of the radicals. Therefore, the rate of reaction, r_c, between radicals and nonradicals should be higher than that of the chain termination step, r_t. Equations (a) and (b) are the analytical expressions for these reactions, where k_c and k_t are the rate constants for chain propagation and chain termination, respectively; $R^{\odot}$ represents all occurring radicals, X any added reagents. The reactivity requirement that must be satisfied for the use of the radical chain reaction in synthesis is given by Equation (c).

$$r_c = k_c[R^{\odot}][X] \quad (a)$$

$$r_t = k_t[R^{\odot}][R^{\odot}] \quad (b)$$

$$1 < \frac{r_c}{r_t} = \frac{k_c \cdot [X]}{k_t \cdot [R^{\odot}]} \quad (c)$$

In most cases, carbon radicals react with each other in a diffusion-controlled manner; the rate constants k_t are about 10^9 L·mol^{-1}·s^{-1}, and only a very small temperature dependence is observed.[9] The concentration of the added reaction partner X is dependent on the reaction conditions. In order to evaluate the magnitude of k_c necessary for synthetic purposes, [X] = 1 mol·L^{-1} should be chosen. The concentrations of radicals in chain reactions also depend on the reaction conditions which, e.g., determine the rate of decomposition of the initiators. Typically, the radical concentrations in chain reactions are around 10^{-7} mol L^{-1}.[9] Inserting these values of [X] and [$R^{\odot}$] into Equation (c), it is seen that in radical chain reactions k_c has to be larger than 10^2 L·mol^{-1} s^{-1}. Accordingly, rate constants greater than 10^2 L·mol^{-1} s^{-1} are required for synthetically useful reactions between carbon radicals and nonradicals. This limiting factor can be of advantage in the planning of a synthesis because it means that a range of functional groups can be tolerated without protection. Thus, the homolysis of O–H and N–H bonds in aliphatic alcohols and amines by alkyl radicals,[9] as well as the addition of alkyl radicals to the C=O groups[10] of ketones and esters, takes place with rate constants k_c that are smaller than 10^2 L·mol^{-1} s^{-1} at room temperature. Therefore, these functional groups are not attacked in intermolecular radical C–C bond-forming reactions. In other words, carbon radicals exhibit high chemoselectivity and their employment in reactions with more complex molecules should be considered. For example, the C-branched carbohydrate **6** can be synthesized from the glucal **4** without the use of protecting groups. The carbon-carbon bond formation, via homolysis of the C–Hg bond in **5**, attack of fumaronitrile on the radical **7**, and subsequent hydrogen transfer, affords the product **6** in about 50% overall yield.[11]



2.2. Selectivity Requirement

The second condition that must be fulfilled in radical chain reactions concerns the selectivities of the radicals. Only when these differ sufficiently from each other will synthetically useful radical chain reactions result. Thus, the formation of products from alkyl halides and alkenes in the presence of tributyltin hydride takes place in good yields when the selectivity of the adduct radicals **2**, due to the substituent Y, is markedly different from that of the radical **1**. If **1** is a nucleophilic alkyl radical, then electron-deficient alkanes, e.g., acrylonitrile, are suitable for use in synthesis. Nucleophilic alkyl radicals, such as the cyclohexyl or *tert*-butyl radical, add to acrylonitrile at 20 °C with rate constants of about 10^6 L·mol^{-1}·s^{-1}.[12] The adduct radical **2** thus formed is much less nucleophilic because of the nitrile group. Accordingly, it adds to acrylonitrile with a rate constant of approximately 10^2 L·mol^{-1} s^{-1}.[12] This is so slow that **2** is trapped by tributyltin hydride before it can react further with acrylonitrile. Hydrogen transfer to alkyl radicals occurs with rate constants of the order of 10^6 L·mol^{-1} s^{-1} at 20 °C,[13] which are only slightly dependent on substituents on the alkyl radical. Accordingly, the ratio of the rate constants for the competing reactions of the radicals **1** and **2** are 1 and 10^4, respectively, thereby fulfilling the requirement of differing selectivity. However, a value of one for radical **1** could lead to the assumption that it reacts completely unselectively with acrylonitrile and tributyltin hydride. This is not the case if the concentration of the alkene is higher than that of tributyltin hydride. However, the concentration ratio acrylonitrile/tributyltin hydride also influences the fate of the adduct radicals **2**. If the excess of acrylonitrile is too large, then **2** would also react noticeably with acrylonitrile. An essential task, therefore, is to find the optimum concentration ratio for the synthesis in question. This is necessary because the alkene substituents exert a strong influence on the rate of addition.[12] Thus, the rate of addition of the cyclohexyl radical increases by four orders of magnitude on going from 1-hexene to acrolein.[14]

The competition between addition to an alkene and H-capture is of no importance for the tributyltin radical **3** because **3** is formed anew upon hydrogen transfer from tributyltin hydride to **3**. In the case of **3**, the competition between addition to the alkene and halogen abstraction from

the alkyl halide is much more decisive synthetically. In fact, alkyl bromides[15] and electron-poor alkenes,[16] such as acrylonitrile, react at comparable rates with **3**. Since a relatively large amount of acrylonitrile is used in these syntheses, the undesired addition of **3** to this alkene cannot be greatly influenced by varying the concentration. It is better to switch from the alkyl bromide to the 10—100 times more reactive alkyl iodide.[15] In contrast to **3**, halogen transfer from monohaloalkanes to the carbon radicals **1** and **2** is unimportant because their rate constants are relatively small.[17]

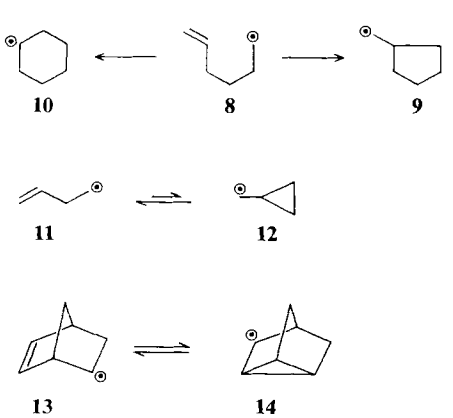
This analysis is typical for the development of radical chain reactions in synthesis. In order to evaluate whether specific reactions are synthetically useful, the magnitudes of the rate constants must be known. Many rate constants for radical reactions have been determined in recent years so that the most important are known.[18] Moreover, neutral radicals have a great advantage over ionic ones in that the solvent has little effect on the reaction.[19]

3. The Tin Method

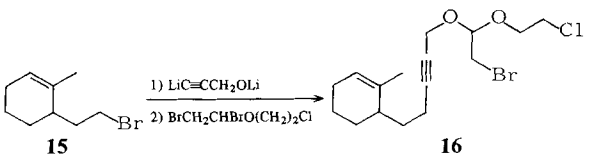
It has been known for over 20 years that the reduction of alkyl halides with trialkyl- and triaryltin hydrides leads to alkyl radicals[20] which undergo all the typical radical reactions. Only C—C bond-forming reactions will be dealt with in this review. We shall distinguish between intramolecular cyclization reactions and intermolecular C—C bond-forming reactions.

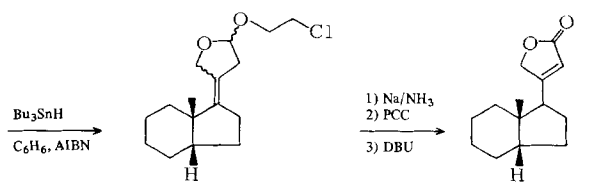
3.1. Intramolecular C—C Bond Formations (Cyclizations)

From the studies of *Lamb* et al.[21] and *Walling* et al.,[22] it is known that in a kinetically controlled reaction the 5-hexenyl radical **8** preferably cyclizes to the five-membered ring **9**, whereas under thermodynamic conditions the six-membered ring **10** is formed.[23] Radical cyclizations have been particularly thoroughly studied by *Beckwith*,[24] *Ingold*,[24b] *Wilt*,[25] *Julia*,[26] and *Surzur*[27] and reviewed in several articles. In the radical addition to alkenes[12,24b] the thermodynamically less stable cyclopentylmethyl radical **9** is rapidly formed via an unsymmetrical transition state, which is sterically more favorable for the formation of a five-membered ring. Also, Baldwin's rules[28] require that five-membered-ring formation (5-*exo-trig* reaction) be faster than six-membered-ring formation (6-*endo-trig* reaction). 6-Heptenyl radicals give the six-membered ring as well as the seven-membered ring. However, simple three- and four-membered rings cannot be formed in this way. Although the homoallyl radical **11** rapidly cyclizes to the cyclopropylmethyl radical **12**, this reverts back very rapidly to the more stable **11**.[29] Only in systems where a large proportion of the ring strain of the three-membered ring is already present in the homoallyl radical, such as the norbornenyl radical **13**,[30] can a cyclic radical such as **14** be trapped.[30,31]

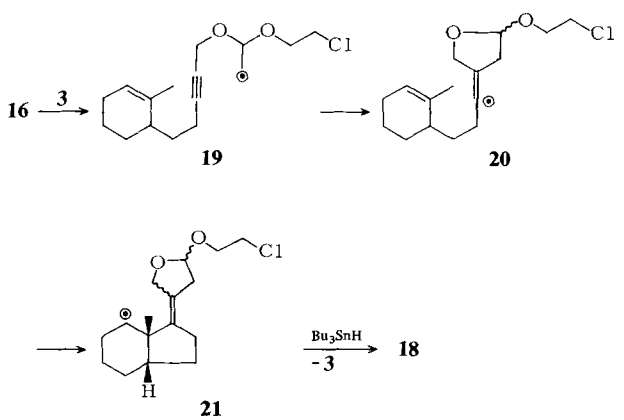


The applications of these cyclization reactions were studied before 1980 in particular by *Julia* and *Beckwith*. Since 1981 these methods have been applied to the synthesis of target molecules almost simultaneously in several laboratories. *Stork*'s work, in which both alkyl and vinyl radicals were used and cyclizations with both open-chain and cyclic double- and triple-bond systems were carried out, was pioneering. The synthesis of the butenolide **18** is a particularly elegant example (PCC: pyridinium chlorochromate, DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene).[32] The radical chain reaction takes place in boiling benzene with the bromide **16** (which is easily obtained from **15**) using 2,2′-azabis(isobutyronitrile) (AIBN) as chain initiator and Bu_3SnH as H-transfer agent.





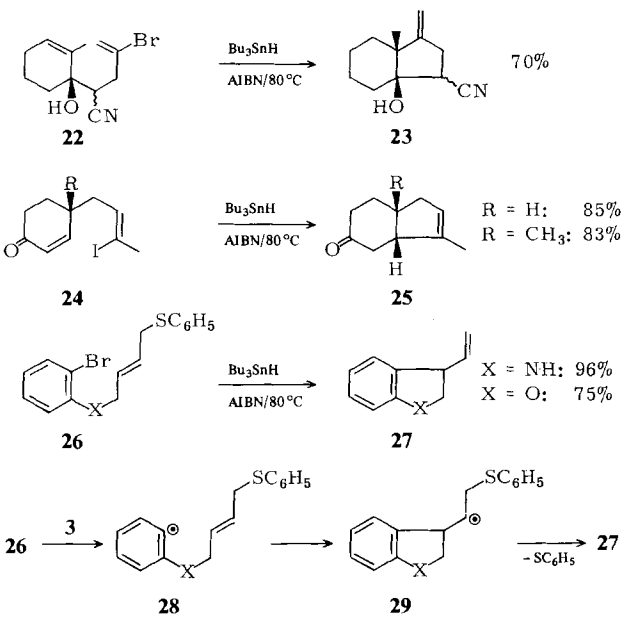
The tributyltin radicals **3** abstract the bromine atom in **16**, leaving the less reactive C—Cl bond intact. The alkyl radical **19** thus formed attacks the triple bond in an *exo-dig* reaction[28] with formation of the vinyl radical **20**, which then reacts with the double bond of the cyclohexene in an *exo-trig* reaction (**20** → **21**). It is only at this stage that



the intermolecular H-transfer from Bu_3SnH intervenes, giving the product **18** and the chain-propagating Bu_3Sn radical; the latter once again cleaves the C–Br bond in **16**.

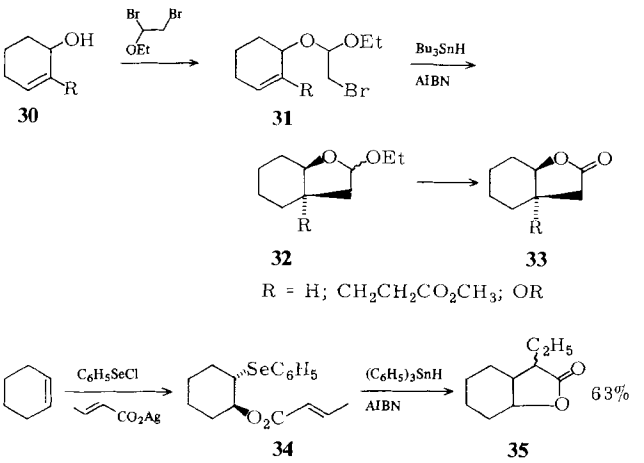
In this reaction, stereoselective *cis* annelation of the five-membered ring occurs to give the six-membered ring. In contrast, the attack of the alkyl radical on the open-chain alkyne (**19** → **20**) is unselective with respect to the β-chloroethoxy group. The vinyl radical **20** thus formed also reacts at both faces with the same rate.

Vinyl radicals can also be formed from vinyl bromides and iodides and afford products with exocyclic (**22** → **23**)[33] as well as endocyclic double bonds (**24** → **25**).[34] The OH group in **22** is not attacked owing to the high chemoselectivity of radical reactions. The facile formation of the quaternary C atom in **23** is also worth mentioning. The use of phenyl bromides such as **26** provides benzoannelated bicycles such as **27**.[35] In this case, an additional step takes place in the formation of the product **27**, namely, a β-bond cleavage (**29** → **27**). Such unimolecular homolyses are particularly fast when sulfur, bromine, iodine, or metal substituents are present in the position β to the radical center.[36] In contrast, the cleavage of the stronger C–O, C–N, C–C, or C–H bonds is much slower than hydrogen transfer from Bu_3SnH.

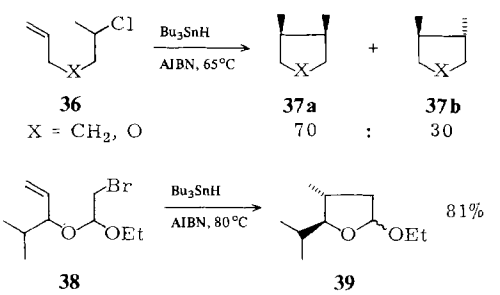


γ-Lactones can be elegantly prepared from alkenes using these radical reactions. Thus, **33** is formed by cyclization of the bromide **31** (obtained from **30**) to **32** and its subsequent oxidation.[37] In the synthesis of the γ-lactone **35**, the radical is generated from the selenide **34**.[38]

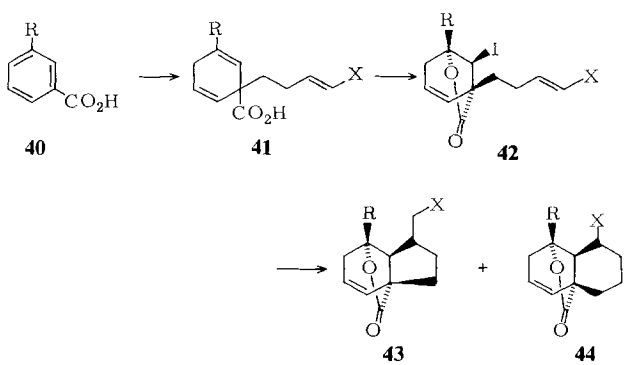
It is typical of these five-membered-ring radical cyclizations that for steric reasons the annelation to cyclic alkenes gives *cis* products. Work by *Beckwith* et al.[39] has shown that also the cyclization of open-chain 5-hexenyl radicals substituted in positions 1 or 3 gives preferentially *cis*-disubstituted pentanes (**36** → **37**). This *cis* cyclization is interpreted in terms of attractive interactions between the methyl group and the π-bond, which can occur in the very



early transition states of radical addition to alkenes. In contrast, with 2- or 4-substituted "5-hexenyl radicals," the *trans*-disubstituted products are preferentially formed, as seen in the formation of **39** from **38**.[37a]

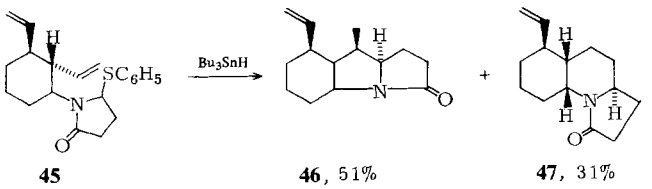


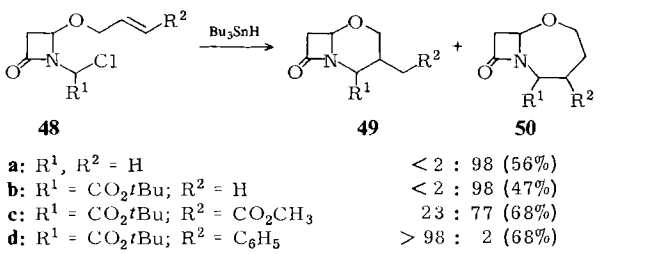
The syntheses of the cyclization products **43** and **44** developed by *Hart* et al.[40] demonstrate that not only five-membered but also six-membered rings can be formed in these radical reactions. Birch reduction and alkylation of **40** followed by iodolactonization of **41** gives **42**, which affords the six-membered-ring compound **44** as well as the five-membered-ring compound **43**. The ratio **43**/**44** can be influenced by substituent variation. Thus, the introduction of a *tert*-butyl ester group at the terminal double bond increases the proportion of the five-membered ring. Presumably, the *tert*-butyl ester group sterically hinders the formation of the six-membered ring, while the formation of the five-membered ring is facilitated by the increased LUMO coefficient at the vinylic C atom in the β position.[12]



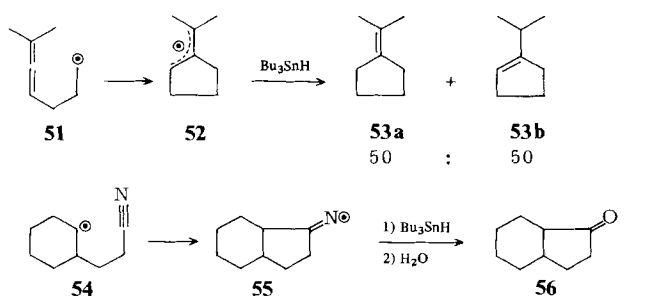
X = H; R = CH_3 70 : 30 (87%)
X = CO_2tBu; R = H > 95 : 5 (93%)

Heterosubstituted alkyl radicals can also be employed in these syntheses. Thus, the amidoalkyl radical formed as an intermediate in the desulfurization of **45** gives rise to the five- and six-membered-ring products **46** and **47**, respectively.[41] A comparison with the work of *Bachi* et al.[42] indicates that the higher proportion of the larger ring may be typical for amidoalkyl radicals. Thus, only the seven-membered-ring compound **50a** is formed from **48a**. Once again, it is possible to favor the formation of the smaller ring by the introduction of sterically demanding, polar, and radical-stabilizing substituents at the terminal olefinic C atoms.





Apart from alkenes and alkynes, also allenes[43] (**51**→**52**) or nitriles[44] (**54**→**55**) can be employed as intramolecular radical traps in C–C bond-forming reactions. In contrast, the C=O bond is not suitable for C–C bond formation, probably because the alkoxy radical undergoes rapid β-bond cleavage.[45]



3.2. Intermolecular C–C Bond Formations

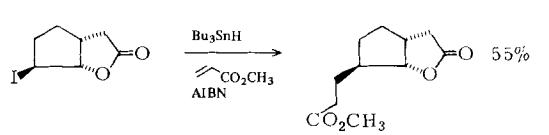
Because of the unfavorable activation entropies, intermolecular reactions are noticeably slower than intramolecular cyclizations. Thus, the activation entropy for the addition of ethyl radicals to 1-hexene is more negative by 14 e.u. than that for the cyclization of the 5-hexenyl radical.[46] In contrast, these two reactions do not differ significantly in their activation enthalpies. This unfavorable entropy effect can be compensated for by electron-withdrawing substituents on the alkene, which lower the activation enthalpy.[47] The rate of addition of cyclohexyl radicals to acrolein at 20°C is almost four orders of magnitude higher than for addition to 1-hexene.[12, 14] The rate constant is about 10^6 L·mol^{-1} s^{-1}.[12] Accordingly, electron-poor alkenes are reactive enough to be employed in these syntheses. Furthermore, the polarity of the radicals changes after addition of nucleophilic alkyl radicals to electron-poor alkenes; consequently, the selectivity condition for radical chain reactions is also fulfilled. The C–C bond-forming reactions of some typical alkenes with primary, secondary, and tertiary alkyl halides are summarized in Table 1.[3, 48]

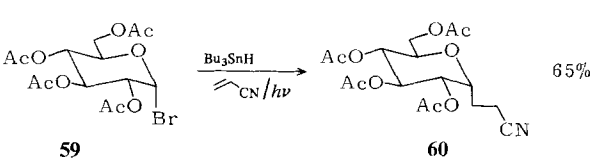
Table 1. Photochemically initiated C–C bond formation between alkyl halides and alkenes (5 molar equivalents) with tributyltin hydride (0.2 molar equivalents) and $NaBH_4$ (1.3 molar equivalents).

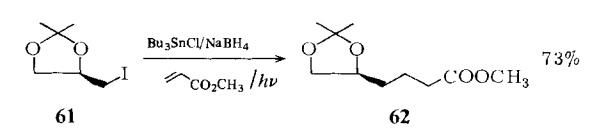
Alkyl halide	Alkene	Product [%]
n-$C_6H_{13}I$	H_2C=CHCN	80
n-$C_6H_{13}Br$	H_2C=CHCN	68 [c]
cyclo-$C_6H_{11}I$	H_2C=CHCN	95
cyclo-$C_6H_{11}I$	H_2C=CHCOCH$_3$	85
cyclo-$C_6H_{11}I$	H_2C=CHCHO	90 [c]
cyclo-$C_6H_{11}I$	H_2C=CHCO$_2$CH$_3$	85
cyclo-$C_6H_{11}I$	H_2C=CHC$_6$H$_5$	83
cyclo-$C_6H_{11}I$	H_2C=CClCN	80 [c]
cyclo-$C_6H_{11}I$	H_2C=C(CH$_3$)CN	91
cyclo-$C_6H_{11}I$	H_2C=CCl_2	87; 90 [c]
cyclo-$C_6H_{11}I$	NCCH=CHCN [a]	72 [c]
cyclo-$C_6H_{11}I$	$H_5C_2O_2CCH$=$CHCO_2C_2H_5$ [a]	78
cyclo-$C_6H_{11}I$	CH$_3$CH=CHCN [b]	86 [d]
cyclo-$C_6H_{11}Br$	H_2C=CHCN	80 [c]
t-C_4H_9I	H_2C=CHCN	87; 98 [c]
t-C_4H_9Br	H_2C=CHCN	62

[a] *trans*-Alkene. [b] 45 : 55 *cis-trans* mixture. [c] Reaction in boiling toluene with 1.2 molar equivalents of tributyltin hydride and AIBN as initiator. [d] Photochemical reaction with 10 molar equivalents of alkene.

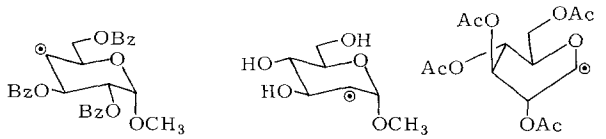
With iodides and bromides, the products are formed in high yields, and it is often possible to work with catalytic amounts of tin hydrides by reducing the tributyltin halide formed with $NaBH_4$ to regenerate the tin hydride. C–C bond-forming reactions do not take place with alkyl chlorides, since these are not capable of competing with the electron-poor alkene for the tributyltin radicals. Examples of the use of this tin method are shown by the C–C bond-forming reactions with the iodolactone **57**,[49] the glucosyl bromide **59**,[50] and the chiral iodide **61**.[51]





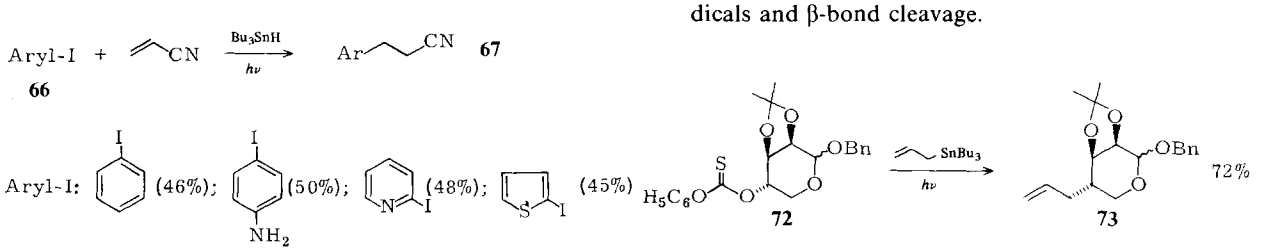


The halides **57**, **59**, and **61** have β C–O bonds that remain intact during the formation and reactions of the radicals, so that no racemization occurs at the chiral center neighboring the radical center during the radical reaction. Moreover, the C–C bond formations take place with high stereoselectivity with the radicals generated from **57** and **59**. The formation of the *C*-deoxyglucoside **60** is surprising in that the new C–C bond is axial even though the carbohydrate radicals **63** (Bz: benzoyl) and **64** are preferably attacked in the equatorial position by acrylonitrile and, particularly, by fumaronitrile.[3,52] According to ESR measurements, the glucosyl radical exists in the boat conformation **65**;[53] thus, **60** is also formed by equatorial attack.

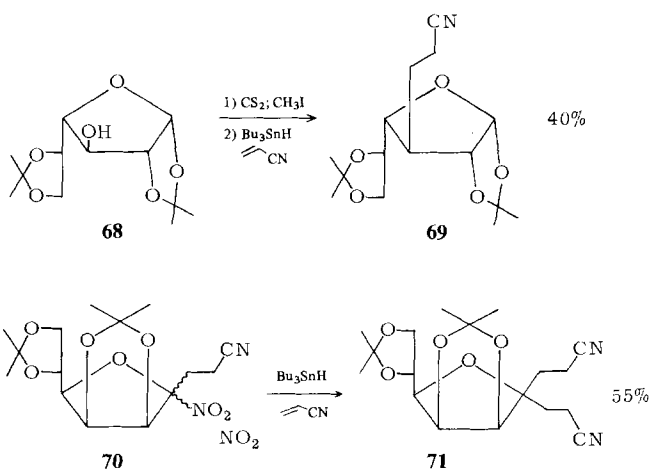


63 **64** **65**

Reaction with the iodides **66** shows that these C–C bond-forming reactions also can be applied to aromatic systems.[48]



In the tin method, alcohols, selenides, and tertiary nitro compounds can be used in place of halides in the C–C bond forming reactions. The alcohols must be transformed into xanthogenates or other thio derivatives as in the reduction according to *Barton* et al.[53] For instance, **69** is exclusively formed from the galactose derivative **68**.[3] Another example from carbohydrate chemistry, the transformation of **70** into **71**, shows the C–C bond-forming reaction with tertiary nitro compounds. In this case, ESR measurements have shown that the sugar radical is only formed after one-electron transfer from the tin radical and elimination of $NO_2^{\ominus}$.[55] Thus, the $S_{RN}1$ reaction typical for many nitro compounds takes place, whereby the tin radical is the electron donor.



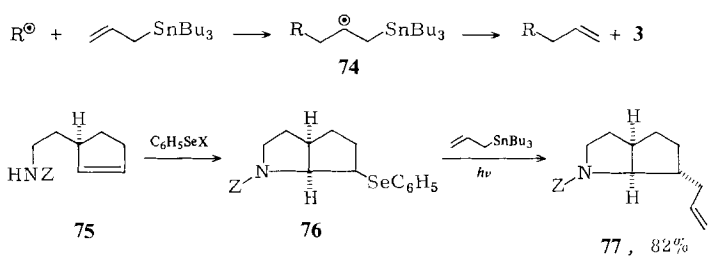
68 **69** **70** **71**

It has so far not been possible to use isocyanides for these C–C bond formations, even though they are readily reduced to hydrocarbons with tributyltin hydride via radical intermediates.[56] As for the chlorides, the reason is that they cannot compete with the added alkene for the tin radicals.

Radical chain reactions taking place via organotin compounds, but which do not involve hydrogen donors, have been worked out by *Keck*, *Danishefsky*, *Baldwin*, and *Stork*. Thus, the reaction of the pentose derivative **72** with the allyltin compound gives the pseudomonic acid derivative **73** (Bn: benzyl).[57] The reaction proceeds via the carbohydrate radical $R^{\odot}$ and the adduct radical **74**, which eliminates a trialkyltin radical by β-bond cleavage. This then attacks the thio group in **72** to regenerate the carbohydrate radical $R^{\odot}$.

Danishefsky et al.[58] used this method on the selenide **76** (Z: benzyloxycarbonyl). The C–Se bond of **76** is homolytically cleaved prior to the formation of the coupling product **77**. *Baldwin* et al.[59] used vinylstannanes, which afforded the substitution products after addition of alkyl radicals and β-bond cleavage.

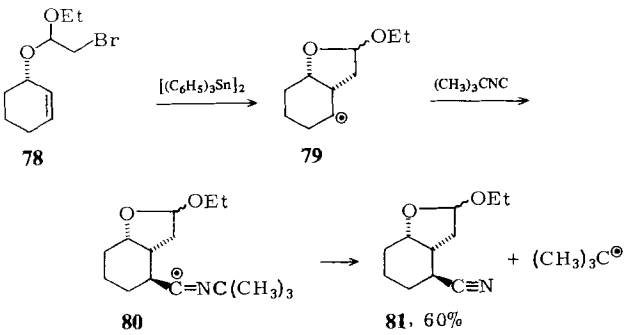
72 **73**



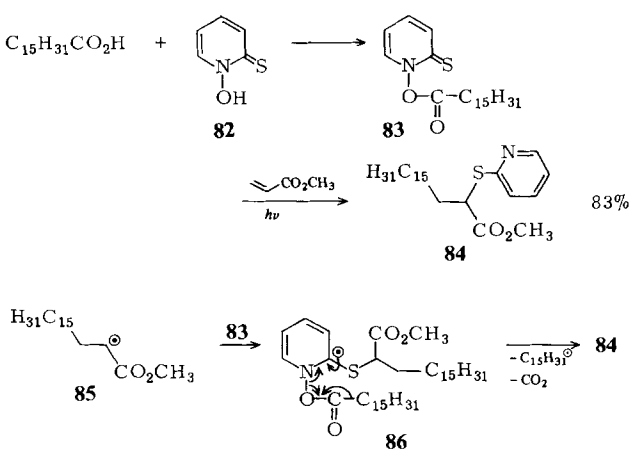
74 **75** **76** **77**, 82%

Stork et al.[60] used equimolar amounts of hexaphenylditin in the synthesis of the nitrile **81**. After homolysis of the hexaphenylditin and abstraction of a bromine atom from **78**, spontaneous cyclization gave the radical **79**, which then reacted with *tert*-butyl isocyanide to give the adduct radical **80**. Subsequent elimination of the *tert*-butyl radical gives the product nitrile **81**. The fate of the *tert*-butyl radical has not been investigated. It is unlikely, however, that it attacks the primary C–Br or Sn–Sn bonds. It is presumably consumed by radical combination and disproportionation reactions so that the synthesis of the nitrile **81** does not involve a radical chain reaction.

Barton et al.[61] have developed a method that avoids the use of tin compounds. It starts with a carboxylic acid, e.g., palmitic acid, which is converted into the mixed anhydride **83** with a thiohydroxamic acid such as **82**. Photolysis in

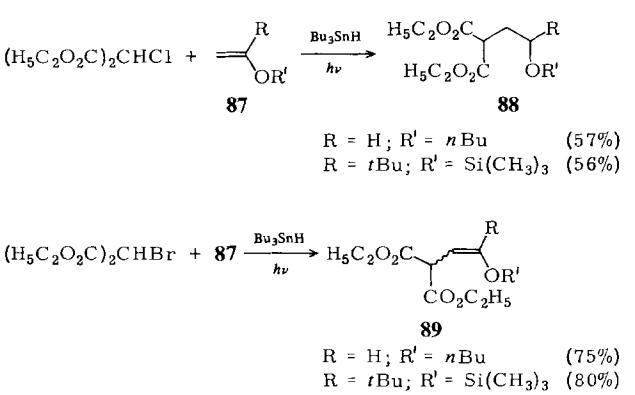


the presence of acrylic ester gives the product **84** possessing a new C–C as well as a C–S bond. This product is formed by attack of the alkyl radical on the alkene and reaction of the adduct radical **85** with the thio compound **83**. Double β-cleavage in **86** generates the product **84** and the chain-propagating alkyl radical.



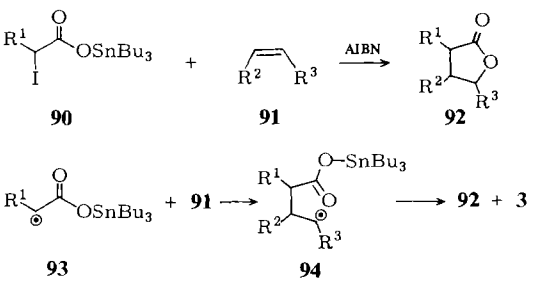
3.2.1. *Electrophilic Radicals*

Intermolecular C–C bond-forming reactions with electrophilic radicals are possible in radical chain reactions if electron-rich alkenes are used. Only then is the reaction rate large enough and the difference in selectivities of the carbon radicals sufficiently pronounced. Thus, the reaction of chloromalonic ester with the enol ethers **87** gives the addition products **88**.[62] In contrast, bromomalonic ester and the enol ethers **87** give the substitution products **89**



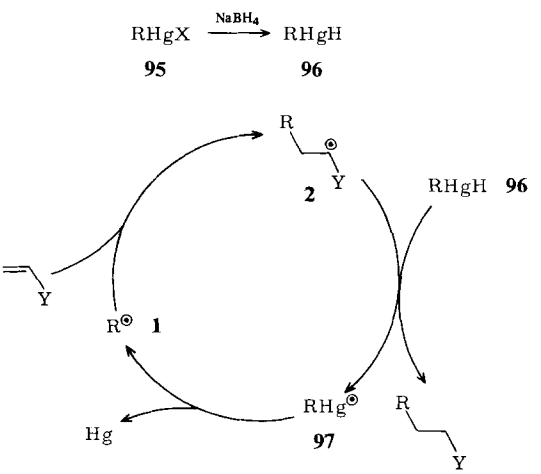
because now the adduct radicals abstract a bromine atom from the bromomalonic ester more rapidly than a hydrogen atom from tributyltin hydride.[62] Subsequent HBr elimination gives the substituted enol ethers. Therefore, photochemically initiated radical reactions can be carried out with bromomalonic esters in the absence of tin hydrides.

An interesting variation of this procedure has recently been carried out by *Kraus* et al.[63] The γ-lactones **92** are formed in good yields by reaction of the α-iodo esters **90** with alkenes in the presence of AIBN as radical initiator. The radicals **93** and **94** are intermediates; **93** adds to the alkenes **91** to give **94**, which undergoes cyclization.



4. The Mercury Method

In addition to organotin compounds, organomercury compounds have proved particularly useful for C–C bond formation in radical chain reactions in recent years. Here, the alkyl radicals are formed by reaction of alkylmercury salts **95** (particularly halides and acetates) with boron[64] or tin hydrides.[11] Stereochemical,[65] polarographic,[66] and kinetic[67,68] studies suggest that an organomercury hydride **96** is formed, which, via hydrogen abstraction, gives the labile alkylmercury radical **97**. This decomposes spontaneously to mercury and an alkyl radical.[69] The alkylmercury hydride **96** plays the role of the hydrogen donor, trapping the adduct radicals **2** prior to their polymerization.



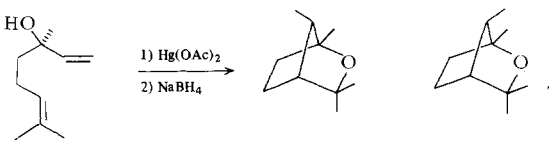
The advantage of the mercury method over the tin method lies in the mild reaction conditions (room temperature, absence of light) and very short reaction times (of the

order of minutes), as well as the unproblematic separation of the mercury. However, since the alkylmercury hydride is a better hydrogen donor[67] than trialkyltin hydride, the mercury method can only be employed in syntheses involving very reactive alkenes.

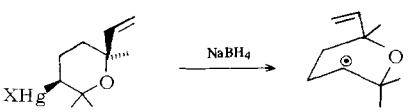
4.1. Intramolecular C–C Bond Formations (Cyclizations)

The 5-hexenyl radical generated from mercury salts behaves just as the radical produced with the aid of **3** and cyclizes to give mainly the five-membered ring. This reaction has been used in kinetic studies of hydrogen abstraction[68] and C–C bond formation.[67] The following examples illustrate some synthetic applications.

The bicyclic compound **99** is formed in 68% yield by mercuration of linalool, **98**, and subsequent reduction.[70] The reaction proceeds via the monocyclic organomercury compound **100**, which is formed by electrophilic attack of mercury acetate on the electron-rich double bond in **98** followed by intramolecular attack by the OH group. Homolysis of the C–Hg bond gives the radical **101**, which is converted into the bicyclic compound **99** after cyclization and hydrogen capture.

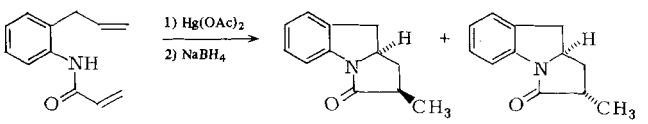


98 **99a**, 52% **99b**, 16%



100 **101**

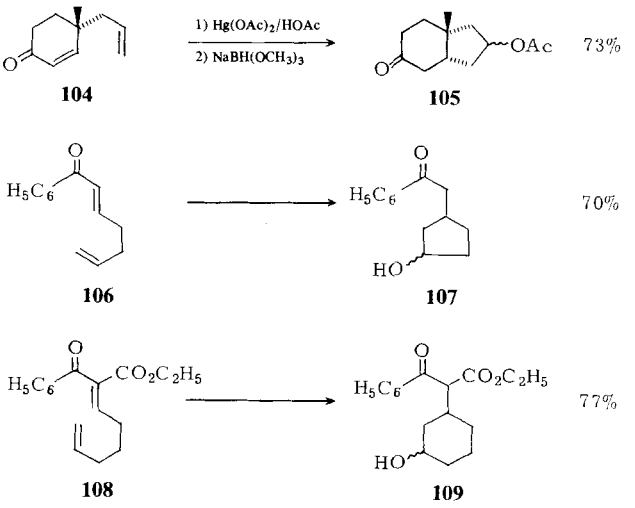
Danishefsky et al.[71] used the diene **102** in the synthesis of the benzoannelated bicyclic compound **103**, whereby the amide function acts as a nucleophilic neighboring group in the mercuration step.



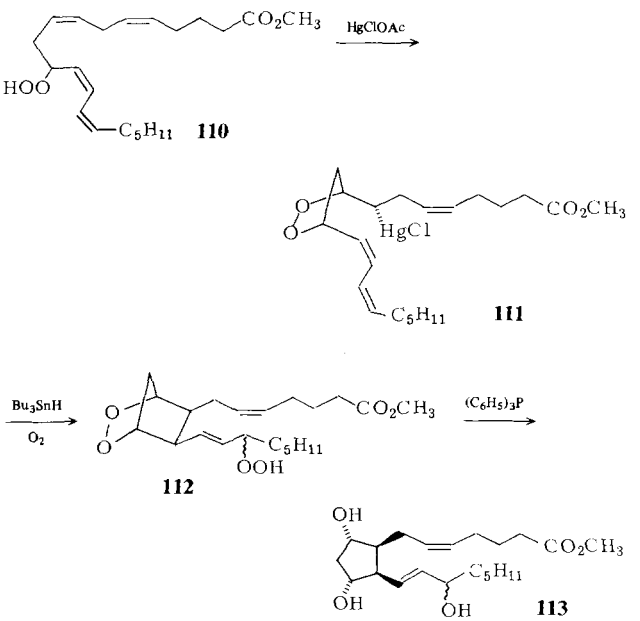
102 **103a**, 34% **103b**, 11%

The different reactivities of double bonds in the electrophilic solvomercuration have also been employed in the syntheses of the cyclization products **105**, **107**, and **109**.[72] However, in these cases, acetic acid or water function as intermolecular nucleophiles in the mercuration step.

In the course of a prostaglandin synthesis it was recently found by *Corey* et al.[73] that the organomercury compound **111** gives the bicyclic compound **112** in which the two



substituents are *cis*. In this radical cyclization reaction the attractive interaction between the double bond systems apparently predominates in the early transition state.



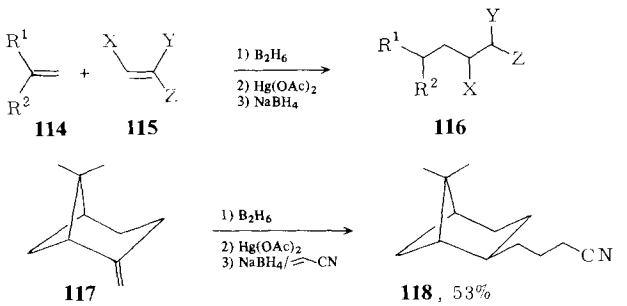
4.2. Intermolecular C–C Bond Formations

The versatility of the mercury method lies in the fact that organomercury salts are easily accessible from alkenes, cyclopropanes, and ketones.

4.2.1. The Use of Alkenes

Alkenes with electron-rich terminal double bonds, **114**, can be reductively coupled with electron-poor alkenes, **115**, in a one-pot reaction.[74] The reaction proceeds via hydroboration of the electron-rich double bond, transformation of the boron-carbon bond into a mercury-carbon bond, and reduction to radicals, which on reaction with **115** give the product **116**. A wide variety of substituents

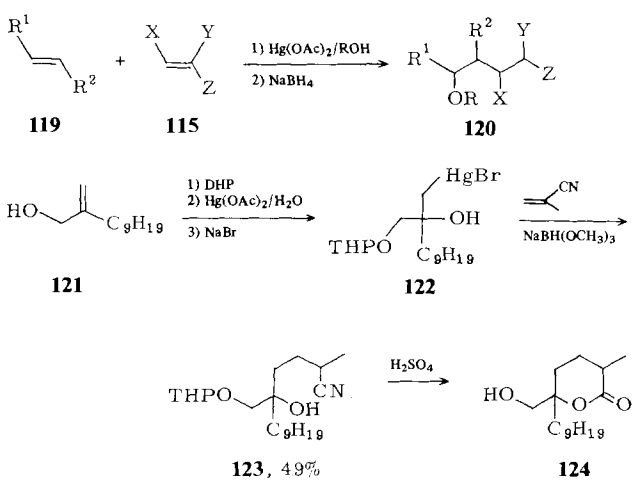
R^1 and R^2 can be present on the double bond of **115**. Acrylonitrile, acrylic esters, α-chloroacrylic esters, and maleic anhydrides are particularly effective radical traps. Thus, for example, β-pinene, **117**, reacts stereo- and regioselectively with acrylonitrile to give the C–C coupling products **118** in 53% overall yield.[74]



114 **115** **116** **117** **118**, 53%

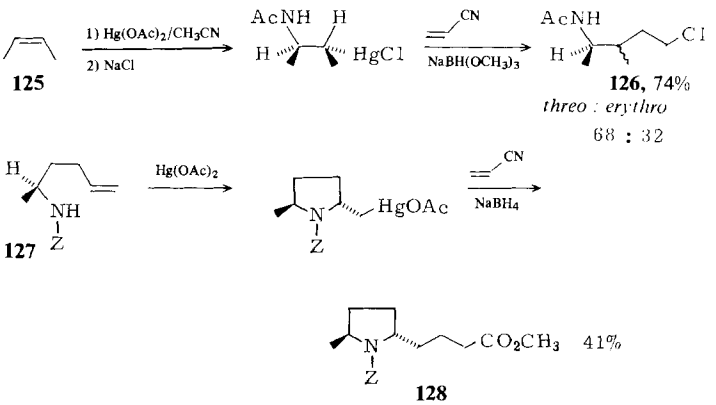
In cases where the attacked alkene contains a group that can be eliminated by rapid β-cleavage, photoinitiated reaction with alkylmercury salts leads to the substitution products.[75] It is possible to introduce an additional functional group in the coupling reaction by generating the organomercury salts through solvomercuration of electron-rich alkenes, **119**.[76] These syntheses can also be carried out as one-pot reactions. After solvomercuration, the reaction mixture is diluted with dichloromethane, the electron-poor alkene is added in about a threefold excess, and the C–C bond in **120** is formed in a radical process by addition of a hydride donor. As shown by *Barluenga* et al.,[77] it is often advantageous to carry out the process as a two-phase reaction in water/dichloromethane using Trilon B as the phase-transfer catalyst.

The introduction of an additional group in this reaction permits subsequent reactions, e.g. lactonization,[78] when the solvomercuration is carried out in the presence of acetic acid or water. *Kozikowski* et al.[79] used this method to synthesize the antibiotic malingolide, **124**, as a racemic mixture of diastereomers from the allyl alcohol **121**, whereby **122** and **123** are intermediates (DHP: dihydropyran, THP: tetrahydropyranyl).



119 **115** **120** **121** **122** **123**, 49% **124**

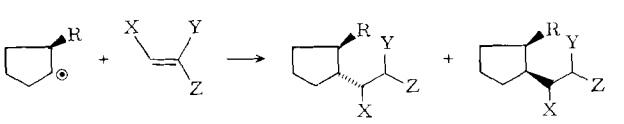
A C–N bond is formed when nitrogen nucleophiles are used. The nucleophile can enter in the reaction either in-



125 **126**, 74% *threo* : *erythro* 68 : 32 **127** **128** 41%

termolecularly,[80] e.g., **125** → **126**,[81] or intramolecularly,[82] e.g., **127** → **128**.[83]

Up to four centers of chirality are created in the formation of **120** from the alkenes **115** and **119**. The first chiral center is introduced in the solvomercuration, a reaction that takes place with quite high diastereoselectivities with both cyclic[84] and open-chain[85] alkenes via asymmetric induction. The homolysis of the C–Hg bond gives radicals; cyclic radicals react selectively. Thus, the C–C bond-forming reaction with α-ethoxy-substituted cyclopentyl radicals **129** ($R = OC_2H_5$) shows that the proportion of *trans* addition increases from 72 to 90% on going from α-chloroacrylonitrile to styrene.[86] This is explained by the decreasing reactivity of the alkenes,[12] because steric effects are more pronounced in the slower reaction with a later transition state than in the earlier transition state of the faster reaction. The introduction of a substituent on the vinyl atom in the alkene to be attacked also leads to an increased stereoselectivity[87] because this substituent increases the steric repulsion during the radical addition.[12] The substituent in the radical also influences the *trans* : *cis* ratio. In this respect an amide group[88] shields the neighboring radical center more strongly than a methyl group.[89] The latter, in turn, exerts a larger influence than an ethoxy group.[86] The selectivities are somewhat smaller for substituted six-membered-ring radicals,[86-89] although in isolated cases, e.g., carbohydrate radicals,[3,11,50,52] they can be quite pronounced.

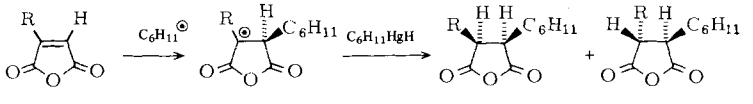


129 **115** **130a** **130b**

R	X	Y	Z	**130a** : **130b**
OC_2H_5	H	Cl	CN	72 : 28
OC_2H_5	H	H	CN	77 : 23
OC_2H_5	H	H	CO_2CH_3	88 : 12
OC_2H_5	H	H	C_6H_5	90 : 10
OC_2H_5	$CO_2C_2H_5$	H	$CO_2C_2H_5$	98 : 2
CH_3	H	H	CN	92 : 8
CH_3	$CO_2C_2H_5$	H	$CO_2C_2H_5$	98 : 2
$NHCOCH_3$	H	Cl	CN	>98 : 2

The last center of chirality is generated by hydrogen abstraction, whereby once more the different shielding of the

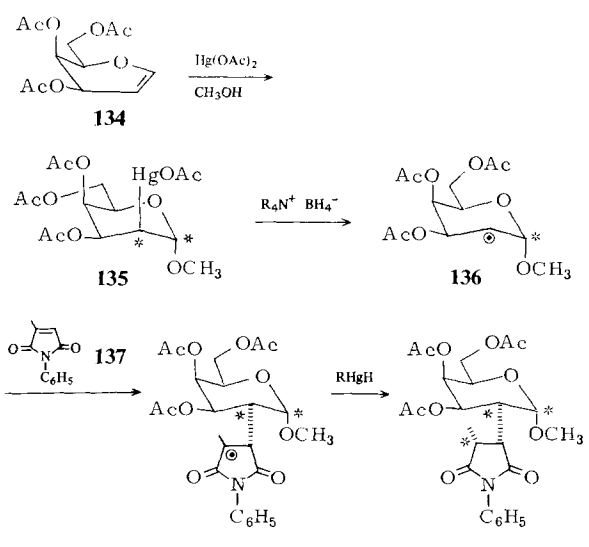
radical centers by the neighboring substituents plays a decisive role. Since, however, the small hydrogen atom is transferred in this process, the thermodynamically less stable *cis* product is preferentially formed. This is illustrated by the hydrogen abstraction reactions of the radicals **132**, generated from cyclohexyl mercury salts and maleic anhydrides **131** in the presence of $NaBH_4$; the *cis* proportion reaches 95%.[90]



131 **132** **133a** **133b**

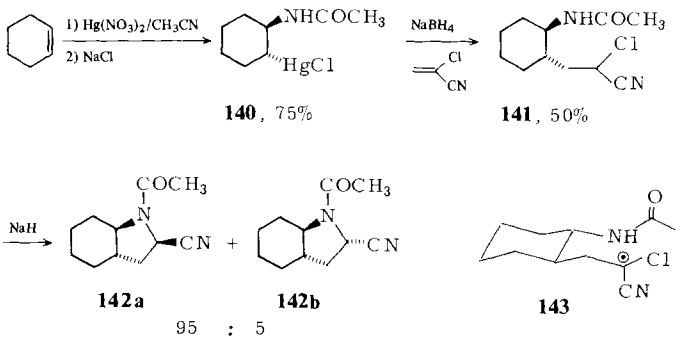
R = CH_3 : 89 : 11
R = *t*Bu : 95 : 5
R = OAc: 94 : 6

The C–C bond formation between the galactal **134** and the methyl maleimide **137** is an example of the asymmetrically induced formation of four centers of chirality.[52] The mercuration takes place *cis* to the directing OAc substituents in the galactal **134**. Subsequent *trans* attack by the nucleophile leads to the organomercury salt **135**, which, via the radical **136**, undergoes equatorial coupling with **137** with over 95% stereoselectivity to give **138**. A *trans* hydrogen transfer to **138** then gives the product **139** in which each of the three indicated centers of chirality were created with over 90% asymmetric induction. Only the fourth center of chirality (on the five-membered ring) consists of roughly equal parts of *R* and *S*. In this one-pot reaction, two diastereomers, each with four new centers of chirality, are obtained in a yield of 55%. The separation of the two diastereomers is readily achieved by column chromatography.



134 **135** **136** **137** **138** **139**

Another example of the high selectivity of this synthetic sequence is given by the preparation of the α-aminonitrile derivative **142** by solvomercuration of cyclohexene to **140** in acetonitrile followed by C–C coupling of **140** with α-chloroacrylonitrile.[88] As shown by the *trans*-annelation of



140, 75% **141**, 50%

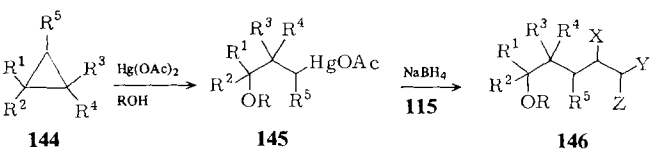
142a **142b** **143**

95 : 5

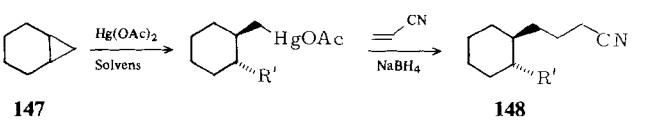
the rings in **142**, the six-membered-ring radical undergoes *trans* C–C coupling. Also, the high selectivity of the hydrogen capture seen in the cyclization of **141** is interesting. The ratio **142a** : **142b** (95 : 5) can be interpreted in terms of a preferred conformation **143** of the adduct radical, which is attacked from the less hindered side.

4.2.2. *The Use of Cyclopropanes*

Cyclopropanes are solvomercurated in an analogous way to alkenes.[91] Here, the mercury salt attacks at the least substituted carbon atom of the cyclopropane **144** to give γ-substituted organomercury salts **145** upon reaction with a nucleophile, e.g., the solvent ROH. The salts **145** react via the corresponding radicals with electron-poor alkenes **115** to give the products **146**.[92] This reaction can also be carried out as a one-pot synthesis,[93] and differently substituted products are obtained in different solvents.[94,95] Starting with norcarane, **147**, the *trans*-disubstituted cyclohexane derivative **148** is obtained.[93b,95]



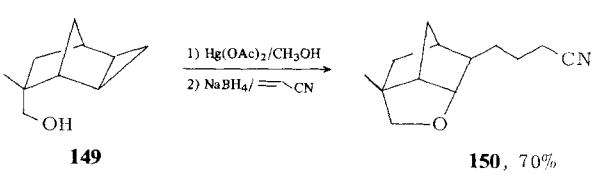
144 **145** **115** **146**



147 **148**

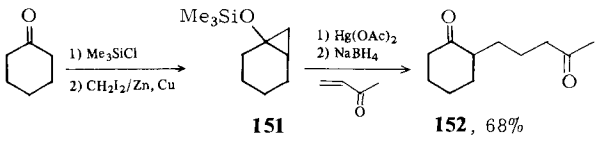
Solvent	R′	**148** [%]
CH_3OH	OCH_3	82
H_2O	OH	62
HOAc	OAc	65
CH_3CN	$NHCOCH_3$	65

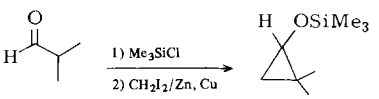
An intramolecular reaction is also possible using cyclopropanes as seen in the formation of **150** from the cyclopropane **149**, which contains a nucleophilic neighboring group.[95]

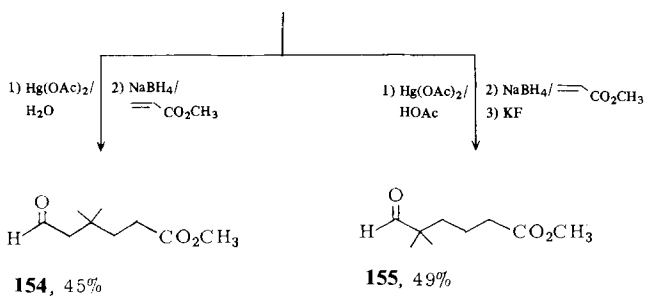


149 **150**, 70%

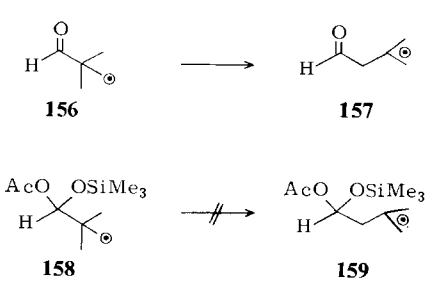
A variation of this cyclopropane method involves the use of ketones or aldehydes to give products of increased chain length via silyl enol ethers, cyclopropanation to siloxycyclopropanes, mercuration, and C–C coupling.[96] In this way the diketone **152** can, for example, be synthesized from cyclohexanone via the cyclopropane **151**. This example shows that 1,6-disubstituted C–C chains can be produced in radical reactions using cyclopropanes—i.e., the products of reactivity umpolung are obtained.[97]







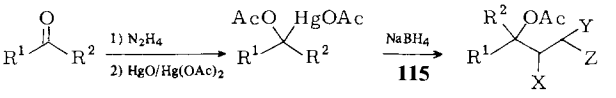
Rearrangements take place when aldehydes are used. Thus, the rearranged product **154** is obtained from isobutyraldehyde via the cyclopropane **153**.[98] If the solvomercuration is carried out in acetic acid rather than water, rearrangement is avoided and **155** is formed. The rearrangement occurs in the case of the β-keto-substituted alkyl radical and is reminiscent of the homoallyl rearrangement (**156** → **157**).[24b] When the aldehyde group is protected by working in acetic acid, the rearrangement (**158** → **159**) can no longer take place.

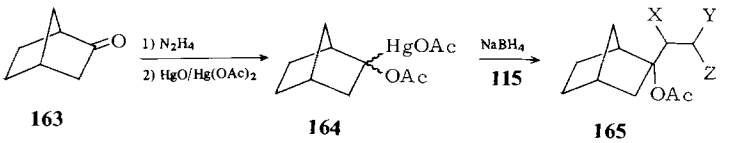


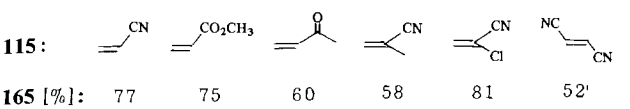
4.3.2. The Use of Ketones

Ketones **160** can be transformed into α-substituted organomercury salts **161** via the hydrazones.[99] The C–C coupling products **162** are formed via reaction of **161** with alkenes.[100] The scope of this synthesis is illustrated by the transformation of norcamphor **163** to **165** via the organomercury salt **164**.[101]

The reaction with methyl vinyl ketone exemplifies the synthesis of 1,4-disubstituted C–C chains, i.e., the products of umpolung, in this radical reaction.[97] In the radical **166**, the *O*-substituted C atom is nucleophilic, in contrast to the corresponding C atom in the starting ketone **160**; it therefore rapidly attacks electron-poor double bonds[12, 102].









5. Outlook

Radical chain reactions in which the decisive reactions are between radicals and nonradicals have proven to be of particular value for the employment of radicals in synthesis. The syntheses take place, in part, with good yields and high selectivities. The mild reaction conditions and the high chemoselectivity are remarkable and permit the use of radical chemistry in reactions with complex molecules. This can give a fresh impetus to, for example, carbohydrate chemistry. Here, a knowledge of the stereochemistry, which should depend on the substituents on both the carbohydrate and the radical trap, is important. Experiments carried out so far have demonstrated surprising conformations and high stereoselectivities of these carbohydrate radicals.[53]

Mechanistic studies have generated a wealth of kinetic data in recent years. Considering the reactivity and selectivity conditions delineated in Section 2, it should be possible, therefore, to find new radical chain reactions for use in synthesis. Thus, for example, it would be desirable to replace the mercury salts by ecologically acceptable hydrogen transfer agents. Also, the search for starting materials that, upon radical formation, can be incorporated into these chains is by no means complete. Furthermore, bonds other than C–C and C–H bonds can be created by varying the radical trap.

Radical chemistry thus opens up a wealth of possibilities for synthesis. It gives the preparative chemist the opportunity to develop new synthetic methods, provided that the fear of kinetic data is overcome.

Our own work in this area was made possible by the generous support of the Deutsche Forschungsgemeinschaft and

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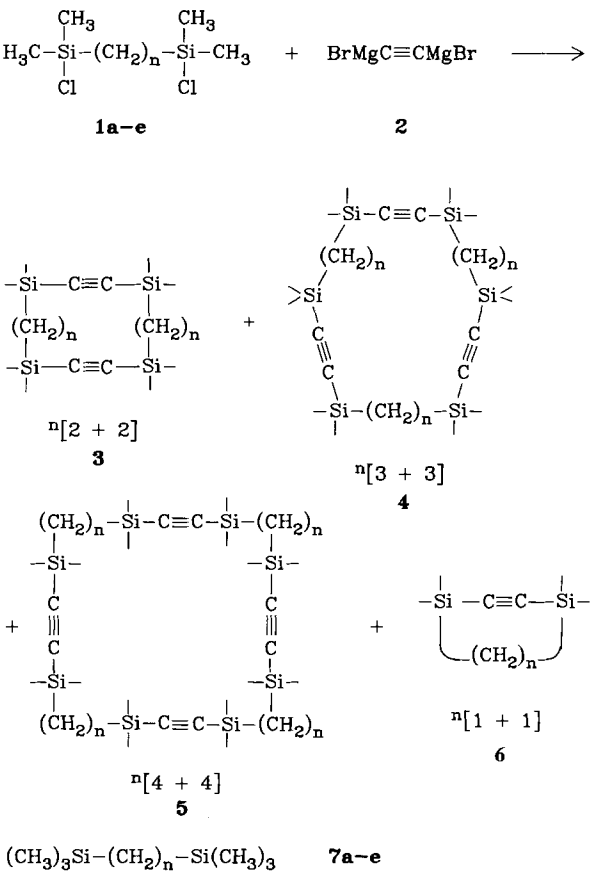
New Silacycloalkynes with up to Four 1,4-Disila-2-alkyne Units in the Ring**

By *Else Kloster-Jensen** and *Gudveig Aamdal Eliassen*

The replacement of C by Si in the α,α′ position of the C≡C bond of 3,3,n,n-tetramethylcycloalkynes involves the consideration of the following factors: the greater steric demand of the $Si(CH_3)_2$ group, the greater length of the Si–C bond, and the smaller force constant for deformation of the C–Si–C angle. Accordingly, such disilacycloalkynes (number of chain links <8) should be more stable than the corresponding cycloalkynes. We have now synthesized low-membered disilacycloalkynes in order to determine the minimum number of chain links.

The syntheses of angle-strained cycloalkynes are all based on the introduction of the triple bond into the final ring system and cannot be transferred to 1,4-disila-2-cycloalkynes. An alternative approach is the coupling twice of an acetylene with an α,ω-disilaalkane of sufficient chain length that is reactive at both ends.

In analogy to the synthesis of 3,3,8,8-tetramethylcyclooctyne,[1,2] the smallest stable[3] cycloalkyne, 2,7-dichloro-2,7-dimethyl-2,7-disilaoctane **1d**[4] was reacted with bis(bromomagnesium)acetylide **2** (Scheme 1). However,



Scheme 1. **a**, n=1; **b**, n=2; **c**, n=3; **d**, n=4; **e**, n=0.

1,1,4,4-tetramethyl-1,4-disila-2-cyclooctyne $^4[1+1]$[5] **6d**, which is formed from one pair of reactants, could be isolated in very small yield only; it was identified by its mass spectrum (*m/z* 196 (M^+)). The main product was $^4[2+2]$ **3d**, which is formed from two pairs of reactants (Scheme 1).

Furthermore, we have investigated the dependence of ring formation ability on the chain length of **1** (n=0–3).

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We were thereby able to isolate cyclic products containing various numbers of coupled reactant pairs. However, 2,6-dichloro-2,6-dimethyl-2,6-disilaheptane **1c**,[4] in analogy to **1d**, yielded mainly ^{3}[2+2] **3c**, formed from two pairs of reactants, along with traces of 1,1,4,4-tetramethyl-1,4-disila-2-cycloheptyne ^{3}[1+1] **6c**, identified by its mass spectrum (*m/z* 182 (M^+)). In contrast, **1b**[4] afforded ^{2}[2+2] **3b** as well as ^{2}[3+3] **4b** and a very small amount of ^{2}[4+4] **5b**. Analogously, **1a**[4] gave the products ^{1}[2+2] **3a**,[6] ^{1}[3+3] **4a**, and ^{1}[4+4] **5a**.

The last member of the **1** series, **1e** (n=0), 2,3-dichloro-2,3-dimethyl-2,3-disilabutane,[4] produced, as expected, octamethyl-1,2,5,6-tetrasila-3,7-cyclooctadiyne ^{0}[2+2] **3e**, which is analogous to 1,5-cyclooctadiyne,[7] as well as ^{0}[3+3] **4e**. These two silacycloalkynes have recently been synthesized in an alternative way by *Sakurai* et al.[8] The compounds synthesized by us are summarized in Table 1.

Table 1. Synthesized silacycloalkynes of the type ^{n}[m+m] [5]. For experimental procedure see [14].

	^{n}[1+1]	^{n}[2+2] mp [°C]	^{n}[3+3] mp [°C]	^{n}[4+4] mp [°C]	Σ Yields [%]
n=4	**6d** (traces)	**3d** 86–87			15
n=3	**6c** (traces)	**3c** 162–162.5			35
n=2		**3b** 122–123	**4b** 153–154	**5b** 135–137	25
n=1		**3a** 103–104	**4a** 107–108	**5a** 118–119	15
n=0		**3e** 139 (139 [8a])	**4e** 146–147 (146–147 [8c])		5

The silacycloalkynes described here are easily crystallizable and sublimable solids; they were obtained in a pure state as shown by mass spectrometry. They are stable in air and can be subjected to gas chromatography without decomposition. An oily residue, which makes up a considerable portion of the crude products, could not be further analyzed.[14]

The high-resolution IR spectra of the isolated silacycloalkynes are very similar to each other and exhibit the bands characteristic for these highly symmetrical compounds. The ^{1}H- and ^{13}C-NMR spectra (Table 2) of ^{n}[2+2] **3a**–**d** are also very similar to one another and are in accordance with the structure given (**3e**[8a]). An X-ray structure determination[9a] of ^{0}[2+2] **3e** confirmed the results of *Sakurai* et al.,[8a] which showed that the ring is planar, as in 1,5-cyclooctadiyne.[7] The homologue ^{1}[2+2] **3a** at −133° adopts a conformation analogous to cyclohexane; both chair and boat forms are present in the same crystal.[9b] Low-temperature NMR spectra of **3a** show conformational changes. The photoelectron spectra of ^{0}[2+2] **3e** and ^{0}[3+3] **4e** were recorded by *Heilbronner* et al.;[10] they are in accord with those of *Gleiter, Sakurai* et al.[11]

Table 2. ^{1}H- and ^{13}C-NMR spectra of silacycloalkynes of the type ^{n}[2+2] **3** (300 MHz, $CDCl_3$ (standard), δ values). **3e**: ^{1}H-NMR: δ=0.25; ^{13}C-NMR: δ=119.46 (−C≡C−), 3.07 (CH_3) [8a].

	^{1}H-NMR			^{13}C-NMR		
	CH_3	$Si-CH_2$	$C-CH_2-C$	C≡C	CH_3	$Si-CH_2$	$C-C-C$
3a	0.19 (s)	−0.14 (s, 4H)		114.95	1.13	2.60 (2C)	
3b	0.15 (s)	0.67 (s, 8H)		113.62	−2.37	9.19 (4C)	
3c	0.14 (s)	0.67 (m, 8H)	1.59 (m, 4H)	113.51	−1.56	21.09 (4C)	18.70 (2C)
3d	0.13 (s)	0.61 (m, 8H)	1.50 (m, 8H)	113.97	−1.56	27.54 (4C)	16.41 (4C)

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1a, 5357-38-0; **1b**, 13528-93-3; **1c**, 2295-06-9; **1d**, 14799-64-5; **1e**, 4342-61-4; **2**, 4301-15-9; **3a**, 25202-43-1; **3b**, 97071-87-9; **3c**, 97071-86-8; **3d**, 97071-85-2; **3e**, 85263-68-9; **4a**, 97071-89-1; **4b**, 97071-88-0; **4e**, 89571-48-2; **5a**, 97071-91-5; **5b**, 97071-90-4; **6c**, 97071-84-6; **6d**, 97071-83-5.

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[14] *Experimental procedure:* The reactions were carried out in anhydrous tetrahydrofuran (THF) under nitrogen on a 10- to 20-mmol scale. The yields are unoptimized crude yields. **1a**–**d** and **1e** were synthesized by chlorodemethylation [4] of **7a** [4], **7b** (Fluka), **7c** [12], **7d** [13], and **7e** (Fluka), respectively. To **2** in THF at 55–60°C were added equivalent amounts of **1** over 15 min with stirring. After stirring for 2 h at this temperature, the reaction mixture was hydrolyzed with 10% NH_4Cl solution and extracted three times with pentane. The combined pentane extracts were washed ten times with saturated NH_4Cl solution and dried over $MgSO_4$. Removal of the solvent left a partly crystalline residue, which was fractionally sublimed at ca. 10^{-2} torr. In some cases, additional recrystallization was necessary. The purity was checked by gas chromatography (3% SP-2100, 190–260°C). **6c** and **6d** were characterized by MS (isotope distribution corresponds to 2 Si); the other products were characterized by IR, ^{1}H-NMR, and ^{13}C-NMR spectroscopy.

Light-Induced [2+2] Cycloaddition Reactions of Nonconjugated Dienes—the Effect of Through-Bond Interaction**

By *Rolf Gleiter** and *Wolfram Sander*

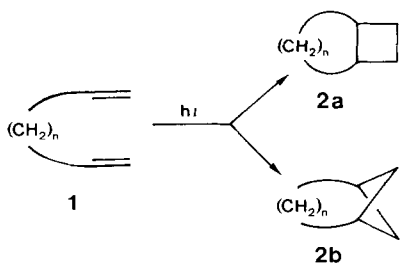
Dedicated to Professor Rolf Huisgen on the occasion of his 65th birthday

Light-induced intramolecular [2+2] cycloaddition reactions of nonconjugated dienes, **1**, lead via parallel cycloaddition to 1,2-bridged cyclobutanes, **2a**, or via cross cycloaddition to 1,3-bridged cyclobutanes, **2b**.[1] As pointed out by *Srinivasan* et al.,[1] the ratio of **2a** to **2b** de-

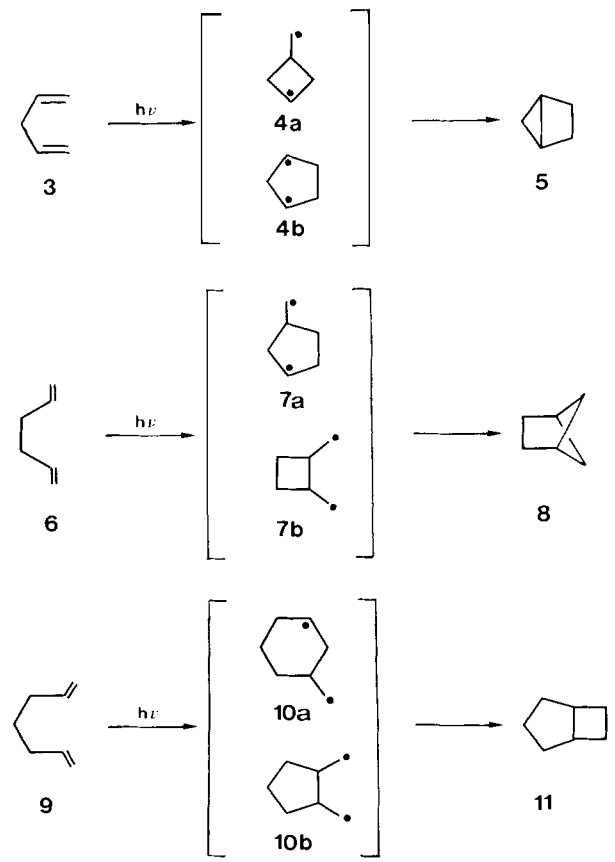
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pends on the number (n) of methylene groups between the double bonds in **1**. For n = 1 and 3, **2a** predominates, while for n = 2, **2b** is mainly formed. The dependence of the product ratio on n is even more drastic in cyclic dienes. Here, in almost all cases, only one product is formed.[1,2]



To rationalize these observations, *Srinivasan* et al. suggested that the initial step, which gives a diradical, involves preferential formation of a five-membered ring ("rule of the five").[1] Scheme 1 shows three examples. The postulated diradical intermediates **4b**, **7a**, and **10b** contain two, one, or no radical centers in the five-membered ring and thus have very different structures. In order to explain the stereochemistry of the reaction, it is assumed that these diradicals are more stable than the other possibilities **4a**, **7b**, and **10a**.



Scheme 1.

We present here an alternative explanation in which electronic factors (as well as steric factors[3]) in the educts and transition states are stressed instead of the relative stabilities of the primary intermediates (e.g., five-membered-ring vs. six-membered-ring diradicals). To demonstrate these electronic factors we constructed a molecular orbital and state correlation diagram, as introduced by *Woodward*

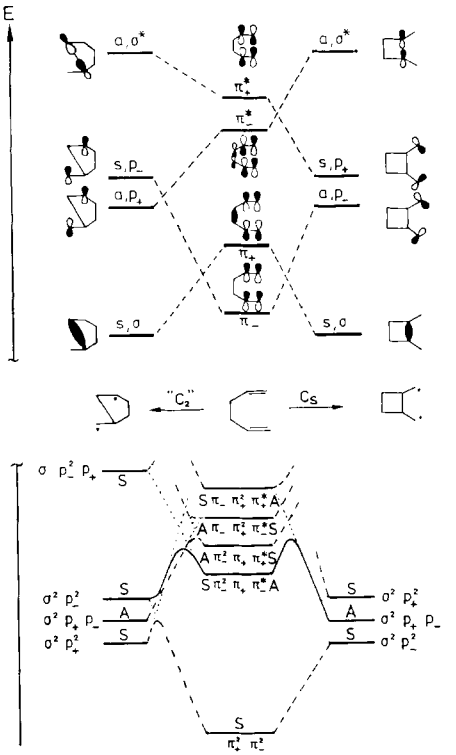


Fig. 1. Orbital (top) and state (bottom) correlation diagrams for the intramolecular cycloaddition of **6** to give **7a** (left) and **7b** (right) assuming local C_2 and C_s symmetry, respectively. The sequence of the frontier orbitals of **7b** is obtained if through-bond effects are assumed to predominate.

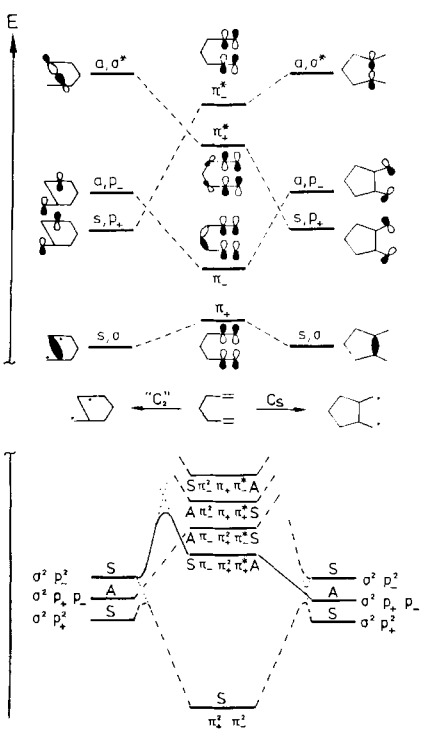
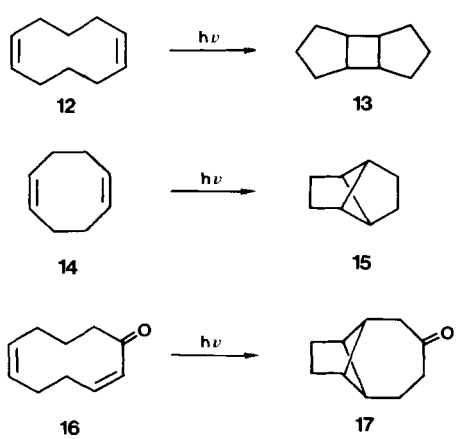


Fig. 2. Orbital (top) and state (bottom) correlation diagrams for the intramolecular cycloaddition of **9** to give **10a** (left) and **10b** (right) assuming local C_2 and C_s symmetry, respectively.

and *Hoffmann*[4] and further developed by *Dauben, Salem,* and *Turro*,[5] for **6**→**8** (via **7a** or **7b**) and for **9**→**11** (via **10a** or **10b**). We assume that the photochemical ring closure occurs via exciplex formation which forces the double bonds of **1** on top of each other.[6] To understand the difference between the two reactions it is important to note that the sequence of the frontier orbitals in **6** and **9** is different (Fig. 1 and 2). For **6**, through-space and through-bond interactions are opposed and, due to the dominance of the latter, the sequence is reversed compared with that obtained for two interacting ethylenes. For **9**, however, the orbital sequence is predicted to be the same as for two interacting ethylenes since through-space and through-bond interactions act in the same direction.

To understand the effect of the sequence of the frontier orbitals on the photochemistry we consider the molecular orbital and state correlation diagrams for the nonconcerted intramolecular cycloaddition (Fig. 1 and 2) of **6** to give **7a** and **7b** and of **9** to give **10a** and **10b**, assuming local C_2 and C_s symmetry, respectively.[8,9] As shown in the lower part of the two figures, both dienes have four excited states of similar energy arising from four $\pi^*_{+,-} \leftarrow \pi_{+,-}$ transitions. Whereas the lowest excited state of **9** correlates with a low-energy state of **10b** without any electronically determined activation barrier, the correlation with **10a** exhibits a barrier. The lowest excited state of **6** correlates with low-energy states of both **7a** and **7b**, but activation barriers are present. The activation energy for **6**→**7a** is lower than that for **6**→**7b** due to the correlation of the lowest excited state of **6** with a lower-energy excited state of **7a** ($\sigma p^2_- p_+$). The corresponding state of **7b** (p^2_-, σ, σ^*, not shown in Fig. 1) is much higher in energy. Thus, the magnitude of the through - bond interaction in **6** and **9** influences strongly their reactivity in the excited state.

The correlations suggest that light-induced parallel [2+2] cycloaddition of nonconjugated dienes should occur if the two double bonds are bridged by an odd number of carbon atoms. If an even number of carbon atoms connect the two double bonds, other reactions of the excited state, such as the cross [2+2] cycloaddition or radiationless transition, are likely to occur. Examples of the latter possibility are shown by *syn*-tricyclo[4.2.0.0^{2,5}]octadiene, which does not yield cubane on irradiation,[3,10] and by hypostrophene, which does not react to give pentaprismane.[3,11] A strong through-bond interaction has been postulated for both dienes on the basis of PE-spectroscopic data.[11,12]



If the two double bonds are connected by two aliphatic chains as in the cyclic dienes **12**, **14** and **16**, larger through-bond interactions are expected. This is in accord with the experimental findings[2] that, in almost all cases, these compounds undergo exclusively parallel [2+2] cycloaddition for odd bridges (**12**→**13**[2a]) and cross [2+2] cycloaddition for even bridges (**14**→**15**[2b] and **16**→**17**[2d]).

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^{15}N-^{29}Si Coupling Constants and ^{15}N Isotope Effect on ^{29}Si Chemical Shifts in Compounds with Natural Isotopic Abundance

By *Ēriks Kupče, Edvards Liepiņš,* and *Edmunds Lukevics**

Coupling constants provide information concerning the structure, bonding, and dynamic processes of molecules.[1] Until recently, ^{15}N-^{29}Si coupling constants have received only scant attention in the literature,[2] mainly because of the necessity for isotopically enriched samples. In an earlier paper[3] we have shown that $^1J(^{15}N\text{-}^{29}Si)$ may be measured from ^{29}Si satellites in ^{15}N-NMR spectra at the natural abundance level of isotopes using an INEPT pulse sequence for accumulation. However, this method is limited by the small values of long-range ^{15}N-^{1}H couplings; therefore, practically only compounds bearing an NH group can be investigated.

We show here that $^1J(^{15}N\text{-}^{29}Si)$ can be easily measured from ^{15}N satellites in ^{29}Si-NMR spectra[4] with ca. 100-fold greater sensitivity. Indeed, for compound **1**, only eight scans (25-s measuring time instead of ca. 1 hour in the case of ^{15}N-NMR spectra) were necessary to obtain the required information (Fig. 1). Since polarization transfer occurs via the methyl groups on the silicon atom, the pres-

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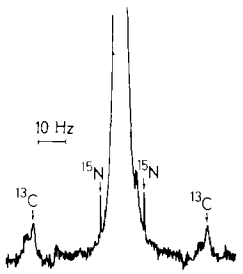


Fig. 1. ^{15}N Satellites in the 71.55-MHz ^{29}Si-NMR spectrum of **1**. In contrast to the ^{15}N satellites, the central signal and the ^{13}C satellites are broadened [5]. Bruker WM-360 spectrometer; ca. 80% solution in $CDCl_3$ at 303 K; 10-mm sample tube; relaxation time: 2 s; INEPT pulse sequence [4]; number of scans: 8.

ence of NH protons is no longer necessary. Furthermore, the ^{29}Si-NMR spectra provide additional information on $^1J(^{13}C\text{-}^{29}Si)$, the ^{29}Si-NMR chemical shifts, the ^{15}N-isotope effect on ^{29}Si chemical shifts, and the quadrupolar relaxation time of ^{14}N nuclei.[5]

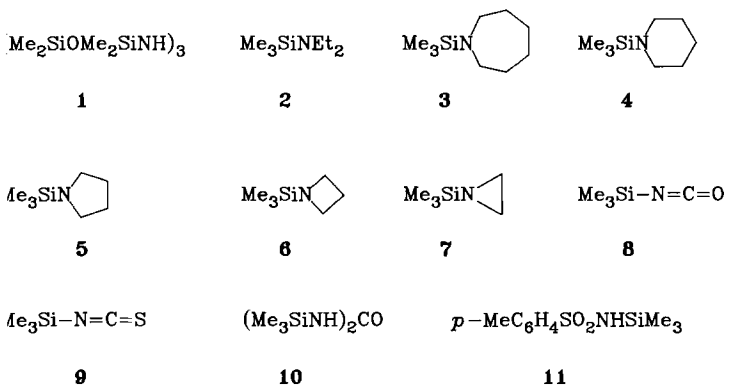


Table 1. NMR parameters of SiN compounds **1**—**9** from ^{29}Si-NMR spectra [a].

Compound	$^1J(^{15}N\text{-}^{29}Si)$ [Hz] [b]	$\Delta\delta(^{29}Si,^{15}N/^{14}N)$ [ppm] [c]	$\delta(^{29}Si)$ [d]	$\Delta\nu_{1/2}$ [Hz] [e]
1	17.2	0.0061	−12.27	1.9
2	19.2	0.0110	3.81	1.5
3	19.6	0.0112	3.53	1.6
4	17.8	0.0120	3.89	1.6
5	16.5	0.0118	2.51	1.3
6 [f]	13.6	0.0115	1.81	1.7
7	< 5	—	14.16	0.3
8	14.5	0.0155	3.90	6.5
9 [g]	12.2	—	5.31	—

[a] Bruker WM-360 spectrometer (71.55 MHz); ca. 50% (vol-%) solutions in $CDCl_3$ at 303 K, INEPT pulse sequence [4], relaxation time: 2 s, 100—200 scans. [b] ±0.1 Hz. [c] ±0.0005. [d] Relative to TMS (±0.1). [e] Line width at half height (±0.2 Hz). [f] In C_6D_6. [g] Measured in ^{15}N-NMR spectrum.

The results obtained (see Table 1) demonstrate that the $^{15}N\text{-}^{29}Si$ coupling constants depend strongly on the nitrogen hybridization and the nature of the N–Si bond. Within the series of cyclic amines **3**—**7**, there is a significant decrease in $^1J(^{15}N\text{-}^{29}Si)$ with diminishing ring size. The same drop in $^1J(^{15}N\text{-}^{31}P)$ had been observed earlier for analogous phosphorus compounds[6] and can be rationalized by the increased pyramidal geometry of nitrogen in smaller rings. Relatively small $^1J(^{15}N\text{-}^{29}Si)$ values were found in compounds **8** and **9**, which contain a C=N bond. This can be possibly attributed either to an increase in the negative contribution of the non-contact terms to ^1J[1] or simply to an increased length of the N–Si bond in **8** and **9**.[7]

We were not able to detect ^{15}N satellites in the ^{29}Si-NMR spectra of trimethylsilyl amides such as **10** and **11**. This may be due to a fast inter- and intramolecular exchange of the trimethylsilyl groups in such compounds.[8]

We have measured for the first time the ^{15}N isotope effect on the ^{29}Si chemical shift (Table 1). The isotope effect depends on the bond length, order, and energy.[9, 10] The high-field shift ($\Delta J = 0.006$—0.015 ppm) of the ^{29}Si-NMR signal of the molecules bearing an ^{15}N isotope is about half the value of the analogous ^{13}C chemical shift.[11]

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1, 86628-00-4; **2**, 996-50-9; **3**, 27001-69-0; **4**, 3768-56-7; **5**, 15097-49-1; **6**, 41268-75-1; **7**, 2116-90-7; **8**, 1118-02-1; **9**, 2290-65-5; **10**, 18297-63-7; **11**, 1015-42-5; ^{15}N, 14390-96-6.

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Total Synthesis of Ulicyclamide**

By *Ulrich Schmidt** and *Peter Gleich*

Dedicated to Professor Gerhard Billek on the occasion of his 60th birthday

Peptides containing thiazole rings have often been found as fungal metabolites. Cancerostatic cyclopeptides containing thiazole and dihydrooxazole rings have been

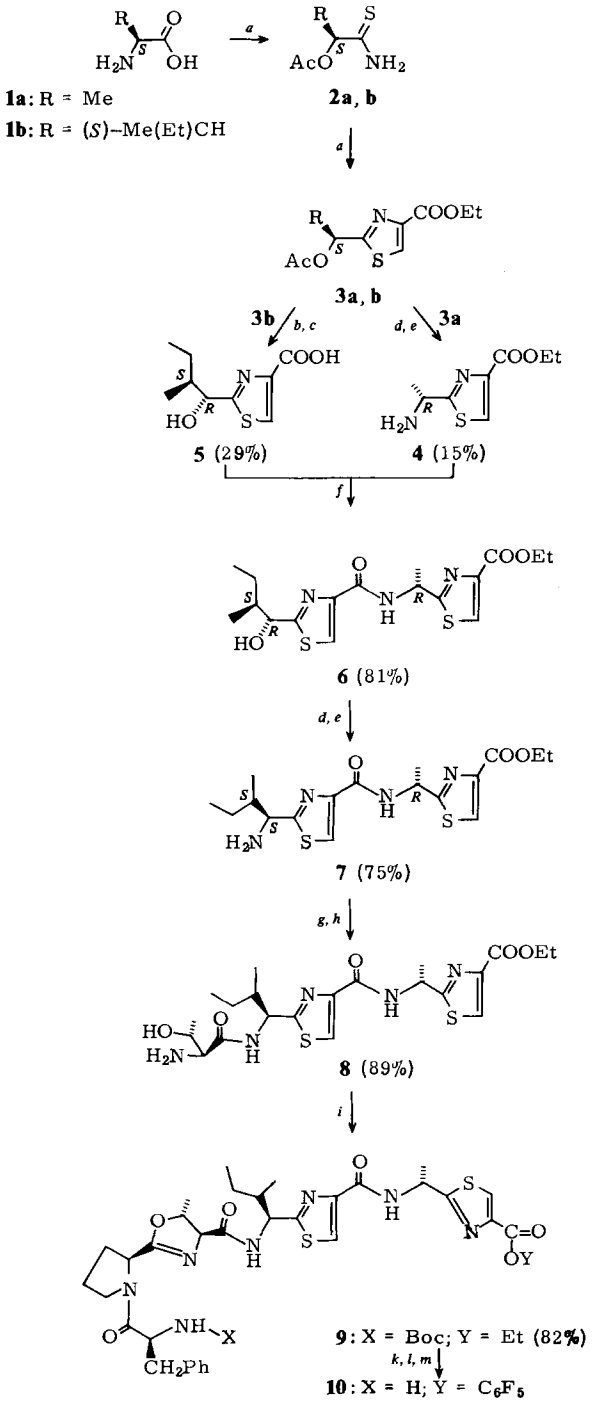
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[**] Amino Acids and Peptides, Part 52. This work was supported by the Fonds der Chemischen Industrie, the Deutsche Forschungsgemeinschaft, and BASF AG.—Part 51: U. Schmidt, J. Wild, *Liebigs Ann. Chem.*, in press.

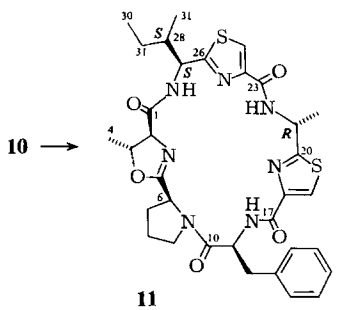
isolated from lower marine organisms (e.g., *Lissoclinum patella*). The biosynthesis of these compounds takes place via cysteine-containing or via threonine- and serine-containing peptides, respectively.

We report here the first total synthesis of a cyclopeptide that contains thiazole *and* dihydrooxazole rings. This compound, ulicyclamide, **11**, was isolated and its structure elucidated by *Scheuer* and *Ireland*.[1,2]

In our synthesis of dolastatin isomers,[3] we prepared (*R*)-(aminoalkyl)thiazolecarboxylic acids from (*S*)-amino acids. This route led, via protected (*S*)-α-hydroxycarbothioamides, to (*S*)-(hydroxyalkyl)thiazolecarboxylic acids, which were transformed with inversion into (*R*)-(aminoalkyl)thiazole compounds. This sequence can also be employed in the synthesis, from (*S*)-alanine, **1a**, of the thiazole compound **4**, which has the (*R*) configuration and is contained in ulicyclamide, **11**. For the construction of the (*S,S*)-2-(1-amino-2-methylbutyl)-4-thiazolylcarbonyl fragment of **7** from (*S*)-isoleucine, **1b**, two inversions were required at the C atom bearing the amino group. The synthesis of ulicyclamide, **11**, is shown in Schemes 1 and 2.



Scheme 1. Synthesis of the linear educt **10** for the ring closure to ulicyclamide. *a*: Analogous to [3]; *b*: diethyl azodicarboxylate, Ph_3P, PhCOOH (inversion); *c*: NaOH, H_2O; *d*: diethyl azodicarboxylate, Ph_3P, HN_3 (inversion); *e*: Pd/H_2; *f*: dipyridyl disulfide, Ph_3P; *g*: Boc-Thr(*t*Bu)-S-pyridyl; *h*: CF_3COOH; *i*: imidic ester of Boc-Phe-Pro; *k*: NaOH, H_2O; *l*: C_6F_5OH, dicyclohexyl carbodiimide, ethyl acetate; *m*: CF_3COOH.



Scheme 2. Ring closure of **10** to ulicyclamide **11**. **10**·4CF_3COOH (0.1 mmol) was added over 8 h to a solution containing 0.4 mmol of 4-pyrrolidinopyridine in 500 mL of dioxane at 95 °C.

The (*R*)-2-(1-aminoethyl)-4-thiazolecarboxylic ester **4** is accessible via a known route from (*S*)-alanine, **1a**.[3] (*S,S*)-2-(1-hydroxy-2-methylbutyl)-4-thiazolecarboxylic acid was prepared analogously from (*S*)-isoleucine, **1b**, and converted via a Mitsunobu reaction[4] with inversion into the thiazole compound **5** containing a side chain having (1*R*,2*S*) configuration. The two thiazoles **4** and **5** are combined to give the amide **6** by redox condensation.

The transformation of the hydroxyl group of **6** into an amino group was achieved in turn via a Mitsunobu reaction[4] with inversion. The compound **7** so obtained is acylated with a protected threonine and, after cleavage of the two protecting groups, the amino alcohol **8** is condensed with Boc-phenyl-alanyl-proline imidic ester to give the dihydrooxazole compound **9**. Hydrolysis of the ester group on the thiazole ring, conversion into the pentafluorophenyl ester,[3,5] and cleavage of the Boc group with trifluoroacetic acid furnishes the tetrakis(trifluoroacetate) of the ω-aminopentafluorophenyl ester **10**. This ester is cyclized under high-dilution conditions to ulicyclamide, **11**, which can be isolated by medium pressure chromatography (20%).[6]

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1a, 56-41-7; **1b**, 73-32-5; **2a**, 96965-14-9; **2b**, 96965-15-0; **3a**, 96965-16-1; **3b**, 96965-17-2; **4**, 96965-18-3; **5**, 96965-19-4; **6**, 96965-20-7; **7**, 96998-86-6; **8**, 96965-21-8; **9**, 96965-22-9; **10**, 4 CF_3CO_2H, 96998-88-8; **11**, 74839-81-9; C_6F_5OH, 771-61-9; **16**, 97011-29-5; **17**, 23420-32-8; 4-pyrolidinopyridine, 2456-81-7; dipyridyl disulfide, 73370-52-2; Boc-Thr (*t*Bu)-S-pyridyl, 97011-29-5; Boc-Phe-Pro-OH, 23420-32-8.

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[6] Note added in proof (April 25, 1985): The synthetic product and the natural product proved to be identical in every respect. The better resolved 300-MHz ^{1}H-NMR spectrum of the synthetic product [7] allowed a more exact assignment of the signals of the protons on C-28 and C-29, which are not resolved in the ^{1}H-NMR spectrum of the natural product [δ = 1.88 (m, 1H) and 1.4 (m, 1H), 1.7 (m, 1H)]. We thank Prof. *C. Ireland* for a sample of ulicyclamide and a copy of the 270-MHz ^{1}H-NMR spectrum.

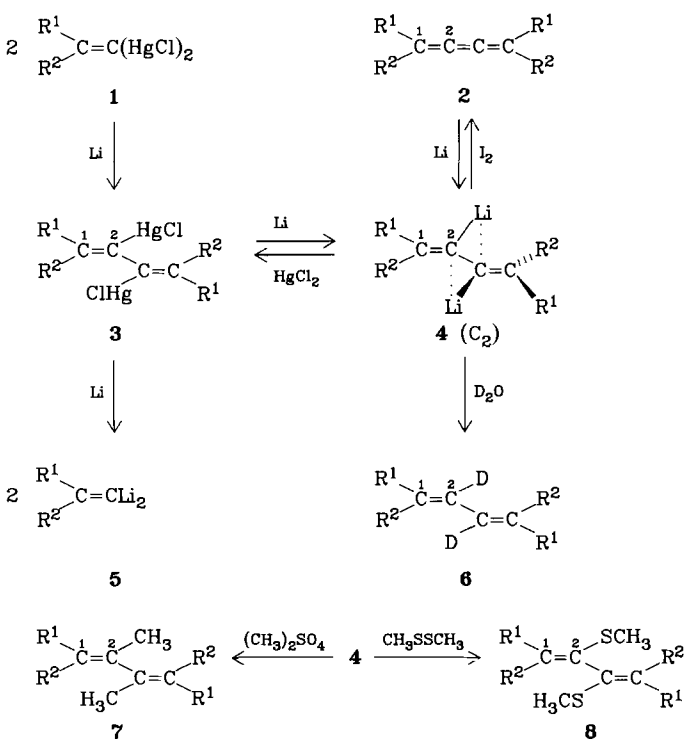
[7] **11**: $[\alpha]_D^{25}$ +59 (c = 0.43, CH_2Cl_2); HPTLC RP-18: R_f = 0.31 (CH_3OH/H_2O 8:2); MS (high resolution): M_r(found) 677.2452, M_r(calcd.) 677.2439 ($C_{33}H_{39}N_7O_5S_2$).—^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 9.11 (d, J = 5.3 Hz, 1H), 8.7 (d, J = 7.6 Hz, 1H), 8.08 (s, 1H), 8.04 (s, 1H), 7.87 (d, J = 10 Hz, 1H), 7.32 (s, 5H), 5.33 (m, 2H), 4.88 (m, 2H), 4.52 (t, J = 7.7 Hz, 1H), 4.29 (d, J = 4.3 Hz, 1H), 3.25 (m, 2H), 2.96 (dd, J = 12.7 Hz, 10.4 Hz, 1H), 2.67 (m, 1H), 2.11 (m, 2H), 1.88 (m, 1H), 1.73 (d, J = 6.6 Hz, 3H), 1.7 (m, 3H), 1.47 (d, J = 6.3 Hz, 3H), 1.4 (m, 1H), 0.89 (t, J = 7.4 Hz, 3H), 0.76 (d, J = 6.7 Hz, 3H).—^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ = 171.2(3), 169.5, 168.9, 160.7, 159.8, 150.7, 148.3, 136.1, 129.7(2), 128.7(2), 127.3, 123.3, 122.9, 82.4, 75.6, 56.6, 53.8, 53.6, 48.7, 47.2, 40.8, 38.1, 28.8, 25.4, 25.1, 24.4, 21.9, 15.9, 9.9.

2,3-Dilithio-1,3-butadienes via Addition of Lithium to Butatrienes**

By *Adalbert Maercker** and *Ralf Dujardin*

Dedicated to Professor Günther Wilke on the occasion of his 60th birthday

In the deuterolysis of (dilithiomethylene)cyclohexane **5a**,[2] which was synthesized from **1a** by direct mercury-lithium exchange, we often obtained up to 7% of the butadiene derivative **6a**[3] as a side product. This suggested the intermediacy of the 2,3-dilithio-1,3-butadiene derivative



a: R^1R^2 = $-(CH_2)_5-$; **b**: R^1 = R^2 = CH_3

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4a, which might have been formed from the mercury compound **3a**. That **3a** is in fact an intermediate in the transformation of **1a** to **5a** could be shown by interrupting the reaction after 10 min: **3a**[4] was formed in 95% yield and could be cleaved to **5a** with additional lithium powder. **4a** is formed as a side product in yields of up to 8%.

In order to synthesize a 2,3-dilithio-1,3-butadiene such as **4** by an independent route, we have attempted to add lithium to the central double bond of the readily accessible tetramethylbutatriene **2b**.[5] Indeed, **4b** was formed in 97% yield.[6,7] It was characterized by deuterolysis to **6b** (yield 86%),[8] reaction with mercury(II) chloride to give **3b** (yield 70%),[9] and reconversion to **2b** with iodine (yield 75%).[10]

Evidence for a doubly bridged structure **4b** or similarly structured aggregates was provided by the ^{13}C-NMR spectrum (100.6 MHz)[11] of the ^{6}Li-labeled compound: the two α-carbon atoms (C-2) exhibit a quintet in [D_8]tetrahydrofuran at -100 °C, $\delta(^{13}C)$ = 188.7, $^1J(^6Li,^{13}C)$ = 6.7 Hz. A second species of the compound **4b** is also detectable in the solution and exhibits only a broad, unresolved signal at $\delta(^{13}C)$ = 187.9 for C-2. Moreover, all remaining ^{13}C-NMR signals appear twice with nearly the same intensity: the singlet of the β-carbon atom (C-1), $\delta(^{13}C)$ = 109.2, 100.9, and the signals of the pairwise differing methyl groups, $\delta(^{13}C)$ = 32.0, 29.6, 23.4, 22.0 (R^1, R^2). A non-bridging, dimeric structure would also be in accord with the ^{13}C-NMR spectroscopic results.[12] An X-ray structure determination of **4b**, which is obtained in crystalline form from diethyl ether, and ab initio calculations are being carried out.[13]

However, 2,3-dilithio-1,3-butadienes **4** are not only of theoretical interest, but also have considerable synthetic potential. Thus, hexamethylbutadiene **7b** (yield 80%)[14] is obtained by reaction of **4b** with dimethyl sulfate, and the 2,3-bis(methylthio)-1,3-butadiene derivative **8b** (yield 75%)[15] by reaction of **4b** with dimethyl disulfide. Interestingly, **4b** is stable towards excess lithium. Only after addition of mercury(II) chloride is it cleaved to 1,1-dilithio-2-methyl-1-propene **5b**.

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CAS Registry numbers:
2b, 2431-31-4; **3a**, 96445-46-4; **3b**, 96445-42-0; **4b**, 96445-43-1; **5b**, 57012-92-7; **6a**, 96445-44-2; **6b**, 96445-45-3; **7b**, 1114-06-3; **8b**, 74152-98-0; $HgCl_2$, 7487-94-7; Li, 7439-93-2.

[1] A. Maercker, M. Theis, *Angew. Chem. 96* (1984) 990; *Angew. Chem. Int. Ed. Engl. 23* (1984) 995.

[2] A. Maercker, R. Dujardin, *Angew. Chem. 96* (1984) 222; *Angew. Chem. Int. Ed. Engl. 23* (1984) 224.

[3] **6a**: ^{13}C-NMR (20.1 MHz, $CDCl_3$): δ = 140.0 (C-1), 116.8 ($^1J(^{13}C,D)$ = 23.1 Hz, C-2), 37.4, 31.2, 28.6, 28.4, 27.5 (R^1, R^2).

[4] **3a** was insufficiently soluble for NMR measurements; it was characterized by mass spectroscopy. MS (70 eV): m/z 662 ($M^{\oplus}$, 0.3%), 460 ($M^{\oplus}$ − Hg, 3.7), 426 ($M^{\oplus}$ − HgCl, 4.2), 331 (0.5 $M^{\oplus}$, 2.4), 202 (Hg, 100), 187 ($M^{\oplus}$ − 2 HgCl − H, 6.2), 94 (C_7H_{10}, 31). Only the highest peak of each mercury cluster is given.

[5] W. Krestinski, *Ber. Dtsch. Chem. Ges. 59* (1926) 1930.

[6] In contrast, alkali metals are known to add to tetraphenylbutatriene via 1,4-addition: A. Zweig, A. K. Hoffmann, *J. Am. Chem. Soc. 84* (1962) 3278; R. Nahon, A. R. Day, *J. Org. Chem. 30* (1965) 1973. In the deprotonation of 1,4-diphenyl-2-butyne by butyllithium/tetramethylethylenediamine (TMEDA), the butyne structure is also largely retained. The nearly orthogonal bisallylic geometry expected on the basis of MNDO calculations is confirmed by the X-ray structure determination of 1,4-dilithio-1,4-diphenyl-2-butyne·2TMEDA: D. Wilhelm, *Dissertation*, Universität Erlangen-Nürnberg 1984; D. Wilhelm, H. Dietrich, P. von R. Schleyer, unpublished.

[7] *General experimental procedure:* **2** (50 mmol) dissolved in 35 mL of diethyl ether is added to lithium powder (1.4 g, 200 mmol, 2% sodium) sus-

pended in 15 mL of anhydrous diethyl ether under argon; the addition is carried out so as to maintain a gentle reflux. After 1 h, the excess lithium is filtered off and the amount of **4** is determined by double titration according to the procedure of *Gilman* et al. [16]; yield >95%.

[8] **6b**: ^{13}C-NMR (20.1 MHz, $CDCl_3$): $\delta = 131.9$ (C-1), 121.0 ($^1J(^{13}C,D) = 23.0$ Hz, C-2), 26.1, 18.0 (R^1, R^2).

[9] **3b**: ^{13}C-NMR (20.1 MHz, [D$_6$]DMSO/C_2H_5OH): $\delta = 150.0$ (C-2), 133.7 (C-1), 20.5, 18.5 (R^1, R^2).

[10] **2b**: ^{13}C-NMR (20.1 MHz, $CDCl_3$): $\delta = 153.1$ (C-2), 107.4 (C-1), 23.8 (R^1, R^2).

[11] We thank Prof. Dr. *H. Günther* and Dr. *P. Schmitt* für the measurements as well as for discussion of the preliminary results. Exact analysis of the ^{1}H-, ^{13}C-, and ^{6}Li-NMR spectra: H. Günther, P. Schmitt, R. Dujardin, A. Maercker, unpublished.

[12] Cf. D. Seebach, R. Hässig, J. Gabriel, *Helv. Chim. Acta 66* (1983) 308; R. Hässig, D. Seebach, *ibid. 66* (1983) 2269.

[13] A. Maercker, R. Dujardin, B. Engelen, W. Buchmeier, R. Seeger, unpublished.

[14] **7b**: b.p. = 85–86°C/100 mbar; ^{13}C-NMR (20.1 MHz, $CDCl_3$): $\delta = 131.6$ (C-1), 123.6 (C-2), 20.7, 19.1 (R^1, R^2), 16.9 (CH_3).

[15] **8b**: b.p. = 102–103°C/10 mbar; ^{13}C-NMR (20.1 MHz, $CDCl_3$): $\delta = 132.3$ (C-1), 125.8 (C-2), 22.3, 20.6 (R^1, R^2), 14.3 (SCH_3).

[16] H. Gilman, A. H. Haubein, *J. Am. Chem. Soc. 66* (1944) 1515.

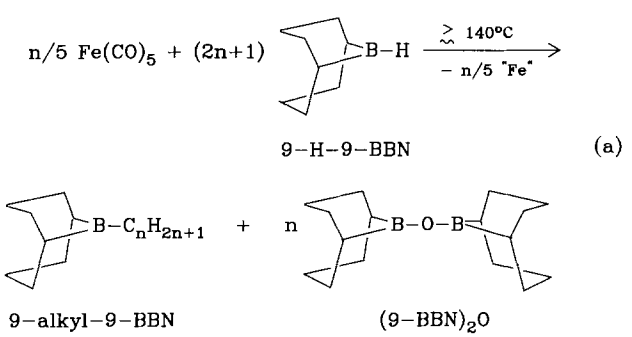
An Organoboron Model System for the Fischer-Tropsch Synthesis**

By *Roland Köster** and *Mohamed Yalpani*

Dedicated to Professor Heinz Hoberg on the occasion of his 60th birthday

Since the discovery of the Fischer-Tropsch synthesis[1] there have been numerous and extensive studies, not only from the standpoint of its technology[2] but also with regard to the reaction mechanism involved[3a,c] and the other variants[3b] of the still very interesting C_1-growth reaction. However, in contrast to the many investigations of assumed part steps, the overall chain formation reaction cannot be followed with a suitable model system.

Herein we report on a quantitative,[4] reductive C_1-polymerization of carbon monoxide, present as mono-, di- or trinuclear metal carbonyl, with 9-borabicyclo[3.3.1]nonane (9-H-9-BBN)[5] to give 9-alkyl-9-borabicyclo[3.3.1]nonanes (9-alkyl-9-BBN). The reaction proceeds according to Eq. (a), giving 9-BBN derivatives with mainly linear alkyl moieties. These have so far been identified up to 9-decyl-9-BBN (n = 10).



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[**] Boron Compounds, Part 67. We thank Mrs. *F. Sagheb* (Dept. Dr. *Schomburg*) for the gas-chromatographic separations and Mr. *W. Schmöller* (Dept. Dr. *Henneberg*) for the mass spectrometric measurements. – Part 66: R. Köster, S. Penadés-Ullate, W. V. Dahlhoff, *Angew. Chem. 97* (1985) 508; *Angew. Chem. Int. Ed. Engl. 24* (1984) 519.

1 Mole of pentacarbonyliron with ≈11 moles of 9-H-9-BBN[6] in e.g. mesitylene or *n*-nonane leads in a strong exothermic reaction within a few minutes on heating at ≈140°C to the formation of a black precipitate, whose composition corresponds to the empirical formula $FeC_2H_{3.5}$. Referred to 9-H-9-BBN, about one equivalent of gas, consisting of ≈2/3 H_2 and ≈1/3 CH_4, is liberated. Small amounts of ethane (<2%) as well as traces of C_3/C_4-hydrocarbons are also detectable (MS analysis). A colorless liquid fraction and a white solid can be recovered from the reaction mixture.[7] The liquid can be separated gas-chromatographically into numerous 9-alkyl-9-BBN compounds whose retention volumes and MS fragmentograms are consistent with those of authentic samples. The solid product is the diboroxane $(9\text{-BBN})_2O$,[8] an organoboron equivalent of the water formed in the Fischer-Tropsch synthesis.—9-Alkyl-9-BBN mixtures of varying composition, as well as the oxide $(9\text{-BBN})_2O$, can also be obtained in an analogous way with $Fe_2(CO)_9$ (≳140°C), with $Fe_3(CO)_{12}$ (≳130°C) or with $Co_2(CO)_8$ (≳90°C) according to Eq. (a).

The reaction mixtures contain, apart from the major products with unbranched alkyl residues, also derivatives with straight alkane chains not bound to C-1 (e.g. 9-*sec*-butyl-9-BBN) and compounds with methyl-branched alkyl groups (e.g. 9-isobutyl-9-BBN) (cf. Table 1).

Table 1. Relative yields [%] of 9-R-9-BBN from metal carbonyls and 9-H-9-BBN [a]. Procedure: [7].

Alkyl C atoms	Name	≥BH/CO-ratio	$Fe(CO)_5$	$Fe_2(CO)_9$	$Fe_3(CO)_{12}$	$Co_2(CO)_8$
		2.0	2.3	2.2	2.3	1.9
1	Methyl		21.3	42.9	50.0	46.7	24.4
2	Ethyl		21.8	14.5	16.1	17.4	13.6
3	Propyl		14.4	8.4	10.0	11.7	10.3
4	Isobutyl		2.2	1.3	1.3	1.6	2.7
	sec-Butyl		0.7	0.4	0.6	0.7	1.0
	Butyl		7.2	4.4	5.0	5.6	5.7
5	$\sum C_5$-Isomers[c]		3.1	2.0	2.0	2.2	3.9
	Pentyl		4.1	2.4	2.7	3.0	2.9
6	$\sum C_6$-Isomers[c]		2.8	1.9	1.3	1.4	3.7
	Hexyl		2.4	1.4	1.4	1.6	1.6
7	$\sum C_7$-Isomers[c]		1.6	0.8	0.8	0.8	2.5
	Heptyl		1.5	1.0	0.8	0.8	1.7
8	$\sum C_8$-Isomers[c]		0.8	0.4	1.4	0.3	1.0
	Octyl		0.8	0.6	0.6	0.5	1.1
9	$\sum C_9$-Isomers[c]		0.9	n. d.	n. d.	n. d.	n. d.
	Nonyl		1.0	0.7	n. d.	0.3	1.9
10	$\sum C_{10}$-Isomers[c]		n. d.	n. d.	n. d.	n. d.	n. d.
	Decyl		0.7	0.4	n. b.	n. d.	n. d.
—	Residual alkyl moieties [b]		12.7	16.8	6.0	5.4	21.0

[a] GC/MS analyses; GC peaks <0.3% ignored; n. d. = not determined. [b] Separation from the highly viscous residue by cooling its pentane solution to –78°C, and filtration. [c] $\sum C_x$ isomers include all alkyl moieties with x carbons, but with the exception of straight chain alkyl residues bonded to the boron atom via C-1.

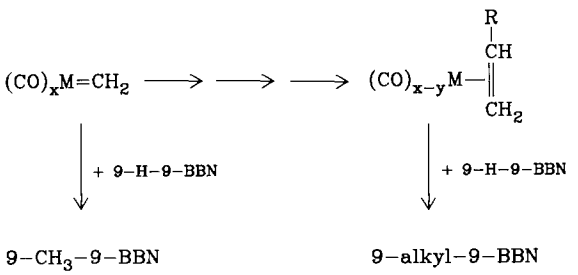
$Fe_2(CO)_9$ reacts with 9-deuterio-9-borabicyclo[3.3.1]nonane[5d] (9-D-9-BBN) in mesitylene >140°C to give 9-alkyl-9-BBN compounds, whose 9-alkyl moieties contain only very little deuterium[9]. Reaction of 9-D-9-BBN with $Co_2(CO)_8$ in heptane at ≈90°C, however, leads to formation of 9-perdeuterioalkyl-9-BBN compounds (degree of deuteriation of the alkyl moieties: >95%). The alkyl groups of the 9-alkyl-9-BBN compounds must therefore be generated by reduction of the metal-coordinated CO ligands. Presumably metal carbenes and/or metal-alkene π-

Table 2. Relative yields [%] of 9-methyl-9-BBN and 9-ethyl-9-BBN as a function of the >BH/CO ratio.

Carbonylmetal compound [b] (solvent)		CO [mmol]	9-H-9-BBN [mmol]	>BH/CO	Yield [a] 9-Me-9-BBN [%]	Yield [a] 9-Et-9-BBN [%]	9-Me-9-BBN / 9-Et-9-BBN
$Fe(CO)_5$	(M)	38.0	87	2.3	42.9	14.8	2.9
	(N)	32.0	67.8	2.1	29.4	24.0	1.2
	(M)	38.0	35.0	0.9	24.2	33.6	0.1
	(M) [c]	35.0	77.8	2.2	5.2	20.0	0.25
	(M) [c]	399.0	79.8	0.2	1.0	21.0	0.05
$Fe_2(CO)_9$	(N)	10.8	48.6	4.5	59.0	21.0	2.8
	(N)	14.4	32.4	2.3	50.3	20.3	2.5
	(N)	16.6	20.8	1.3	30.1	33.8	0.9
$Co_2(CO)_8$	(M)	27.2	50.0	1.8	18.6	30.1	0.6
	(M) [d]	27.2	51.4	1.9	35.4	17.6	2.0

[a] GC peaks; conditions for separation: capillary column (36 m); dexsil 300; injection block: 150°C; column: 40—280°C (6°/min). [b] Standard conditions: carbonylmetal compound and 9-H-9-BBN in mesitylene (M) or in nonane (N) heated for ≈1 h at ≥140°C. [c] Portionwise addition (≈3 h) of solid 9-H-9-BBN to the solution of $Fe(CO)_5$ at 140°C. [d] Heated at ≈90°C.

complexes are formed as intermediates in the synthesis (cf. Scheme 1).



Scheme 1. Possible mode of the 9-alkyl-9-BBN formation.

Different rates of the reduction and CO-insertion reactions lead, depending upon the amount of monomeric 9-H-9-BBN available in solution, to varying amounts of 9-methyl-, 9-ethyl-, and higher 9-alkyl-9-BBN homologues. Thus, at low >BH/CO ratios the amount of 9-methyl-9-BBN drastically decreases, e.g. on slow addition of 9H-9-BBN (cf. Tables 1 and 2).

We presume that the higher 9-alkyl-9-BBN compounds (alkyl ≳ C_2H_5) are only formed on polynuclear metal clusters or on the surfaces of metal particles which separate from the original homogeneous solutions of the metal carbonyls.

The composition of the 9-alkyl-9-BBN mixture depends on the molar ratio of the reactants and on the reaction conditions, i.e. the temperature, the heating rate, or additives, e.g. alkali metal alkoxides. The metal carbonyl/9-H-9-BBN system is thus suitable as a readily variable, easily accessible reaction mixture for the investigation of the Fischer-Tropsch synthesis.

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CAS Registry numbers:
9R-9-BBN (R = methyl), 23418-81-7; 9R-9-BBN (R = ethyl), 52102-17-7; 9R-9-BBN (R = propyl), 1127-78-2; 9R-9-BBN (R = butyl), 23532-74-3; (9-BBN)$_2$O, 74744-62-0; 9H-9-BBN, 280-64-8; $Fe(Co)_5$, 13463-40-6; $Fe_2(Co)_9$, 15321-51-4; $Co_2(Co)_8$, 10210-68-1; $Fe_3(Co)_{12}$, 17685-52-8.

[1] Patent (DRP 484337), entitled "Verfahren zur Gewinnung mehrgliedriger Paraffinkohlenwasserstoffe aus Kohlenoxyden und Wasserstoff auf katalytischem Wege", filed 60 years ago (July 22, 1925) by *Franz Fischer* and *Hans Tropsch* (Mülheim a. d. Ruhr).

[2] *Ullmanns Encyklopädie der Technischen Chemie, Vol. 14*, 4th Edit., Verlag Chemie, Weinheim 1977, p. 329—355; R. B. Andersen: *The Fischer-Tropsch Synthesis*, Academic Press, London 1984.

[3] a) C. Masters, *Adv. Organomet. Chem. 17* (1979) 61; C. K. Rofer-De Poorter, *Chem. Rev. 81* (1981) 447; G. Henrici-Olivé, S. Olivé: *The Chemistry of the Catalyzed Hydrogenation of Carbon Monoxide*, Springer, Berlin 1984; b) S. L. Suib, K. C. McMahon, L. M. Tau, C. O. Bennett, *J. Catal. 89* (1984) 20; c) W. A. Herrmann, *Angew. Chem. 94* (1982) 118; *Angew. Chem. Int. Ed. Engl. 21* (1982) 117.

[4] Compare the yields of the Fischer-Tropsch products with those of other metal carbonyl reductions: A. Wong, J. D. Atwood, *J. Organomet. Chem. 199* (1980) C9; *210* (1981) 395; C. Masters, C. van der Woude, J. A. van Doorn, *J. Am. Chem. Soc. 101* (1979) 1633.

[5] a) R. Köster, *Angew. Chem. 72* (1960) 626; b) R. Köster, P. Binger, *Inorg. Synth. 15* (1974) 141; c) cf. Houben-Weyl: *Methoden der Organischen Chemie, Bd. XIII/3a*, 4th Edit., Thieme, Stuttgart 1982, p. 330; d) see [5c], p. 339f.

[6] a) For determination of the hydride number (HZ_{BBN}), the 9-H-9-BBN consumed by the metal carbonyls was measured at ≈140°C [6b]: $Fe(CO)_5$ ($HZ_{BBN} = 11$); $Fe_2(CO)_9$ (20); $Fe_3(CO)_{12}$ (26.5); $Co_2(CO)_8$ (16). The consumption of open-chain alkyldiboranes(6) [5b,c] is greater (HZ [6b] > HZ_{BBN}); complex mixtures of trialkylboranes, trialkylboroxines and tetraalkyldiboroxanes; are formed; b) R. Köster, L. Synoradzki, *Chem. Ber. 117* (1984) 2850.

[7] *Experimental:* The yellow-orange slurry of 9-H-9-BBN [5b, c] (8.21 g, 67.8 mmol) and $Fe(CO)_5$ (1.21 g, 6.16 mmol) (>BH : Fe ≈ 11.1; >BH : CO ≈ 2.2 : 1) in nonane (≈8 mL) was heated slowly under protective gas; the color changed from orange-yellow through yellowish gray (50–80°C) to black. At ≥80°C 4.5 mmol of gas (MS: 68.5% H_2, 31.9% CH_4, ≈1.3% C_2H_6, ≈1% C_4H_{10}) were liberated. After stirring for ≈30 min (bath: ≈140°C; exothermic reaction up to ≈160°C) nonane (5.8 g; 14 torr; bath: ≲70°C) and a 9-alkyl-9-BBN mixture [≈1 g (calc. 0.96 g); 0.001 torr; bath: ≲90°C] ($\delta^{11}B = 88.2$) were distilled off (composition: cf. Table 1) under vacuum. From the highly viscous residue by sublimation in vacuo (0.001 torr; bath: 90—100°C) 7.75 g(calc. 7.95 g) of colorless (9-BBN)$_2$O remained [MS: $m/z = 258$; $\delta^{11}B = 59.3$]. After heating in boiling heptane one obtains 520 mg Fe-containing black solid (≈67% Fe).

[8] See [5c], pp. 816, 819.

[9] 9-D-9-BBN [5c] transforms at ≳140°C via dehydroboration/deuterioboration into partially deuterated 9-H-9-BBN compounds.

X-Ray Structure Determination of [α-(Phenylsulfonyl)benzyllithium-Tetramethylethylenediamine]$_2$: Chirality of an α-Sulfonyl "Carbanion"**

By *Gernot Boche,* Michael Marsch, Klaus Harms,* and *George M. Sheldrick*

Dedicated to Professor Rolf Huisgen on the occasion of his 65th birthday

α-Sulfonyl "carbanions" ($R^1R^2C^{\ominus}-SO_2R^3M^{\oplus}$) play an important role in synthetic chemistry.[1] The high acidity of

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the corresponding CH compounds and the fact that optically active α-sulfonyl "carbanions" can be prepared from optically active sulfones led early to numerous experimental[2] and theoretical[3] studies into the nature of the stabilization of a negative charge by a neighboring sulfonyl group ($-SO_2R^3$) and the origin of the chirality in the "carbanion." The central question was whether the anionic C atom was pyramidal or planar, and, if planar, what conformation the substituents on the S atom adopted with respect to those on the anionic C atom. The position of the counterion $M^{\oplus}$ is of particular current interest.

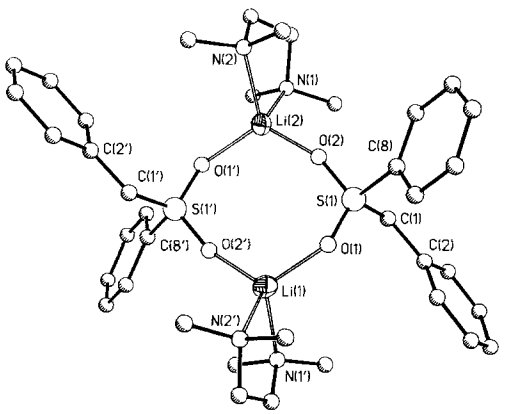


Fig. 1. Crystal structure of **1**. Space group $Pna2_1$, $a = 1705.1(6)$, $b = 1001.7(2)$, $c = 2375.9(30)$ pm, $Z = 8$ (one dimer per asymmetric unit). $R = 0.064$ for 3103 reflections with $F > 3\sigma(F)$. The dimer has approximately C_i symmetry, but could not be brought into accord with an inversion center of a centrosymmetric space group. The probable direction of the polar axis was determined by the use of an η-refinement [6]. The hydrogen atoms were refined according to a riding model with C–H 96 pm. An attempt to refine freely the H atoms on C(1) and C(1') gave only approximate positions with large standard deviations. Important distances (mean values) [pm] and bond angles (mean values) [°]: C(1)–S 164.1(5); C(8)–S 178.4(5); S–O 146.5(4); Li–N 213.6(10); Li–O 189.0(9); C(1)–C(2) 143.7(8). O–S–O 115.4(2); S–C(1)–C(2) 125.8(4). Dihedral angles (mean value) [°]: O–S–C(1)–C(2) ±45.6(6) and ±175.4(5); C(8)–S–C(1)–C(2) ±70.4(6); S–C(1)–C(2)–C ±3.1(9) and ±176.8(30). Further details of the crystal structure investigation may be obtained on request from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2, by quoting the depository number CSD 51257, the names of the authors, and the journal citation.

We report here the X-ray structure investigation of α-(phenylsulfonyl)benzyllithium-tetramethylethylenediamine **1** (Fig. 1).[4, 5]

1 crystallizes as a dimer in which the Li atoms are coordinated only by the tetramethylethylenediamine (TMEDA) molecules and the O atoms of the sulfonyl group, but not by the "anionic" C atoms! IR and Raman studies on $C_6H_5SO_2CH_2Li$ in solution indicate a contact to the C atoms as well.[2o] In the polymeric benzyllithium-triethylenediamine complex, the Li atom bridges three carbon atoms (corresponding to C(1), C(2), and C(3) in Fig. 1)[7] and in the monomeric 2-lithio-2-phenyl-1,3-dithiane-tetrahydrofuran-tetramethylethylenediamine, a C–Li bond to the benzylic C atom is present.[8] Ab initio calculations on $LiCH_2SO_2CH_3$ give two different Li positions as minima on the potential surface.[3c]

The C(1)–S distance (164.1 pm) is appreciably shorter than the corresponding distance in sulfones (mean value of 58 bond lengths: 180.6 pm).[9] By comparison, the CS double bond in thioformaldehyde is 161.08 pm,[10] which is only 3 pm shorter than C(1)–S in **1**! The increased CS bond order in **1** is in accord with an increased force constant in $C_6H_5SO_2CH_2Li$,[2o] as determined by vibrational spectroscopy.

The S–O distance in **1** (146.5 pm) is only a little larger than that in sulfones (mean value of 53 bond lengths: 143.4 pm).[9] A larger S–O distance was indicated by the force constants of α-sulfonyl "carbanions" as determined by IR spectroscopy.[2o] The S–C(1)–C(2)–C dihedral angles show that the short CS bonds lie in the plane of the phenyl ring, in accord with sp^2 hybridization of the carbon atom C(1) as well as with the results of most of the studies (mainly kinetic)[2m–o] on α-sulfonyl "carbanions" in solution. The chirality of an α-sulfonyl "carbanion" could therefore be due to a chiral conformation and hindered rotation around the C(1)–S bond, rather than to a tetrahedral configuration of the anionic C atom.[11] Up to now, kinetically controlled anion formation has been presumed to be responsible for the formation of a chiral conformation.[2a, e, k, l] The dihedral angles around the C(1)–S bonds (see above and Fig. 2) indicate that a local chiral conformation is thermodynamically favored in the crystal of **1**; the p orbital on C(1) is approximately *gauche* to the two O atoms on the sulfur.

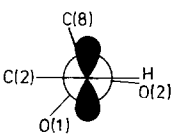


Fig. 2. Dihedral angles around the C(1)-S bonds.

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CAS Registry numbers:
1, 96705-29-2.

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[4] An X-ray structure determination of $[(CH_3SO_2)_3C]^{\ominus}NH_4^{\oplus}$ was already carried out earlier: K. Hoogsteen, *Dissertation*, Universität Groningen (Netherlands) 1957; see also P. H. Laur in A. Senning (Ed.): *Sulfur in Organic and Inorganic Chemistry, Vol. 3*, Marcel Dekker, New York 1972, p. 235.

[5] Preparation of **1** (attempt No. 56 to prepare suitable crystals): Benzylphenylsulfone (100 mg, 0.43 mmol) was dissolved in 4 mL of tetrahydrofuran (THF) and treated first with 1.2 molar equivalents of TMEDA and then with 1.2 molar equivalents of *n*-butyllithium in hexane at 0°C. After 1 h at 0°C, the THF was removed at 10^{-4} torr and the residue dis-

solved in 1 mL of diethyl ether. After 16 h at 20°C, the yellow crystals were freed of diethyl ether by means of a syringe, washed with 0.5 mL of diethyl ether, and dried at 10^{-4} torr.
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[11] Since we could not locate the H atom on C(1) with sufficient accuracy, only a suitable substitution would allow a definitive statement to be made regarding the configuration of this C atom.

Solvent Exchange on Magnesium([15]Crown-5) Complexes—a First- and Second-Order Reaction**

By *Franz L. Dickert** and *Manfred F. Waidhas*

Dedicated to Professor Helmut Behrens on the occasion of his 70th birthday

Solvent molecules (S) in the first coordination sphere of metal ions M^{2+} can be distinguished from the free solvent by NMR spectroscopy.[1] The use of DNMR, in particular, allows the dynamics of the exchange process to be studied:

$$[M(S)_6]^{2+} + S^* \rightleftharpoons [M(S)_5S^*]^{2+} + S \qquad (1)$$

Variations in temperature and pressure indicate, in terms of activation entropy[1] and activation volume,[2] that this reaction has mainly dissociative character. In order to study the mechanism of Eq. (1), it would be desirable, in addition, to vary the concentration of the solvent molecule (S). The limited solubility of solvated metal ions in non-coordinating cosolvents, such as CH_3NO_2 and CH_2Cl_2, can be overcome by the use of crown ethers to make the metal ions hydrophobic. Thus, [15]crown-5 (15C5) forms 1:1 complexes[3] with metal ions M^{2+}, in which, in addition to the macrocycle, two solvent molecules are coordinated in *trans* positions[4] (Fig. 1). The investigations of the mobility of the solvent molecules described here were carried out on the complex $[Mg(15C5)(DMF)_2](ClO_4)_2$ (DMF = dimethylformamide). In this system, no complications arise due to formation of the complex $[Mg(15C5)(DMF)]^{2+}$.

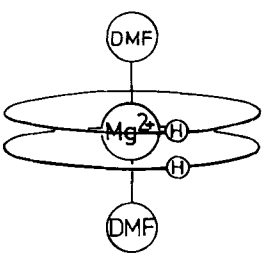


Fig. 1. Structure of $[Mg([15]crown-5)(DMF)_2]^{2+}$; the fluctuational crown ether [3] is indicated by the two ellipses.

The kinetic studies can be performed particularly advantageously with the DNMR method, using the HCO proton absorption of DMF: this absorption is shifted downfield by 0.17 ppm upon coordination of DMF to the Mg complex. As shown in Figure 2, the reciprocal residence time

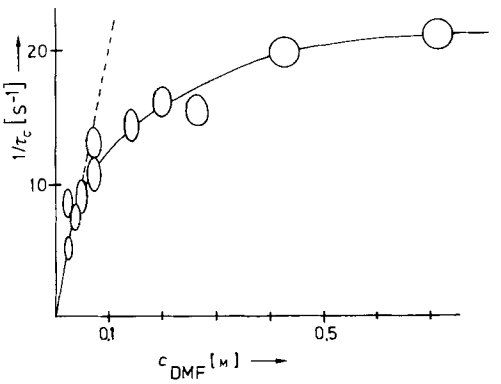


Fig. 2. Reciprocal residence times $1/\tau_c$ of DMF, coordinated in the complex $[Mg([15]crown-5)(DMF)_2]^{2+}$, as a function of the concentration of free DMF in CD_3NO_2 at 40°C.

$1/\tau_c$ of the DMF molecules in the first coordination sphere of the magnesium ion increases with increasing concentration of the uncoordinated DMF in CD_3NO_2/DMF mixtures and finally reaches a plateau value. In order to interpret this result, Equation (1) must be modified. The solvated and hydrophobic ion $[Mg(15C5)(DMF)_2]^{2+}$ forms an aggregate with free DMF in the inert solvent CD_3NO_2. However, the displacement of DMF from the first coordination sphere of the magnesium ion[5] [Eq. (2)] is rate-determining:

$$\begin{array}{l} [Mg(15C5)(DMF)_2]^{2+} + DMF^* \\ \qquad\qquad K^0 \uparrow\downarrow \\ [Mg(15C5)(DMF)_2]^{2+}\cdots DMF^* \\ \qquad\qquad k_1 \uparrow\downarrow k_1 \\ [Mg(15C5)(DMF)(DMF^*)]^{2+}\cdots DMF \\ \qquad\qquad K^0 \uparrow\downarrow \\ [Mg(15C5)(DMF)(DMF^*)]^{2+} + DMF \end{array} \qquad (2)$$

The life-times τ_c for the coordinated DMF molecules are obtainable directly from the NMR spectra and can be described by Eq. (3);[6] c_{DMF} is the concentration of free DMF, which is bound neither in the complex $[Mg(15C5)(DMF)_2]^{2+}$ nor in the aggregate $[Mg(15C5)(DMF)_2]^{2+}\cdots DMF$:

$$1/\tau_c = \frac{k_1 \cdot K^0 \cdot c_{DMF}}{1 + K^0 \cdot c_{DMF}} \qquad (3)$$

The experimental results in Figure 2 can be explained by the reaction scheme in Eq. (2) using Eq. (3). For high concentrations of DMF ($c_{DMF} \cdot K^0 \gg 1$), a first-order rate constant (k_1) is obtained, which is characteristic for the solvent exchange process in a coordinating solvent. From this kinetic viewpoint, the solution of 0.5 M $[Mg(15C5)(DMF)_2]^{2+}$ and 0.8 M DMF in CD_3NO_2 already behaves remarkably

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like such a system due to the strong hydrophobic interaction between the complex and DMF (K^0 in Eq. (2)). When the concentration of free DMF is decreased, on the other hand, the transition to a second-order rate law is observed ($c_{DMF} \cdot K^0 \ll 1$, Eq. (3)), the rate constant of which, k_{12}, can be derived from the slope of the tangent to the curve through the origin of $1/\tau_c$ (Fig. 2). The constants defined by Eq. (3) have the following values ($T = 40\,^\circ C$):

$k_1 = 24.7 \pm 2\,s^{-1}$; $\Delta H_1^{\neq} = 81 \pm 44\,kJ\,mol^{-1}$;
$\Delta S_1^{\neq} = 41 \pm 5\,J\,K^{-1}\,mol^{-1}$

$K^0 = 7.8 \pm 2\,L\,mol^{-1} \longrightarrow k_{12} = K^0 \cdot k_1 = 193 \pm 40\,L\,mol^{-1}\,s^{-1}$

The DMF exchange in the complex $[Mg(15C5)(DMF)_2]^{2+}$ is therefore 10^4 times slower than in $[Mg(DMF)_6]^{2+}$.[7] This phenomenon is general[3] and is due to an increased interaction between Mg^{2+} and DMF caused by the coordination of 15C5.[8]

Solvent exchange and complex formation with macrocyclic ligands is very important for the understanding of ion transfer through biological membranes. Thus, according to the carrier mechanism,[9] in which the ions are made hydrophobic, the coordinated solvent molecules must be displaced in an initial step.

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CAS Registry numbers:
$[Mg(15C5)(DMF)_2](ClO_4)_2$, 96482-90-5; DMF, 68-12-2.

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1,5-Diazocines**

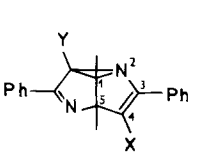
By *Christoph Schnieders, Walter Huber, Johann Lex,* and *Klaus Müllen**

Diazocines, diaza derivatives of cyclooctatetraene, are not well known.[1] The thermolysis of semibullvalenes carried out by *Paquette* et al. has provided access to specifically substituted cyclooctatetraenes.[2] The 2,6-diazasemibullvalenes **1**[3] recently described by us, now also open up a route to 1,5-diazocines **2**. Herein, we describe the synthesis, structure, and reduction of the first representative of this class of compounds.

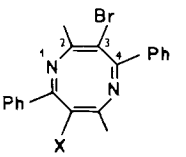
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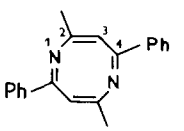
When a degassed solution of the diazasemibullvalene **1a** in tetrahydrofuran (THF) is kept at 90 °C for 8 h, the 2,6-dimethyl-4,8-diphenyl-1,5-diazocine **2a** is formed quantitatively. The kinetics of this transformation can be monitored by NMR spectroscopy. The activation parameters are $\Delta G^{\neq} = 27 \pm 0.5$ kcal/mol (25 °C) and $\Delta S^{\neq} = 2 \pm 2$ cal $K^{-1}mol^{-1}$ (25 °C). **1b** and **1c** are transformed increasingly more rapidly [$t_{1/2}$(25 °C) ca. 12 h] into **2b** and **2c**, respectively. The thermal instability of **1b** and **1c** is consistent with observations made by *Gompper* et al. when synthesizing a tetrazocine.[4] Compound **2c**, yellow rectangular crystals, melts at 105 °C with decomposition.



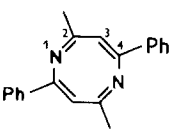
1a: X = Y = H
1b: X = Br, Y = H
1c: X = Y = Br



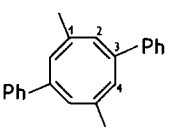
2b: X = H
2c: X = Br



2a'



2a''



3

The 1,5-diazocine **2a** exists in the form of two double-bond isomers,[5] **2a'** and **2a''**, which (irrespective of the temperature) are generated in the ratio 3 : 2 in the thermolysis.[6] Differentiation of the two isomers is based on the finding that a pronounced allyl coupling $^4J_{HH} = 2.5$ Hz between the ring protons and the methyl protons occurs only in the case of **2a'**. The isomers cannot be separated, but the synthesis of pure **2a'** is possible if the dianion $\mathbf{2a}^{2\ominus}/2\,K^{\oplus}$ is reoxidized with oxygen or iodine at low temperatures. On warming the solution to room temperature the equilibrium between **2a'** and **2a''** is rapidly reestablished.

According to the NMR spectra, the bromodiazocines **2b** and **2c** exist only in the form of one of the double-bond isomers. The X-ray structure analysis[7] of **2c** leads to the same conclusion, and, moreover, shows that the ring is tub-shaped and contains alternating double and single bonds.

Characteristic for **2a** and **2c** are the low-field resonances of C-2 and C-4 and the high-field resonance of C-3.[8]

We were able to prepare the carbon analogue of **2a**, 1,4-dimethyl-3,7-diphenylcyclooctatetraene **3**,[9] by flash thermolysis of the semibullvalene[10] corresponding to **1a**. However, this reaction requires substantially higher temperatures (340–360 °C) than the reaction **1a** → **2a**.

On reduction with alkali metal, **2a** and **3** are converted into stable anions, which, on the basis of their spectroscopic data,[11] can be described as bond-delocalized, diatropic 10π systems.[12, 13]

Considering the structure of $\mathbf{2a}^{2\ominus}/2\,K^{\oplus}$, the product of the one-electron reduction of **2a**, the radical anion $\mathbf{2a}^{\odot\ominus}/K^{\oplus}$, behaves in a surprising manner. Here, the number and multiplicity of the ESR-spectroscopically determined ^1H-

and ^{14}N-coupling constants[14] are consistent with an unsymmetrical structure which arises as a result of localization of spin (or charge) density in one part of the ring. The ^1H-ENDOR-spectroscopically determined coupling constants of the protons sensitively depend upon changes in the counterion-solvent system (and, hence, the ion-pair structure).[15]

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1a, 82445-03-2; **1b**, 82445-09-8; **1c**, 96689-59-7; **2a**, 96689-60-0; **2a**·2K, 96689-77-9; **2a**··K^+, 96689-62-2; **2b**, 96689-62-2; **2c**, 96989-63-3; **3**, 96689-64-4; semibullvalene, 32139-60-9.

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[3] C. Schnieders, H.-J. Altenbach, K. Müllen, *Angew. Chem. 94* (1982) 638; *Angew. Chem. Int. Ed. Engl. 21* (1982) 637; *Angew. Chem. Suppl. 1982*, 1353.

[4] R. Gompper, M.-L. Schwarzensteiner, *Angew. Chem. 95* (1983) 553; *Angew. Chem. Int. Ed. Engl. 22* (1983) 543; *Angew. Chem. Suppl. 1983*, 812.

[5] L. A. Paquette, J. M. Photis, G. D. Ewing, *J. Am. Chem. Soc. 95* (1975) 3538.

[6] ^1H NMR ([D$_8$]THF): **2a′**: $\delta = 2.08$ (CH_3), 5.65 (H-3), 7.3—7.85 (C_6H_5); **2a″**: $\delta = 2.21$ (CH_3), 5.89 (H-3), 7.3—7.85 (C_6H_5).

[7] **2c**: space group $P\bar{1}$, $a = 8.178(1)$, $b = 10.258(1)$, $c = 11.905(2)$ Å, $\alpha = 101.24(1)$, $\beta = 89.44(1)$, $\gamma = 109.27(1)°$; $Z = 2$. 2910 observed reflections, $R = 0.041$, $R_w = 0.44$. Further details of the crystal structure investigation are available on request from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2, on quoting the depository number CSD 51407, the names of the authors, and the full citation of the journal.

[8] ^{13}C NMR ([D$_8$]THF): **2a′**, **2a″**: $\delta = 22.3$, 26.4 (CH_3); 106.1, 108.2 (C-3); 126.5–131.4 (C_6H_5); 137.9, 138.6q (C_6H_5); 154.9, 158.4 (C-4); 165.4, 169.5 (C-2); **2c**: $\delta = 20.3$ (CH_3), 94.9 (C-3), 128.4 (C_6H_5), 128.9 (C_6H_5), 131.4 (C_6H_5), 134.4q (C_6H_5), 154.2 (C-4), 164.3 (C-2). The assignment of the signals of C-2 and C-4 in **2a** follows in analogy to that in **2c** and is not confirmed experimentally.

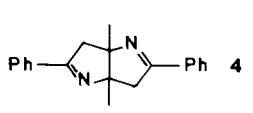
[9] **3**: yield 57%; m.p. 104°C; ^1H NMR ($CDCl_3$): $\delta = 1.96$ (CH_3), 5.90 (H-4), 6.20 (H-2), 7.2–7.4 (C_6H_5).

[10] R. Askani, *Tetrahedron Lett. 1971*, 447; D. Paske, R. Ringshandl, J. Sellner, H. Sichert, J. Sauer, *Angew. Chem. 92* (1980) 464; *Angew. Chem. Int. Ed. Engl. 19* (1980) 456.

[11] ^1H NMR ([D$_8$]THF, −30°C): **2a**$^{2\ominus}$/2$K^{\oplus}$: $\delta = 2.94$ (CH_3), 6.70 (H-3), 6.60 (*p*-H); 7.00 (*m*-H), 8.18 (*o*-H); **3**$^{2\ominus}$/2$Li^{\oplus}$: $\delta = 2.85$ (CH_3), 5.92 (H-2,4), 6.70 (*p*-H), 7.05 (*m*-H), 7.50 (*o*-H).

[12] L. A. Paquette, J. F. Hansen, T. Kakihana, *J. Am. Chem. Soc. 93* (1971) 168; L. A. Paquette, T. Kakihana, J. F. Hansen, *Tetrahedron Lett. 1970*, 529; H.-J. Altenbach, H. Stegelmeier, M. Wilhelm, B. Voss, J. Lex, E. Vogel, *Angew. Chem. 91* (1979) 1028; *Angew. Chem. Int. Ed. Engl. 18* (1979) 962; M. Breuninger, B. Gallenkamp, K.-H. Müller, H. Fritz, H. Prinzbach, J. J. Daly, P. Schönholzer, *ibid. 91* (1979) 1030 and *18* (1979) 964.

[13] The bicycle **4** cannot be detected after the protonation of **2a**$^{2\ominus}$/2$K^{\oplus}$. In contrast, *Gompper* was able to obtain the analogous bicyclo[3.3.0]octane system by protonation of a tetrazocine dianion: R. Gompper, Lecture given on March 27, 1984, in Konstanz (Chemie-Dozententagung).



4

[14] ESR coupling constants (K, THF, −70°C): **2a**$^{\odot\ominus}$: 0.514 (1 H), 0.342 (1 H), 0.320 (1 H), 0.257 (3 H), 0.089 (1 H), 0.065 (1 H), 0.023 (3 H), 0.289 (1 N), 0.067 (1 N) mT.

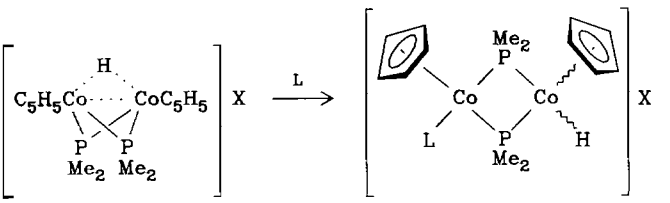
[15] ^1H-ENDOR coupling constants (e.g. K, dimethoxyethane, −85°C): **2a**$^{\odot\ominus}$: 0.487 (1 H), 0.285 (1 H), 0.235 (1 H), 0.169 (3 H), 0.089 (1 H), 0.085 (1 H), 0.023 (3 H).

Stepwise Formation of a Dinuclear μ-Aminocarbyne- and a μ-Formimidoyl-Metal Complex by Insertion of Methyl Isocyanide into an MHM Bridge**

By *Ralf Zolk* and *Helmut Werner**

Dedicated to Professor Helmut Behrens on the occasion of his 70th birthday

The cation of the dinuclear complex **1** contains a closed CoHCo-three-center bond which can be split by trimethylphosphane or trimethylphosphite.[1] The hydride ligand in **1** is thereby transferred from a bridging to a terminal position in **2**.



1 *cis/trans*-**2**

a, X = BF_4; **b**, X = PF_6
L = PMe_3, $P(OMe)_3$

We were interested to know whether such a reaction is also possible with CO or CNMe and, if so, whether the complexes **2** with L = CO and CNMe react by *intramolecular* reduction of carbon monoxide or methyl isocyanide, respectively. Studies of this type are of current importance in connection with the proposed mechanism of the Fischer-Tropsch synthesis.[2]

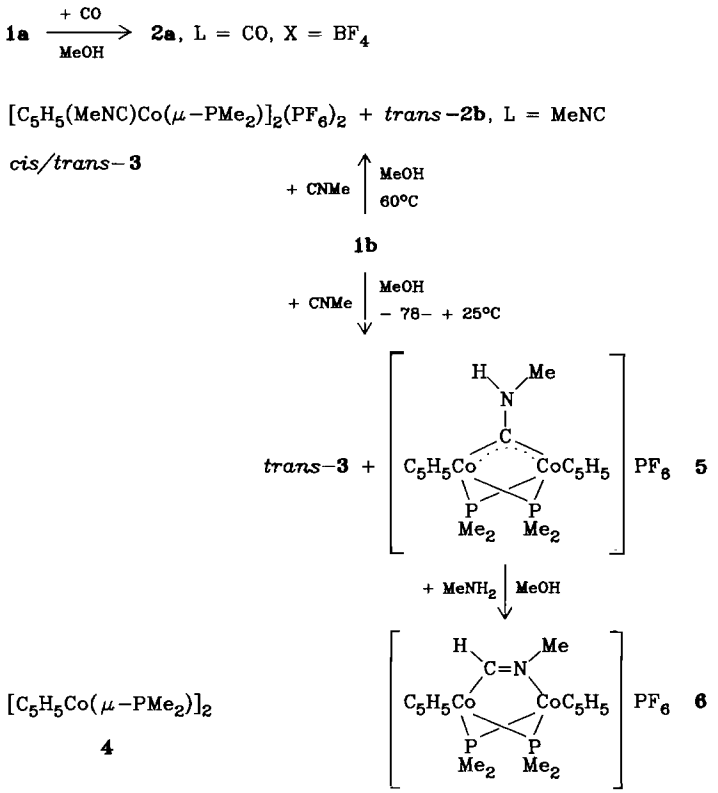
Compound **1a** reacts with CO in methanol at 40°C to produce the dinuclear carbonyl(hydrido) complex **2a**, L = CO, which after chromatography on Al_2O_3 (Woelm, activity grade V, acetone) and recrystallization from acetone/ether is isolated in 67% yield.[3] Warming a solution of **2** or photolysis does *not* lead to the formation of a bridged formyl complex; decomposition occurs instead of a hydride transfer.

The reaction of **1b** with methyl isocyanide in methanol at room temperature gives a mixture of products which contains compounds *trans*-**2b**, L = MeNC, and **5** as well as minor amounts of the neutral complex **4**[1] and the PF_6 salts **3** with *cis*- and *trans* cations.[4] At 60°C (in MeOH), the main product is the hydrido(methylisocyanide) complex **2b**, L = MeNC, for which by comparison with reference data[5] a *trans*-orientation of the cyclopentadienyl ligands is proposed;[6] a small quantity of **3** (*cis* and *trans*, yield 7%) is also formed. Under the same reaction conditions, a rearrangement of complex **2b** into **5** or **6** cannot be observed.

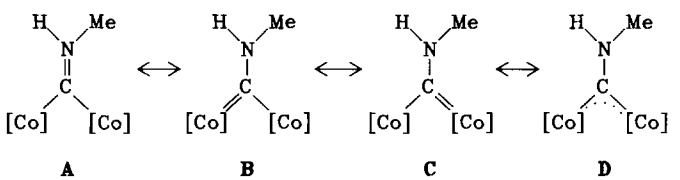
Addition of methyl isocyanide to a solution of **1b** in methanol at −78°C followed by warming to room temperature gives compound **5** containing a bridging aminocarbyne ligand in excellent yields.[7] Similar insertions of isocyanides into the MHM bridge of Fe_3- or Os_3-clusters are known and have recently been discussed elsewhere.[8] The structure proposed for **5** is based mainly on ^1H-NMR data (e.g., a doublet-of-triplets for the NCH_3 protons caused by coupling with the adjacent NH proton and the two equivalent ^{31}P nuclei) and the IR spectrum.[7] The ν(CN)

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stretching frequency lies between that of a C=N double bond and a C–N single bond, indicating that the resonance forms **B** – **D** must be considered in addition to **A** for the bonding of the bridging unit ([Co] = $C_5H_5Co(\mu\text{-}PMe_2)$).



In the presence of methylamine (in MeOH) the aminocarbyne complex **5** rearranges *quantitatively* to produce the μ-*N*-methylformimidoyl complex **6**.[9] We assume that an abstraction of the N*H*Me proton occurs initially, followed by protonation of the carbon atom of the transiently formed μ-isocyanide compound by NH_3Me^+; subsequent cleavage of one Co–C bond and coordination of the nitrogen at the second cobalt atom leads to the Co–CH=NMe–Co bridge. It should be noted that the formation of bridging *N*-alkyl- and *N*-arylformimidoyl ligands by insertion of isocyanides into M–H and M–H–M bonds has previously been observed[8,10] but there was no evidence that this process could occur via aminocarbyne complexes as intermediates. A thermal rearrangement of **6** to give (or *trans*-**2b**, L = MeNC) does not take place. We assume that the *cis* isomer of **2b** is a short-lived intermediate in the reaction of **1b** and CNMe to form **5**, whereas at higher temperature *trans*-**2b** is formed as the thermodynamically preferred product.

The structure of the cation of **6** is shown in Figure 1.[11] The midpoints of both cyclopentadienyl rings and the Co1, C1, N, and Co2 atoms are nearly coplanar and define a non-crystallographic mirror plane; C2 is displaced by 9(2) pm out of this plane. The distance C1–N (126(2) pm) is very slightly shorter than the C=N double bond in protonated methaneimine (129 pm)[12] and comparable to the C–N distance in other μ-formimidoyl complexes.[8] The Co···Co separation of 319.1(3) pm is significantly larger than in the cation of **1** (251.7 pm)[1] and is evidence against the existence of a metal-metal bond.

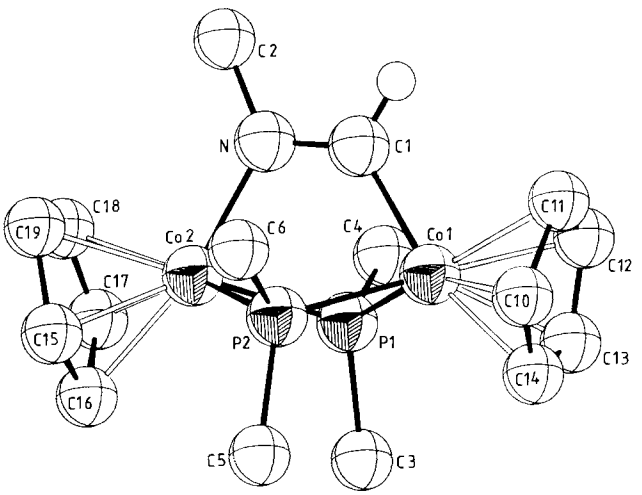


Fig. 1. Structure of the cation of **6** in the crystal. Selected bond lengths [pm] and angles [°]: Co1···Co2 319.1(3), Co1–C1 191.0(14), Co1–P1 216.8(4), Co1–P2 217.2(5), Co2–N 195.8(12), Co2–P1 219.1(5), Co2–P2 217.3(5), C1–N 126(2), C2–N 144(2), Co1–C1–N 123.8(13), Co2–N–C1 116.2(11), Co2–N–C2 126.0(10), C1–N–C2 117.6(14), Co1–P1–Co2 94.1(2), Co1–P2–Co2 94.5(2).

The formation of a formimidoyl bridge during the reaction of **1b** with isocyanides probably depends on the substituent R. This follows from preliminary results which indicate that CNPh behaves similarly to CN*t*Bu seems to prefer a different reaction path.

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CAS Registry numbers:
1a, 87973-15-7; **1b**, 69277-87-8; **2a**, 96790-99-7; *trans*-**2b**, 96760-05-3; *cis*-**3**, 96760-07-5; *trans*-**3**, 96844-09-6; **4**, 69277-85-6; **5**, 96760-09-7; **6**, 96760-11-1; methyl isocyanide, 593-75-9.

[1] a) H. Werner, W. Hofmann, *Angew. Chem. 91* (1979) 172; *Angew. Chem. Int. Ed. Engl. 18* (1979) 158; b) H. Werner, W. Hofmann, R. Zolk, L. F. Dahl, J. Kocal, A. Kühn, *J. Organomet. Chem., 289* (1985) 173.
[2] a) C. K. Rofer-De Poorter, *Chem. Rev. 81* (1981) 447; b) W. A. Herrmann, *Angew. Chem. 94* (1982) 118; *Angew. Chem. Int. Ed. Engl. 21* (1982) 117.
[3] **2a**, L = CO: Brown crystals, dec. temp. (DTA) 142°C; equivalent conductivity (CH_3NO_2): $\Lambda = 70\ cm^2 \cdot \Omega^{-1} \cdot mol^{-1}$; IR [KBr]: $\nu(CO) = 2010\ cm^{-1}$; ^{1}H-NMR (CD_3NO_2): $\delta(C_5H_5) = 5.34$ (s) and 4.94 (s), $\delta(PCH_3) = 2.19$ (vt, $N = 12.4$ Hz) and 1.90 (vt, $N = 14.6$ Hz), $\delta(CoH) = -13.45$ (t, $J_{PH} = 64.0$ Hz); ^{31}P-NMR ([D$_6$]acetone, −23°C): $\delta(PCH_3) = -22.87$ (s).
[4] The mixture of *cis*/*trans* **3** as well as the pure *trans* isomer have also been prepared by a different route using $[(C_5H_5Co)_2(\mu\text{-}PMe_2)_2(\mu,\eta^2\text{-}ONO)]PF_6$ as the starting material [5].
[5] R. Zolk, Dissertation, Universität Würzburg 1985.
[6] *trans*-**2b** (L = MeNC) is prepared by stirring a suspension of **1b** (520 mg, 1.0 mmol) and CNMe (70 μL, 1.2 mmol) in methanol (20 mL) at 60°C for 2 h. After removing the solvent and extraction with pentane to remove **4**, the residue is dissolved in 10 mL acetone and the solution chromatographed on Al_2O_3 (Woelm, activity grade V). Recrystallization from acetone/ether/pentane (1 : 2 : 2) gives brown crystals; yield 285 mg (51%). Dec. temp. (DTA) 260°C; equivalent conductivity (CH_3NO_2):

$\Lambda = 86$ cm$^2 \cdot \Omega^{-1} \cdot$mol^{-1}; IR [KBr]: ν(CN) = 2202 cm^{-1}; ^{1}H-NMR ([D$_6$]acetone): $\delta(C_5H_5) = 5.23$ (t, $J_{PH} = 0.3$ Hz) and 4.91 (t, $J_{PH} = 0.3$ Hz), $\delta(NCH_3) = 3.78$ (s), $\delta(PCH_3) = 2.14$ (vt, $N = 11.5$ Hz) and 1.76 (vt, $N = 14.8$ Hz), δ(CoH) = −13.12 (t, $J_{PH} = 64.0$ Hz); ^{31}P-NMR ([D$_6$]acetone, −23 °C): $\delta(PCH_3) = -29.34$ (s), δ(PF) = −145.02 (sept, $J_{PF} = 708.6$ Hz).

[7] **5** is prepared by addition of CNMe (25 μL, 0.45 mmol) to a suspension of **1b** (205 mg, 0.40 mmol) in methanol (10 mL) with stirring at −78 °C. The mixture is slowly warmed to room temperature over a period of 4 h. After stirring for 20 h, the reaction mixture is worked up as described in [6]; yield 165 mg (75%). Orange crystals, dec. temp. (DTA) 285 °C; equivalent conductivity (CH_3NO_2): $\Lambda = 94$ cm$^2 \cdot \Omega^{-1} \cdot$mol^{-1}; IR [KBr]: ν(NH) = 3327, ν(CN) = 1511 cm^{-1}; ^{1}H-NMR ([D$_6$]acetone): $\delta(C_5H_5) = 5.02$ (t, J(PH) = 0.4 Hz) and 4.88 (t, J(PH) = 0.3 Hz), $\delta(NCH_3) = 3.61$ (dt, J(HH) = 3.6 Hz, J(PH) = 2.5 Hz), $\delta(PCH_3) = 2.17$ (vt, $N = 11.6$ Hz) and 1.81 (vt, $N = 12.2$ Hz), δ(NH) not exactly assignable; ^{31}P-NMR ([D$_6$]acetone, −33 °C): $\delta(PCH_3) = -69.37$ (s), δ(PF) = −145.02 (sept, J(PF) = 708.6 Hz).

[8] a) R. D. Adams, *Acc. Chem. Res. 16* (1983) 67; b) E. Singleton, H. E. Oosthuizen, *Adv. Organomet. Chem. 22* (1983) 209.

[9] For the preparation of **6** 2 mL of methylamine is added to a suspension of **5** (200 mg, 0.36 mmol) in methanol (2 mL) at −78 °C and the suspension is slowly warmed to room temperature over a period of 4 h. After stirring for 20 h the solvent and excess amine are removed and the residue recrystallized from acetone/ether/pentane (1 : 2 : 2); yield 192 mg (96%). Red crystals, dec. temp. (DTA) 330 °C; equivalent conductivity (CH_3NO_2): $\Lambda = 77$ cm$^2 \cdot \Omega^{-1} \cdot$mol^{-1}; IR [KBr]: ν(CN) = 1519 cm^{-1}; ^{1}H-NMR ([D$_6$]acetone): δ(HCN) = 10.94 (s, br), $\delta(C_5H_5) = 5.15$ (t, J(PH) = 0.3 Hz) and 5.12 (s, br), $\delta(NCH_3) = 3.67$ (d, J(HH) = 1.2 Hz), $\delta(PCH_3) = 2.19$ (vt, $N = 12.7$ Hz) and 1.73 (vt, $N = 14.8$ Hz); ^{31}P-NMR ([D$_6$]acetone, −23 °C): $\delta(PCH_3) = 7.38$ (s), δ(PF) = −145.02 (sept, J(PF) = 708.6 Hz).

[10] a) D. W. Prest, M. J. Mays, P. R. Raithby, *J. Chem. Soc. Dalton Trans. 1982*, 2021; b) H. C. Aspinall, A. J. Deeming, *J. Chem. Soc. Chem. Commun. 1983*, 838.

[11] Crystals by diffusion of ether into a solution of **6** in acetone. Orthorhombic, $P2_12_12_1$, $Z = 4$; $a = 1368.3(2)$, $b = 1812.4(3)$, $c = 907.5(3)$ pm, $V = 2250.5 \times 10^6$ pm^3; $\rho_{calc.} = 1.64$, $\rho_{exp.} = 1.65$ g/cm^3; $3° \leq 2\theta \leq 48°$ ($Mo_{K\alpha}$, $\lambda = 71.069$ pm); 2002 independent reflections, Lorentz and polarization corrections, position of the hydrogen atoms partly from difference Fourier syntheses, partly calculated from ideal geometry; $R_1 = 0.077$, $R_2 = 0.095$ for 1936 structure factors ($F_0 \geq 3.0\sigma(F_0)$). Further details of the crystal structure analysis are available on request from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2, on quoting the depository number CSD 51425, the names of the authors, and the journal citation.

[12] A. Streitwieser, *Introduction to Organic Chemistry*, McMillan, New York 1976, p. 13.

1,4-Additions of Dihalocarbenes**

By *Herbert Mayr** and *Ulrich W. Heigl*

Dedicated to Professor Rolf Huisgen on the occasion of his 65th birthday

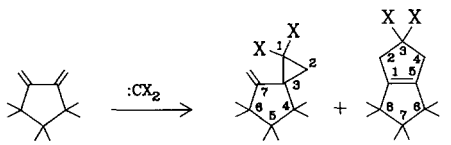
Singlet carbenes usually undergo 1,2-addition with 1,3-dienes to give vinylcyclopropanes.[1] Theoretical studies indicate that the transition state of the likewise orbital symmetry allowed concerted 1,4-addition is destabilized by closed-shell repulsions,[2a] particularly the four-electron interaction between ψ_1(diene) and σ(carbene).[1,2] This type of reaction is preferred only in exceptional cases, for example in the homo-1,4-additions of dihalocarbenes to norbornadiene[3a] or the benzvalene synthesis via intramolecular carbene addition.[3b] Apart from some compounds which have been interpreted as sequential products of 1,4-adducts,[4a] so far the only indication of an intermolecular 1,4-addition of a singlet-carbene to a 1,3-diene comes from 0.6% 1,4-adduct isolated in the reaction of dichlorocarbene with 1,2-bis(methylene)cycloheptane.[4b]

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1,1,2,2,3,3-Hexamethyl-4,5-bis(methylene)cyclopentane, **1**, which can readily be prepared by bromination and twofold HBr-elimination from octamethylcyclopentene,[5] is a predestined model for 1,4-additions, since it contains a *cis*-fixed 1,3-diene system in which access to the 2- and 3-positions is sterically hindered.

Treatment of **1** in petroleum ether with chloroform and potassium *tert*-butoxide for four hours at 0 °C leads to formation of a mixture of **2a** and **3a** (73 : 27) in 76% yield (Table 1). **2a** is stable under the reaction conditions, since the



1 **2a, b** **3a, b**

Table 1. 1,2- and 1,4-addition of CX_2 to the 1,3-diene **1**.

	X	Reaction conditions	**2** : **3**
a	Cl	KO*t*Bu/$CHCl_3$/petroleum ether/0 °C	73 : 27
a	Cl	$PhHgCCl_3$/toluene/100 °C/1 h	79 : 21
b	Br	KO*t*Bu/$CHBr_3$/petroleum ether/0 °C	70 : 30
b	Br	$PhHgCBr_3$/toluene/80 °C/1 h	73 : 27

same product ratio is observed even after 30 hours' reaction time. The analogous reaction with bromoform leads to formation of the adducts **2b** and **3b** (70 : 30) in 80% yield. **2a** and **3a** can be separated chromatographically and unequivocally characterized by their NMR spectra (Table 2).[6] Pure **3a** is also obtained by flash thermolysis of the mixture **2a/3a** in a quartz tube at 350 °C.

Table 2. ^{13}C-NMR data of the carbene addition products **2** and **3**. The assignment of the values in parentheses is unclear.

	C-1	C-2	C-3	C-4	C-5	C-6	C-7	=CH_2 or C-8
2a	67.63	26.29	(45.46)	(46.31)	(47.81)	(48.95)	159.39	107.31
	methyl signals at 20.32 (doubled int.), 23.07, 26.94, 28.64, 29.66							
2b	38.18	27.85	(45.39)	(46.37)	(46.68)	(49.58)	160.37	107.98
	methyl signals at 20.38, 20.41, 23.49, 27.90, 28.51, 29.85							
3a	145.00	51.39	92.22	51.39	145.00	(46.35)	(51.02)	≙C-6
	methyl signals at 21.78 and 23.84 (doubled int.)							
3b	145.97	54.12	65.83	54.12	145.97	(46.41)	(51.33)	≙C-6
	methyl signals at 21.84 and 23.84 (doubled int.)							

If the two carbenes are generated from phenyl(trihalomethyl)mercury[7] in toluene at 100 °C (CCl_2) and 80 °C (CBr_2), respectively, a ratio **2** : **3** of 79 : 21 and 73 : 27, respectively, is observed after one hours' heating. Hourly analysis of the reaction mixtures shows that **2a** and **2b** slowly decompose under these reaction conditions to hitherto unidentified products. Within 5 h the ratio **2** : **3** falls to 72 : 28 and 65 : 35, respectively. The slow change of the product pattern clearly demonstrates, however, that the adducts **3a**, **b** observed after one hours' reaction time cannot be interpreted as rearrangement products of **2a** and **2b**.

Since the reaction of CCl_2 and CBr_2 with **1** yields 1,2- and 1,4-addition products in comparable amounts, diene **1**

is a suitable model to check theoretical predictions about 1,4-additions[2] and to examine proposals on the two-step mechanism of certain carbene additions.[8] It is obvious that **1**, a 1,3-diene with normal 1,4-reactivity but greatly reduced 1,2-reactivity, may also be used as a mechanistic probe for other reactions in which 1,3-dienes usually participate as $_{\pi}2$-units.

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[1] R. A. Moss, M. Jones, Jr. in R. A. Moss, M. Jones, Jr. (Ed.): *Reactive Intermediates, Vol. 2*, Wiley, New York 1981, Chap. 3.

[2] a) H. Fujimoto, R. Hoffmann, *J. Phys. Chem. 78* (1974) 1167; b) W. W. Schoeller, E. Yurtsever, *J. Am. Chem. Soc. 100* (1978) 7548; W. W. Schoeller, N. Aktekin, *J. Chem. Soc. Chem. Commun. 1982*, 20; c) for another interpretation: N. L. Bauld, D. Wirth, *J. Comput. Chem. 2* (1981) 1.

[3] a) C. W. Jefford, nT. Kabengele, J. Kovacs, U. Burger, *Helv. Chim. Acta 57* (1974) 104; for more recent work see [1]; b) U. Burger, G. Gandillon, *Tetrahedron Lett. 1979*, 4281.

[4] a) H. Hart, J. W. Raggon, *Tetrahedron Lett. 24* (1983) 4891; L. W. Jenneskens, F. J. J. de Kanter, L. A. M. Turkenburg, H. J. R. de Boer, W. H. de Wolf, F. Bickelhaupt, *Tetrahedron 40* (1984) 4401; b) L. A. M. Turkenburg, W. H. de Wolf, F. Bickelhaupt, *Tetrahedron Lett. 23* (1982) 769; see also L. W. Jenneskens, W. H. de Wolf, F. Bickelhaupt, *Angew. Chem. 97* (1985) 568; *Angew. Chem. Int. Ed. Engl. 24* (1985) 585.

[5] H. Klein, H. Mayr, *Angew. Chem. 93* (1981) 1069; *Angew. Chem. Int. Ed. Engl. 20* (1981) 1027.

[6] ^{1}H NMR ($CDCl_3$): **2a**: $\delta = 0.86$, 0.90, 1.00, 1.06 (doubled int.), 1.15 (5s; CH_3), 1.53 (s; CH_2), 4.64, 5.04 (2s; vinyl-H); **2b**: $\delta = 0.85$, 0.91, 1.06, 1.10 (doubled int.), 1.17 (5s; CH_3), 1.70 (s; CH_2), 4.60, 5.08 (2s; vinyl-H); **3a**: $\delta = 0.87$ (s; $2CH_3$), 0.96 (s; $4CH_3$), 3.15 (s; $2CH_2$); **3b**: $\delta = 0.86$ (s; $2CH_3$), 0.95 (s; $4CH_3$), 3.38 (s; $2CH_2$).

[7] D. Seyferth, *Acc. Chem. Res. 5* (1972) 65.

[8] E. V. Dehmlow, R. Kramer, *Angew. Chem. 96* (1984) 700; *Angew. Chem. Int. Ed. Engl. 23* (1984) 706; B. Giese, W.-B. Lee, C. Neumann, *ibid. 94* (1982) 320 and *21* (1982) 310.

Octaphenyl-1,5,2λ^5,3,4λ^5,6λ^5,7,8λ^5-diazahexaphosphocine**

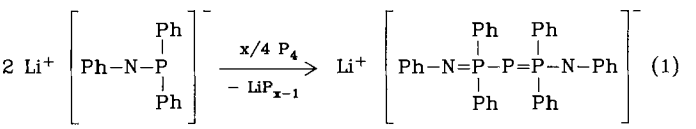
By *Alfred Schmidpeter** and *Günther Burget*

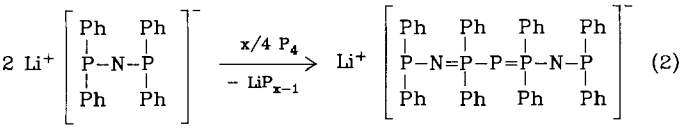
Dedicated to Professor Rolf Huisgen on the occasion of his 65th birthday

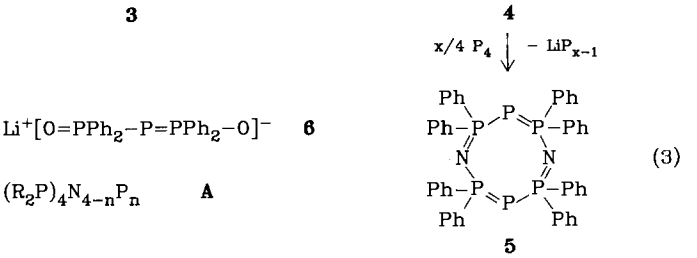
Two-coordinated nitrogen in organic aromatic heterocycles such as pyridine or the azoles can be replaced by two-coordinate phosphorus with retention of the bonding system. We now wanted to know whether this exchange is also possible in the case of inorganic ring systems with delocalized double bonds, such as cyclotetraphosphazenes; that is, whether compounds of the series **A** can be prepared.

Nucleophilic P_4-degradation analogous to that with alkali metal phosphinites[1] was considered a promising synthetic strategy. Thus, for example, lithium diphenylphosphinoanilide **1** also effects the disproportionation of white phosphorus according to equation (1) on boiling under reflux in tetrahydrofuran (THF). Tetramethylethylenediamine (TMEDA) accelerates the reaction. According to the reaction stoichiometry and C,H-analysis, the insoluble black polyphosphide that separates during the reaction has the composition $(thf)_2LiP_{13}$.[2] The oxidation product **2** can be isolated from the reaction solution as analytically pure crystals.

The corresponding reaction (2) with lithium bis(diphenylphosphino)amide **3**[3] proceeds rapidly enough even without the aid of TMEDA and leads to formation of the lithium salt **4** containing a seven-membered anion; **4** is again a lithium phosphinoamide and therefore reacts further in a second step (3) with white phosphorus to give the eight-membered ring **5** ≡ A, n = 2.[5] The reaction cannot be stopped just at the stage of the intermediate product **4**, even by a high $3/P_4$ ratio (7:2). For the polyphosphide precipitate, the reaction stoichiometry gives a Li/P ratio of 1:8 corresponding to Li_2P_{16};[4] excess P_4 remains unchanged.







An iterative spectral analysis confirms the spin-system AA'A''A'''MM' of **5**, but does not allow a satisfactorily accurate enough determination of the remaining coupling constants. The ^{31}P-upfield shift and PP coupling constant correspond to those in anionic[1] and cationic[6] systems consisting of a central twofold coordinated phosphorus atom and two tetrahedrally coordinated phosphorus atoms. **5** is thermally stable up to at least 200°C. In hydrous THF, **5** hydrolyzes within a few days with formation of $(Ph_2P)_2NH$. It is slowly degraded by $Li^+Ph_2PO^-$ at 60°C, reforming **4** and **3** and yielding the salt **6**.[1] Like the crystals of many cyclophosphazenes,[7] those of **5** also incorporate solvent molecules.

Attempts to prepare the end member of the series of compounds **A**, namely **9** with n = 4, remained unsuccessful. It is thermodynamically less stable than the mixture of tetraphenyldiphosphane **10** and P_4. Formally, **9** could be formed by disproportion of P_4 with the nucleophile lithium diphenylphosphide **7** according to equation (4). Indeed, the reaction does proceed in the desired direction but only up to the first (corresponding to **3**) stage **8**.[8] Compound **8** does not formally take up P^+ from further P_4 (**8** ↛ **9**), but gives up P^- to P_4 according to equation (5). The reaction proceeds the same with sodium or potassium salts instead of lithium salts.[8]

A hexaphosphocine **12**, in which the two nitrogen members of **5** are replaced by NCC members in the sense of the cyano-displacement principle, could be detected in the

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[**] Phosphazenes, Part 78. This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.—Part 77: A. Schmidpeter, M. Nayibi, P. Mayer, T. Tautz, *Chem. Ber. 116* (1983) 1468.

$$2\ Li^+Ph_2P^- \xrightarrow[-\ LiP_{x-1}]{x/4\ P_4} Li^+[Ph_2P-P-PPh_2]^- \xrightarrow{P_4} (Ph_2P)_4P_4 \quad (4)$$

7 **8** **9**

$$\xrightarrow{x/4\ P_4} \quad \downarrow -\ LiP_{x+1} \quad (5)$$

Ph_2P-PPh_2

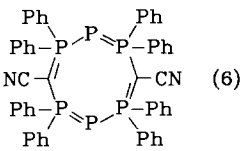
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reaction (6) of lithium cyanobis(diphenylphosphino)methanide **11**[9] with [18]crown-6-potassium dicyanophosphide[10] (not with P_4), but could not be isolated.

$$^+[(Ph_2P)_2CCN]^- \quad \textbf{11}$$

$$\xrightarrow[-\ 2\ Li^+\ CN^-]{2\ [18]crown-6-K^+\ [P(CN)_2]^-} \quad (6)$$

$$-2\ [18]crown-6-K^+\ CN^-$$



12

Experimental procedure and physical data

2: A vigorously stirred mixture of **1** (40 mmol) and P_4 (9.91 g, 80 mmol) in THF (100 mL) was heated under reflux for 24 h. A black precipitate separated from the orange-red solution; it was separated from the hot reaction mixture by filtration on a frit and washed with THF. The filtrate and washings were evaporated down to 80 mL and diluted with 80 mL of *n*-hexane. A colorless, crystalline precipitate of **2**·THF separated out; this was recovered by filtration and washed with *n*-hexane (yield: 5.70 g (43%). ^{31}P NMR (THF/TMEDA): A_2M, $\delta(A) = +31.7$, $\delta(M) = -119.6$, $J(AM) = 410$ Hz.

4: ^{31}P NMR (THF): A_2B_2M, $\delta(A) = +45.7$, $\delta(B, \text{terminal}) \approx +49.6$, $\delta(M) = -122.5$, $J(AM) = 410$, $J(AB) = 68$ Hz.

5: A vigorously stirred mixture of **3** (11.74 g, 30 mmol) and P_4 (8.43 g, 68 mmol) in THF (200 mL) was heated under reflux for 24 h. The solution turned deep-red in color and a violet-black precipitate separated out. The hot solution was filtered on a frit and the precipitate was washed with THF. On cooling the filtrate and washings to room temperature, **5**·THF separated out as light yellow, fine needle-like crystals (first fraction); after filtration, the filtrate was evaporated down to 100 mL and treated with 100 mL of *n*-hexane. This provided a second crop of **5**·THF. Total yield of **5**·THF (m.p. 220°C (dec.)): 65%; ^{31}P NMR (THF): AA'A''A'''MM', $\delta(A) = +35.0$, $\delta(M) \approx -141.5$, $J(AM) = 429$ Hz. On using benzonitrile, crystals of **5**·C_6H_5CN having the same appearance were obtained.

12: ^{31}P-NMR (THF): AA'A''A'''MM', $\delta(A) = 36.3$, $\delta(M) = -141.2$, $J(AM) = 425$ Hz.

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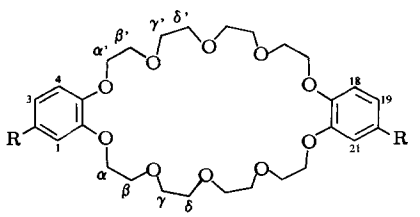
CAS Registry numbers:
1, 96688-80-1; **2**, 96688-81-2; **3**, 73785-70-3; **4**, 96688-82-3; **5**, 96688-83-4; **11**, 96688-84-5; **12**, 96688-85-6; [18]crown-6-K$^+$[P(CN)$_2$]$^-$, 81043-01-8; P_4, 7723-14-0.

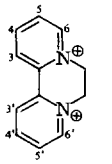
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[2] Cf. $(thf)_4LiP_{13}$: G. Fritz, J. Härer, K. Stoll, T. Vaahs, *Phosphorus Sulfur 18* (1983) 65.
[3] J. Ellermann, M. Lietz, *Z. Naturforsch. B35* (1980) 64.
[4] M. Baudler, O. Exner, *Chem. Ber. 116* (1983) 1268.
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[8] A. Schmidpeter, G. Burget, *Phosphorus Sulfur 22* (1985) 323.
[9] Prepared from $(Ph_2P)_2CHCN$ (H. Schmidbaur, T. Costa, private communication) and *n*-butyllithium.
[10] A. Schmidpeter, G. Burget, F. Zwaschka, W. S. Sheldrick, *Z. Anorg. Allg. Chem. 527* (1985), in press.

A Macrobicyclic Receptor Molecule for the Diquat Dication**

By *Billy L. Allwood, Franz H. Kohnke, J. Fraser Stoddart,* and David J. Williams**

Recently, we have demonstrated[1] that, although the macrobicyclic receptor molecule **6** provides enhanced complexation of the diquat dication ([Diquat]$^{2+}$) relative to that exhibited by dibenzo-[30]crown-10, **1**,[2] and its derivatives **2**—**4**,[3] its [Diquat]$^{2+}$ receptor site is larger than is necessary for a good supramolecular match. In view of the biological significance of [Diquat]$^{2+}$, and its relevance and importance in redox processes and photochemical systems,[4] synthetic modifications of **6**, so as to achieve an improved receptor molecule, constitute one of our prime objectives.





[Diquat]$^{2+}$

	1	2	3	4	5
R	H	CH_3	CH_2OH	CHO	CH_2Br

	6	7
R–R	CH_2-O-CH_2 	CH_2-O  O-CH_2

We (1) describe here the synthesis[5] of the macrobicyclic receptor molecule **7** from **5**, (2) report on ^{1}H-NMR spectroscopic investigations in solution (Fig. 1, Table 1), designed to probe the kinetics and thermodynamics of its complexation with diquat bishexafluorophosphate[6] in relation to its conformational behavior and mode of binding (Fig. 2), and (3) provide, from X-ray crystallographic investigations, details of the solid-state structures of both the free (i.e., **7**) and complexed ([Diquat]$^{2+}$) states[5,7] (Fig. 3 and 4).

At room temperature in the ^{1}H-NMR spectrum of [Diquat·**7**][PF_6]$_2$ recorded[8] at 400 MHz in [D_6]acetone, all the signals for the diquat and *O*-methylene protons are very broad. On cooling the solution, the spectrum becomes well resolved, until, by −20°C (Fig. 1), all eight bipyridinium protons and two sets of *N*-methylene protons in the complexed [Diquat]$^{2+}$ can be identified as separate signals in addition to the AB system arising from the benzylic methylene protons of **7**. Analyses of the temperature-dependent spectra afforded the kinetic and thermodynamic data listed in Table 1 for the processes illustrated in Figure 2:

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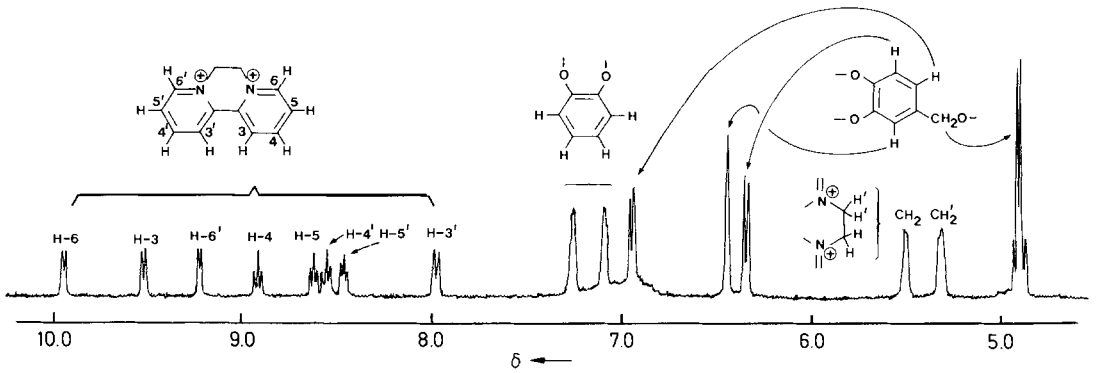


Fig. 1. The partial 400-MHz ^{1}H-NMR spectrum of [Diquat·7][PF_6]$_2$ recorded at -20°C in [D_6] acetone [8]. Although the assignment of signals to primed and unprimed protons is arbitrary, the two sets of pyridinium ring protons have been identified by double irradiation experiments.

the assumption was made[9] that the exchange processes for [Diquat·7]$^{2+}$ depend solely upon a unimolecular dissociation-recombination mechanism.[10] The temperature-dependent behavior of the ^{1}H-NMR spectrum of [Diquat·7][PF_6]$_2$ can most reasonably be interpreted in terms of a 1:1 molecular complex in which the substrate becomes desymmetrized ($C_{2v}\rightarrow C_s$) within the dissymmetric cavity of the receptor.

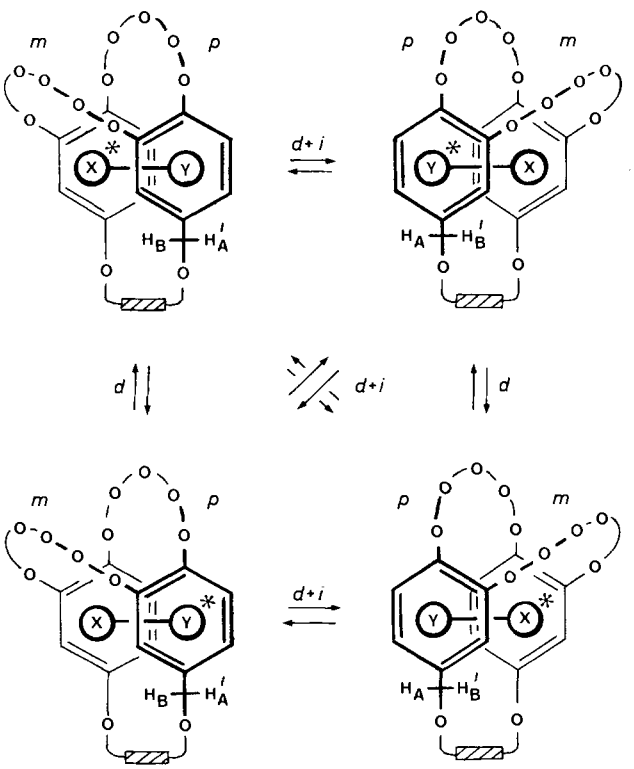


Fig. 2. Exchange processes [($d+i$) and d] for the complex of [Diquat]$^{2+}$ with 7 (schematic). d is dissociation with recombination, i is conformational inversion of 7 (see [c] in Table 1). The site exchanges for the benzylic methylene protons (A⇄B) and for the constitutionally homotopic protons (X⇄Y) on the bipyridinium nucleus (X–Y) of [Diquat]$^{2+}$ are shown (m = *meta* and p = *para* polyether chain). The prime is replaced by an asterisk for X and Y.

Confidence in this interpretation of events in solution comes from the following observations: (1) The degenerate conformational change proposed for the receptor molecule in Figure 2 can be detected (Table 1), employing the benzylic methylene protons as probes, at much lower temperatures in the ^{1}H-NMR spectrum of the free receptor **7** recorded in CD_2Cl_2. (2) A charge-transfer absorption band is observed in the UV spectrum of [Diquat·7][PF_6]$_2$ in acetone and a quantitative analysis of it provides evidence for the 1:1 stoichiometry of the solution complex, together with a value of $>9\times10^5$ M^{-1} for its stability constant.[11] (3) X-Ray crystallography[5,7] of **7** and [Diquat·7][PF_6]$_2$ demonstrates (Fig. 3) that the receptor molecule undergoes a conformational change[11] in order to encapsulate [Diquat]$^{2+}$. A consequence of the shortening of the diether

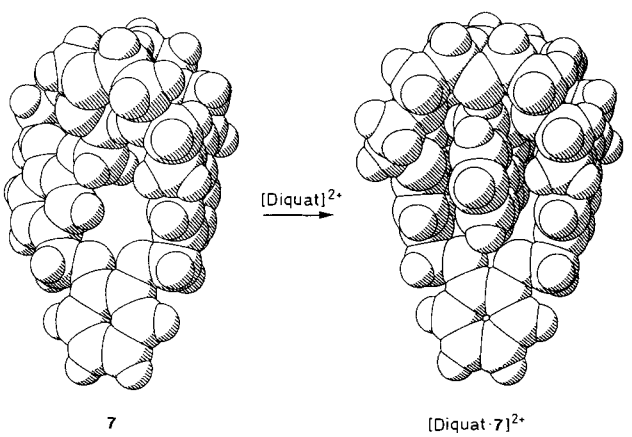


Fig. 3. The conformational change experienced by 7 in the solid state when it complexes [Diquat]$^{2+}$ (space-filling models).

bridge in [Diquat·7]$^{2+}$ relative to that of [Diquat·**6**]$^{2+}$[1] is a better match between [Diquat]$^{2+}$ and the host cavity. This is reflected in a loss of structural disorder in the two bridging polyether chains. As in [Diquat·**6**]$^{2+}$, there is approximate alignment of the bipyridinium nitrogen atoms with the catechol oxygen atoms O1, O13, O16, and O28 (Fig. 4). Uncharacteristically, the O1–C2 bond is nearly orthogonal to the plane of the attached benzo rings and the associated N1···O1 distance[12] (2.89 Å) is shortened dramatically compared with the other constitutionally related $N^+\cdots O$ distances in both [Diquat·**6**]$^{2+}$ and [Diquat·7]$^{2+}$. This N1···O1 distance is comparable with that normally found for $N^+-H\cdots O$ hydrogen bonds and is very much shorter than we have previously observed for

Table 1. Temperature-dependent ^{1}H-NMR spectroscopic data and kinetic and thermodynamic parameters for **7** and its 1:1 complex [Diquat·**7**][PF_6]$_2$ [a].

Species	^{1}H-NMR signal	Spectral changes [b]	T_c, ±3 [°C]	$\Delta\nu$, ±2(°C) [Hz]	J_{AB}, ±0.5 [Hz]	k_c [s^{-1}]	$\Delta G_c^{\neq}$, ±0.3 [kcal mol^{-1}]	Process [c]
7	CH_2-Aryl	A/B→AB	−59	25 (−59) [a]	9	74	10.6	*i*
[Diquat·**7**][PF_6]$_2$	CH_2-Aryl	A/B→AB	+10	16 (−60)	9	60	14.2	*d*+*i*
	H-3/3′	X/Y→XY	+35	632 (−60)	—	1400	13.8	*d*
	H-4/4′	X/Y→XY	+20	144 (−60)	—	319	13.8	*d*
	H-5/5′	X/Y→XY	+10	62 (−60)	—	138	13.8	*d*
	H-6/6′	X/Y→XY	+28	304 (−60)	—	675	13.7	*d*
	CH_2−$N^{\oplus}$	A/B→AB	+17	82 (−60)	15 [b]	200	13.9	*d*

[a] All spectra were recorded at 400 MHz on a Bruker WH400 spectrometer with Me_4Si as internal standard. The spectra of the 1:1 complexes were obtained in [D_6]acetone. In this solvent, the low temperature spectra for **7** showed no temperature dependence of the signal for the benzylic methylene protons other than line broadening: however, in CD_2Cl_2, an AB system separated out below −59°C with a chemical shift separation for the A and B protons that is strongly temperature dependent and results in the signal assuming a singlet character again below −90°C. Abbreviations: T_c, coalescence temperature; $\Delta\nu$, frequency separation for the appropriate ^{1}H-NMR signal with the temperature at which it was measured in parenthesis (in the case of **7**, $\Delta\nu$ was obtained by extrapolation of ν_A and ν_B below T_c back to this temperature); J_{AB}, coupling constant between the benzylic protons H_A and H_B; k_c, exchange rate constant at T_c calculated from the approximate expressions $k_c = \pi[\Delta\nu^2 + 6J_{AB}^2]^{1/2}/(2)^{1/2}$ when the protons undergoing exchange are mutually coupled, and $k_c = \pi\Delta\nu/(2)^{1/2}$ when the protons undergoing exchange are not mutually coupled; $\Delta G_c^{\neq}$, free energy of activation at T_c calculated from the Eyring equation. [b] Sites are designated X/Y for uncoupled two-site systems (H-3/3′, H-4/4′, H-5/5′, and H-6/6′ in Fig. 1). Sites that represent two time-averaged signals are designated XY. Sites are designated A/B for coupled AB systems (CH_2-Aryl in Fig. 1). Sites that represent two time-averaged signals from such systems are designated AB. Since the broadened singlets observed for the $CH_2N^{\oplus}$ protons at −60°C constitute an AA′BB′ system, the half-peak width was equated with J_{AB}. [c] Process *i* is ascribed to the degenerate conformational inversion of **7** in which the polyether chain *meta* to the diether bridge passes through the macrocyclic ring formed by the bridge and the polyether chain *para* to it. Processes *d*+*i* and *d*, respectively, refer to dissociation-recombination of [Diquat·**7**]$^{2+}$ with and without conformational inversion of **7**.

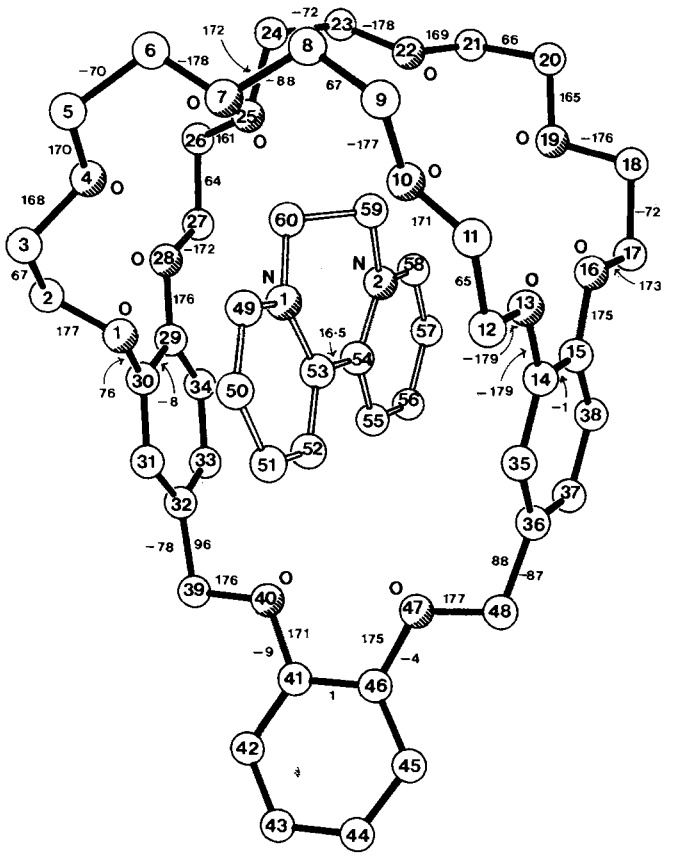


Fig. 4. Structure of [Diquat·**7**][PF_6]$_2$ in the crystal (anion not shown). Torsional angles [°] (O–C–C–O and C–C–O–C) associated with the polyether chains and the diether bridge are shown beside the relevant C–C and C–O bonds in the structure. Selected hydrogen contact distances, C···O, H···O [Å], and C–H···O angles [°] at H atoms assuming normal trigonal or tetrahedral geometry: C49···O4 3.20, H49···O4 2.69, 114; C49···O7 3.12, H49···O7 2.25, 150; C49···O10 3.07, H49···O10 2.89, 92; C58···O19 3.16, H58···O19 2.47, 128; C59···O25 3.27, H59···O25 2.63, 124; C60···O4 3.20, H60···O4 2.88, 101; C60···O7 3.24, H60···O7 2.35, 154; C60···O10 3.24, H60···O10 2.78, 109; C60···O25 3.29, H60···O25 2.69, 121. Separation [Å] between pyridinium ring nitrogen atoms in the guest and phenolic oxygen atoms in the host: N1···O1 2.89; N2···O16 3.45. Twist angle between the pyridinium rings in the guest: 17°. Separation of the overlapping regions between the benzo rings in the host; 6.15 Å with a 17° departure from a parallel alignment of their mean planes.

electrostatic interactions of this type. The conformational change undergone in **7** during complexation entails more than a 60° rotation of one of the benzo rings relative to the other. Although the conformation of **7** is not totally preorganized prior to complexation, a substantial portion of the macrobicyclic receptor is correctly arranged for binding [Diquat]$^{2+}$. This investigation demonstrates the need[13] to introduce at least one further bridging unit between the two benzo rings of **1** in order to provide a more rigidly defined receptor site for the diquat dication.

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3, 96746-18-8; **5**, 96746-19-9; **7**, 96746-20-2; [Diquat·**7**][PF_6]$_2$, 96746-21-3; catechol, 120-80-9; [Diquat][PF_6]$_2$, 67994-94-9.

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[5] Experimental: Bromination (PBr_3, C_6H_6) of **3** [1] afforded **5** [83%, m.p. 96—97°C, ^{1}H-NMR ($CDCl_3$, 220 MHz): δ = 3.67, 3.73, 3.86, 4.13 (32H, 4×m, δ/δ′-, γ/γ′-, β/β′-, and α/α′-OCH_2 protons, respectively), 4.42 (4H, s, 2×CH_2Br), 6.75—6.95 (6H, m, arom. H)]. Reaction of **5** (NaH, THF) with equimolar amounts of catechol gave **7** [22%, m.p. 127—128°C, ^{1}H-NMR ([D_6]acetone, 400 MHz): δ = 3.60—3.68 (20H, m, δ/δ′-, γ/γ′-, β- or β′-OCH_2), 3.70—3.73 (4H, m, β- or β′-OCH_2), 3.81—3.84, 4.13—4.16 (8H, 2×m, α/α′-OCH_2), 6.83 (2H, d, J = 8 Hz, H-4, 18), 6.87 (2H, d×d, J = 2, 8 Hz, H-3, 19), 7.02 (2H, d, J = 2 Hz, H-1, 21), 6.97, 7.12 (4H, AA′BB′ V system, remaining aromatic protons)]. Single crystals of **7** suitable for X-ray analysis were grown by very slow vapor diffusion of pentane into a $CHCl_3$ solution of **7**. To obtain single crystals (m.p. 216°C) of [Diquat·**7**][PF_6]$_2$, [Diquat][PF_6]$_2$ (7 mg, 0.015 mmol) and **7** (10 mg, 0.015 mmol) were dissolved in acetone (0.5 mL) and the solution was subjected to vapor diffusion with petroleum ether. All new compounds and the 1:1 complex gave satisfactory elemental analyses and spectroscopic data.

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[7] **7**: orthorhombic, a = 9.034(2), b = 28.871(6), c = 31.402(9) Å, V = 8190 Å^3, Pcab, Z = 8, ρ_{calcd} = 1.19 g cm^{-3}.—[Diquat·**7**][PF_6]$_2$: triclinic,

$a = 12.762(2)$, $b = 13.176(2)$, $c = 19.196(5)$ Å, $\alpha = 106.32(2)$, $\beta = 95.13(2)$, $\gamma = 111.74(1)°$, $V = 2809$ Å^3, $P\bar{1}$, $Z = 2$, $\rho_{calcd} = 1.39$ g cm^{-3}. Nicolet R3m diffractometer, ω-scan, graphite-monochromated $Cu_{K\alpha}$ radiation. Both structures were solved by direct methods and refined anisotropically to give $R = 0.166$ ($R_w = 0.166$) and $R = 0.082$ ($R_w = 0.083$), respectively, for 2693 and 4225 independent observed reflections [$\theta \leq 50°$, $|F_o| > 3\sigma(|F_o|)$]. The high R value for **7** is a consequence of disorder in the polyether chains and also reflects the presence of disordered solvent fragments in the lattice. Further details of the crystal structure investigations can be obtained from the Director of Cambridge Crystallographic Data Centre, Lensfield Road, Cambridge CB2 1EW (England), by quoting the full literature citation.

[8] We thank Dr. *B. E. Mann* and Dr. *C. M. Spencer* for recording these spectra on the Bruker WH 400 spectrometer.

[9] Cf. M. R. Johnson, I. O. Sutherland, R. F. Newton, *J. Chem. Soc. Perkin Trans. I 1979*, 357.

[10] F. de Jong, D. N. Reinhoudt, C. J. Smit, R. Huis, *Tetrahedron Lett. 1976*, 4783; F. de Jong, D. N. Reinhoudt, R. Huis, *ibid. 1977*, 3985; F. de Jong, D. N. Reinhoudt, *Adv. Phys. Org. Chem. 17* (1980) 279.

[11] $K_a > 9 \times 10^5$ M^{-1} corresponds to a free energy of complexation of > 8.1 kcal mol^{-1}. Comparing this complex strength with the value of 13.8 kcal mol^{-1} (Table 1) found for the free energy of activation for dissociation of the complex suggest that the association of the complex is not diffusion controlled. A free energy of activation for association of up to 5.7 kcal mol^{-1} indicates a somewhat slower recombination process which is probably associated with an energy-demanding conformational change within **7**, prior to it complexing with the diquat dication.

[12] The angle between the N1···O1 vector and the C30–O1–C2 plane is 21°. This is consistent with a pole-dipole interaction between the positively charged N1 atom and an O1 lone pair.

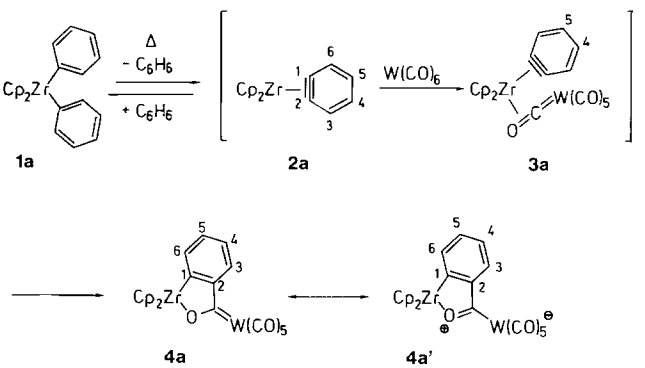
[13] From a comparison of the complexation strength ($K_a = 2 \times 10^5$ M^{-1}) of [Diquat·**6**]$^{2+}$ (see [1]) with that ($K_a > 9 \times 10^5$ M^{-1}) of [Diquat·**7**]$^{2+}$, it is clear that, although shortening of the diether bridge has increased the thermodynamic and kinetic stabilities of the diquat complex, the question of making the receptor site more rigid has still to be addressed.

Reaction of Thermally Generated (η^2-Aryne)zirconocene with $W(CO)_6$, a Novel Route to Carbene Complexes**

By *Gerhard Erker,* Ulrich Dorf, Richard Mynott, Yi-Hung Tsay,* and *Carl Krüger*

Variations of *Fischer*'s original route to heteroatom-substituted transition-metal carbene complexes are probably still the most widely used approach to this important class of compounds.[1] In some cases, however, the classical two-step pathway is unsuitable because side reactions at the stage of the acylmetalate intermediate can prevent or interfere with the otherwise smooth course of the carbene complex synthesis.[2] The formation of the carbene complex via concerted CC bond formation to a coordinated CO ligand would solve this general problem. A possible way of realizing such a one-step synthesis is a reaction analogous to the presumably concerted bis(olefin)metallocene→bis(cyclopentadienyl)metallacyclopentane ring closure reaction using an "oxyphilic" early transition metal.[3] We selected the (η^2-aryne)zirconocene **2** as a very reactive (η^2-olefin)metal complex precursor for this proposed reaction sequence. Compound **2a**, which cannot be isolated as such, may be generated easily as a reactive intermediate by elimination of benzene from diphenylzirconocene, **1a**, at 80 °C.[4]

1a reacts smoothly with hexacarbonyltungsten at 80 °C to give the zirconiumoxycarbenetungsten complex **4a**. The coupling of the *ortho*-phenylene moiety at the bent metallocene with the CO ligand is established unequivocally from the spectroscopic data[5]. The formation of **4a** via an aryne intermediate is supported by a classical experiment:[6] The thermolysis of di-*para*-tolylzirconocene **1b** affords the unsymmetrically substituted arynezirconocene complex **2b** (Me on C4),[4a] which should react with $W(CO)_6$ to give two intermediates **3** (**b**: Me on C5; **c**: Me on C4). We observed the formation of a 60:40 mixture of the correspondingly substituted, isomeric zirconiumoxycarbene complexes **4b** (Me on C5) and **4c** (Me on C4) in the reaction of **1b** with $W(CO)_6$ at 80 °C.[7]



While the X-ray structure analysis[8] shows that **4a** exhibits the characteristic properties of a Fischer-type carbene complex[1] with a large W–C(carbene) distance, the C(carbene)–O bond is remarkably short. The corresponding Zr–O bond is long. Two crystallographically independent molecules of **4a** are present in the unit cell. They mainly differ in the conformation of the bent metallocene fragment: in one molecule, the two cyclopentadienyl ligands are, to a first approximation, staggered, while in the other one, they are eclipsed (Fig. 1).

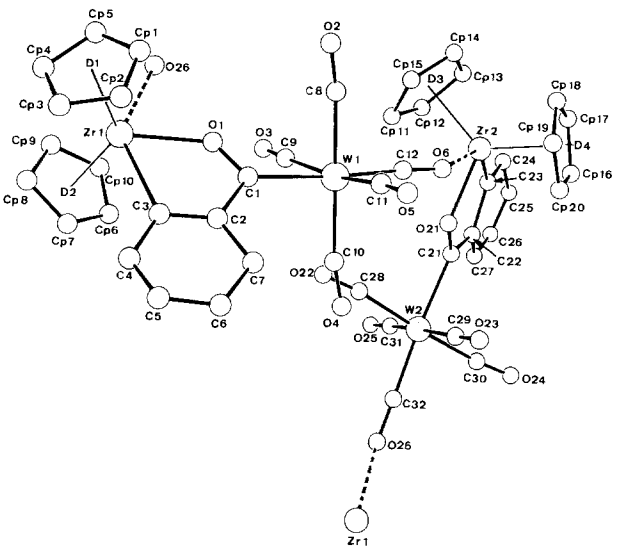


Fig. 1. Crystal structure of **4a**: geometry of the two crystallographically independent molecules: intermolecular interactions between Zr1 and O26 and between Zr2 and O6 are indicated.

The most noticeable feature of the solid-state structure of **4a** is the intermolecular linkage of the crystallographically independent units via the CO ligands *trans* to the car-

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bene carbon. Although the resulting interaction (Zr2–O6: 2.49(2) Å) is weak (and certainly unstable in solution) in comparison with that in the metallocyclic five-membered-ring skeleton (Zr1–O1 2.16(2) Å), it is sufficient to connect the monomeric zirconiumoxycarbene–$W(CO)_5$ units in the solid specifically to give a polymeric helical molecular chain. The two independent units of **4a** together form the repeating structural unit of the helix (see Fig. 2). Solvent molecules (in this case, toluene) occupy positions between the chains in a disordered fashion. However, the incorporated solvent is only weakly bound. It is rapidly released, with destruction of the crystal structure, upon passing a stream of inert gas over the solid.

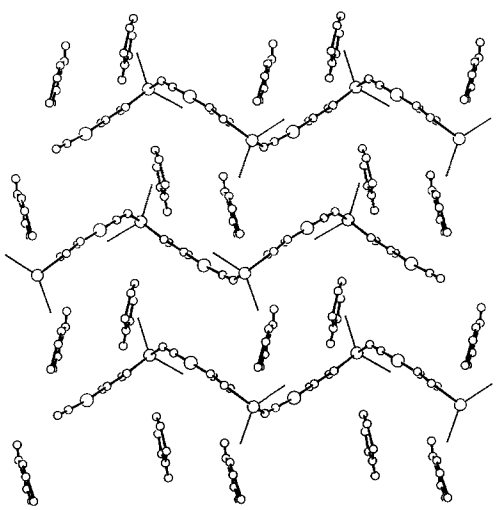


Fig. 2. Crystal structure of **4a**: a view of the helical molecular chains. For simplification, only the $-Zr(C_3O)-W-(CO)-$ skeletal units are drawn.

The formation of the polymeric helix structure of **4a** in the solid state is possibly an indication of the importance of a dipolar resonance structure **4a'** in describing the properties of this zirconiumoxycarbene complex:[9] The unusually electrophilic Zr center is attacked by the negative end of the dipole, the oxygen of the carbonyl group, in a manner that is typical[10] of a carbonylmetalate ion.

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CAS Registry numbers:
1a, 51177-89-0; **1b**, 63672-39-9; **2a**, 71191-32-7; **2b**, 96866-24-9; **4a**, 96896-91-2; **4a** · PhMe, 96896-92-3; **4b**, 96896-93-4; **4c**, 96896-94-5; $W(CO)_6$, 14040-11-0.

[1] a) E. O. Fischer, A. Maasböl, *Angew. Chem.* 76 (1964) 645; *Angew. Chem. Int. Ed. Engl.* 3 (1964) 580; *Chem. Ber.* 100 (1967) 2445; b) K. H. Dötz, H. Fischer, P. Hofmann, F. R. Kreissl, U. Schubert, K. Weiss: *Transition Metal Carbene Complexes*, Verlag Chemie, Weinheim 1983.

[2] See, e.g., C. M. Jensen, C. B. Knobler, H. D. Kaesz, *J. Am. Chem. Soc.* 104 (1984) 5926; W. Wong, K. W. Chiu, G. Wilkinson, A. M. R. Galas, M. Thornton-Pett, M. B. Hursthouse, *J. Chem. Soc. Perkin Trans. 1983*, 1557; A. W. Parkins, E. O. Fischer, G. Huttner, D. Regler, *Angew. Chem.* 82 (1970) 635; *Angew. Chem. Int. Ed. Engl.* 9 (1970) 633.

[3] a) A. Stockis, R. Hoffmann, *J. Am. Chem. Soc.* 102 (1980) 2952; b) V. Skibbe, G. Erker, *J. Organomet. Chem.* 241 (1983) 15; G. Erker, K. Engel, U. Dorf, J. L. Atwood, W. E. Hunter, *Angew. Chem.* 94 (1982) 915, 916; *Angew. Chem. Int. Ed. Engl.* 21 (1982) 913, 913; *Angew. Chem. Suppl. 1982*, 1974, 1984.

[4] a) G. Erker, *J. Organomet. Chem.* 134 (1977) 189; G. Erker, K. Kropp, *J. Am. Chem. Soc.* 101 (1979) 3659; K. Kropp, G. Erker, *Organometallics 1* (1982) 1246; b) J. Dvorak, R. J. O'Brien, W. Santo, *J. Chem. Soc. D 1970*, 411; H. Masai, K. Sonogashira, N. Hagihara, *Bull. Chem. Soc. Jpn.* 41 (1968) 750; E. G. Berkovich, V. E. Shur, M. E. Vol'pin, B. Lorenz, S. Rummel, M. Wahren, *Chem. Ber.* 113 (1980) 70, and references cited therein; U. B. Shur, E. G. Berkovich, M. E. Vol'pin, B. Lorenz, M. Wahren, *J. Organomet. Chem.* 228 (1982) C36.

[5] **4a**: Synthesized by heating a suspension of **1a** (7.9 g, 21 mmol) and $W(CO)_6$ (7.0 g, 20 mmol) in 1000 mL of heptane at 90 °C for 5 h; yield (after crystallization from the hot, filtered heptane solution) 6.7 g (52%); m.p. (benzene) = 132 °C (decomp.); correct elemental analysis; MS (70 eV): *m/z* 648 ($M^{\oplus}$), 620 ($M^{\oplus}-CO$); IR (C_6D_6): ν(CO) = 2061 (s), 1973 (m), 1933 (vs), 1917 cm^{-1} (sh); ^1H NMR (CD_2Cl_2, see the formula for numbering): $\delta = 6.46$ (Cp), 8.31 (H3), 7.12, 7.20 (H4, H5), 7.00 (H6); ^{13}C NMR (CD_2Cl_2, ^1J(CH) [Hz] in parentheses: $\delta = 115.7$ (d, 175, Cp), 194.0 (s, C1), 169.8 (s, C2), 140.3 (d, 159, C3), 126.3 (d, 161, C4), 130.4 (d, 159, C5), 138.1 (d, 158, C6), 329.7 (^1J(WC) = 93, carbene C), 200.4 (^1J(WC) = 128, *cis*-CO), 206.7 (^1J(WC) = 125, *trans*-CO). The ^{13}C-NMR signals were assigned with the help of a 2D RELAY spectrum (sequence C3–C6) and selective proton decoupling (^3J[C(carbene)H3)]).

[6] R. W. Hoffmann: *Dehydrobenzene and Cycloalkynes*, Academic Press, New York 1967, p. 27, 253.

[7] **4b** and **4c** (mixture). Correct elemental analysis. **4b**: ^1H NMR (CD_2Cl_2): $\delta = 6.45$ (Cp), 8.19 (H3), 7.08 (H4), 6.80 (H6), 2.30 (C5–Me); ^{13}C NMR (CD_2Cl_2): $\delta = 115.5$ (d, 174, Cp), 194.4 (s, C1), 167.7 (s, C2), 140.3 (d, 157, C3), 127.2 (d, 159, C4), 141.1 (s, C5), 138.8 (d, 155, C6), 21.8 (q, 126, Me), 326.8 (Carbene C), 200.5 (^1J(WC) = 128, *cis*-CO), 206.7 (*trans*-CO). – **4c**: ^1H NMR (CD_2Cl_2): $\delta = 6.44$ (Cp), 8.13 (H3), 7.06 (H5), 6.88 (H6), 2.41 (C4–Me); ^{13}C NMR (CD_2Cl_2): $\delta = 115.5$ (d, 174, Cp), 189.9 (s, C1), 169.8 (s, C2), 141.0 (d, 155, C3), 135.9 (s, C4), 131.7 (d, 156, C5), 138.1 (d, 157, C6), 21.3 (q, 126, Me), 329.3 (Carbene C), 200.5 (^1J(WC) = 128, *cis*-CO), 206.7 (*trans*-CO).

[8] Cell data: $a = 14.994(4)$, $b = 11.658(2)$, $c = 15.752(2)$ Å, $\beta = 97.27(1)°$, $V = 2731.25$ Å^3, $\rho_{calcd.} = 1.80$ g cm^{-3}, $\mu = 47.12$ cm^{-1}, $Z = 2$, Pa, 10170 reflections, 5923 observed reflections with $I \geq 2\sigma(I)$; 556 refined parameters, $R = 0.036$, $R_w = 0.036$. Selected bond lengths [Å] and bond angles [°]: Zr1–D1 2.211, Zr2–D3 2.226, Zr1–D2 2.246, Zr2–D4 2.209, Zr1–O1 2.16(2), Zr2–O21 2.15(1), Zr1–C3 2.350(9), Zr2–C23 2.28(1), Zr1–O26 2.40(2), Zr2–O6 2.49(2), W1–C1 2.250(8), W2–C21 2.25(1), W1–C12: 1.955(8), W2–C32 1.98(1), O1–C1 1.21(2) (shortened, *trans* to the longer intermolecular linkage Zr2–O6), O21–C21 1.36(2), O6–C12 1.17(2), O26–C32 1.21(2); D1–Zr1–D2 133.8, D3–Zr2–D4 128.9, O1–Zr1–C3 69.9(5), O21–Zr2–C23 70.7(5), C1–W1–C12 173.6(3), C21–W2–C32 175.6(4), C12–O6–Zr2 147(1), C32–O26–Zr1 152(1). Further details of the crystal structure investigation are available on request from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2, by quoting the depository number CSD 51262, the names of the authors, and the journal citation.

[9] Further possible examples of this new type of reaction are the coupling of two CO ligands or of butadiene with CO on the zirconium moiety. a) G. Erker, U. Dorf, R. Benn, R.-D. Reinhardt, J. L. Petersen, *J. Am. Chem. Soc.* 106 (1984) 7649; b) D. H. Berry, J. E. Bercaw, A. J. Jircitano, K. B. Mertes, *ibid.* 104 (1982) 4712; C. P. Casey, R. F. Jordan, A. L. Rheingold, *Organometallics 3* (1984) 504.

[10] Reviews: C. K. Rofer-DePoorter, *Chem. Rev.* 81 (1981) 447; C. P. Horwitz, D. F. Shriver, *Adv. Organomet. Chem.* 23 (1984) 219.

1,4-Addition of Dihalocarbenes to 1,3-Dienes**

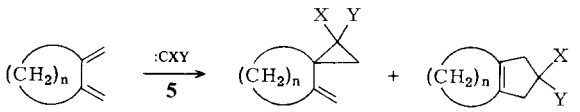
By *Leonardus W. Jenneskens, Willem H. de Wolf,* and *Friedrich Bickelhaupt**

The 1,4-addition of singlet carbenes to 1,3-dienes is not ruled out on the basis of theoretical calculations even though it may be difficult in comparison with the known 1,2-addition.[1] However, until now, it has been observed directly[2] or indirectly[3] in only a very limited number of cases.[4,5] Earlier, we found the first example of an unequivocal intermolecular 1,4-addition in the reaction of dichlorocarbene with 1,2-bis(methylene)cycloheptane and explained this on the basis of the cisoid conformation of the 1,3-diene.[2b] We report here a new investigation which had as its goal the more exact determination of the scope of this novel reaction.

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For this purpose, we allowed the 1,2-bis(methylene)cycloalkanes **1–4** to react with dihalocarbenes CXY **5** under largely standardized conditions.[6] In addition to the expected main products **6**, the 1,2-adducts, we found varying amounts of the 1,4-adducts **7** (Table 1), depending on the ring size and the halogen substituents.



1–4 **6** **7**

Table 1. 1,2- and 1,4-additions of CXY, **5**, to 1,2-bis(methylene)cycloalkanes **1–4**. Both diastereomers of **6c** are formed in the additions of **5c**.

	n	5	CXY	Method	Yield	
					6 + 7 [%]	6 : 7
1	3	**5b**	CCl_2	[a]	51	0.98 : 0.02
		5c	CBrCl	[a]	53	0.98 : 0.02
		5d	CBr_2	[a]	60	0.96 : 0.04
2	4	**5b**	CCl_2	[a]	60	0.97 : 0.03
		5c	CBrCl	[a]	46	0.96 : 0.04
		5d	CBr_2	[a]	31	0.90 : 0.10
3	5	**5a**	CF_2	[b]	70	1.00 : 0.00
		5b	CCl_2	[a]	88	0.99 : 0.01
		5c	CBrCl	[a]	80	0.92 : 0.08
		5d	CBr_2	[a]	79	0.81 : 0.19
				[c]	69	0.87 : 0.13
				[d]	89	0.89 : 0.11
		5e	CI_2	[e]	37	1.00 : 0.00
4	6	**5b**	CCl_2	[a]	78	0.99 : 0.01
		5c	CBrCl	[a]	47	0.93 : 0.07
		5d	CBr_2	[a]	90	0.90 : 0.10
				[c]	95	0.88 : 0.12
				[d]	75	0.86 : 0.14

[a] According to *Skattebøl* [7] from CHX_2Y and *t*BuOK in *n*-pentane at 25°C (cf. [6]). [b] According to *Dolbier* and *Sellers* [8] from $[Ph_3PCF_2Br]^{\oplus}Br^{\ominus}$ with KF at 25°C (20 h). [c] According to *Seyferth* [9] from $PhHgCBr_3$ in benzene at 80°C (2 h). [d] According to *Seyferth* [9] from $PhHgCBr_3$ in toluene at 110°C (2 h). [e] According to *Baird* [10] from CHI_3 and *t*BuOK in *t*BuOH at −20°C and 16 h stirring at room temperature.

Control experiments with 2,3-dimethylbutadiene and the same dihalocarbenes gave exclusively 1,2-adducts; no 1,4-adducts were observed within the limits of experimental error (^{1}H NMR, GLC: <0.1% **7**). As we have already shown earlier, **6b** (n = 5) does not rearrange to **7b** (n = 5) under the reaction conditions used; similarly **6d** (n = 5) does not afford **7d** (n = 5), even at 110°C. The surprisingly general 1,4-addition that occurs for **1–4** must be ascribed to their cisoid conformation. A radical mechanism or a nucleophilic addition of a trihalomethane anion is very unlikely since, in these cases, 1,4-adducts of 2,3-dimethylbutadiene would also be expected. The only alternative is thus a more or less concerted addition; whether a short-lived common intermediate[11] is involved cannot be determined on the basis of our experiments.

An analysis of the results in Table 1 allows the following preliminary conclusions to be drawn:

1) The relative yields of **6** and **7** are not strongly dependent on the mode of generation of the dihalocarbenes. This conclusion results from the roughly constant molar ratio of **6d** and **7d** formed from **3** and **4** when dibromocarbene, **5d**, is prepared by either the Skattebøl[7] or the Seyferth[9] method. Although minor differences are observed, they may be ascribed to temperature effects, as shown by the monotonic decrease in the amount of **7d** with increasing temperature (e.g., **7d** from **3**: 0.19/25°C, 0.13/80°C, 0.11/110°C). One may therefore assume that free carbene is involved in these reactions.

2) Electronic factors play an important role in the 1,4-addition. Difluoro- and diiodocarbene, **5a** and **5e**, respectively, do not engage in 1,4-addition; the optimal reaction occurs for dibromocarbene, **5d**. Remarkably, difluorocarbene tends to engage most strongly in homo 1,4-addition to norbornadiene;[4,5] different factors are apparently decisive in the two types of reaction.

3) Steric factors also have a major influence on the competition between 1,2- and 1,4-addition. However, caution is urged here since rate comparisons using a variety of substrates would be necessary before drawing definite conclusions; the product ratios of Table 1 reflect only the competition with respect to the same substrate. It is noticeable, however, that for the relatively small dichlorocarbene, **5b**, there is hardly any dependence on the ring size, whereas for bromochlorocarbene, **5c**, such a dependence is evident and for dibromocarbene, **5d**, it is strongly pronounced. Furthermore, it is noteworthy that, especially for dibromocarbene, the highest yield of the 1,4-adduct is obtained for the seven-membered ring **3** even though its 1,3-diene system is not coplanar and the distance between the carbon atoms 1 and 4 of this system is less favorable than, for example, in the five-membered ring **1**.

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1, 20968-70-1; **2**, 2819-48-9; **3**, 58738-52-6; **4**, 64306-16-7; **5a**, 2154-59-8; **5b**, 1605-72-7; **5c**, 13590-47-1; **5d**, 4371-77-1; **5e**, 4371-79-3; **6a** (n=5), 96761-16-9; **6b** (n=3), 96761-11-4; **6b** (n=4), 96761-14-7; **6b** (n=5), 80281-35-2; **6b** (n=6), 96761-20-5; *cis*-**6c** (n=3), 96761-12-5; *trans*-**6c** (n=3), 96761-31-8; *cis*-**6c** (n=4), 96761-15-8; *trans*-**6c** (n=4), 96761-32-9; *cis*-**6c** (n=5), 96761-17-0; *trans*-**6c** (n=5), 96761-33-0; *cis*-**6c** (n=6), 96761-21-6; *trans*-**6c** (n=6), 96761-34-1; **6d** (n=3), 96761-13-6; **6d** (n=4), 52326-72-4; **6d** (n=5), 96761-18-1; **6d** (n=6), 82735-52-2; **6e** (n=5), 96761-19-2; **7b** (n=3), 96761-22-7; **7b** (n=4), 96761-25-0; **7b** (n=5), 80281-34-1; **7b** (n=6), 80281-41-0; **7c** (n=3), 96761-23-8; **7c** (n=4), 96761-26-1; **7c** (n=5), 96761-28-3; **7c** (n=6), 96761-29-4; **7d** (n=3), 96761-24-9; **7d** (n=4), 96761-27-2; **7d** (n=5), 66730-97-0.

[1] a) H. Fujimoto, R. Hoffmann, *J. Phys. Chem. 78* (1974) 1167; b) W. W. Schoeller, N. Aktekin, *J. Chem. Soc. Chem. Commun. 1982*, 20; c) N. L. Bauld, D. Wirth, *J. Comput. Chem. 2* (1981) 1.
[2] a) U. Burger, G. Gandillon, *Tetrahedron Lett. 1979*, 4281; b) L. A. M. Turkenburg, W. H. de Wolf, F. Bickelhaupt, *Tetrahedron Lett. 23* (1982) 769; c) H. Mayr, U. Heigl, *Angew. Chem. 97* (1985) 567; *Angew. Chem. Int. Ed. Engl. 24* (1985) 579.
[3] a) H. Hart, J. W. Raggon, *Tetrahedron Lett. 24* (1983) 4891; b) L. W. Jenneskens, F. J. J. de Kanter, L. A. M. Turkenburg, H. J. R. de Boer, W. H. de Wolf, F. Bickelhaupt, *Tetrahedron 40* (1984) 4401.
[4] Survey of the older, in part contradictory, literature: R. A. Moss, M. Jones, Jr. in R. A. Moss, M. Jones, Jr. (Ed.): *Reactive Intermediates, Vol. 2*, Wiley, New York 1981, chap. 3.
[5] For related homo 1,4-addition see: a) C. W. Jefford, nT. Kabengele, J. Kovacs, U. Burger, *Helv. Chim. Acta 57* (1974) 104; b) C. W. Jefford, V. de los Heros, U. Burger, *Tetrahedron Lett. 1976*, 703; c) P. M. Kwantes, G. W. Klumpp, *ibid. 1976*, 707.
[6] The experiments using the Skattebøl method [7] were carried out as follows: the appropriate haloform ($CHCl_3$, $CHBr_2Cl$, or $CHBr_3$: 10 mmol) and potassium *tert*-butoxide (10 mmol) were added to **1–4** (5 mmol) in *n*-pentane (5 mL) and stirred for 18 h at 25°C. Following the usual work-up, the yields of **6** and **7** were determined by weighing and the ratio **6** : **7** by ^{1}H-NMR spectroscopy and gas chromatography of the reaction mixture. **6** and **7** were isolated by preparative gas chromatography (15% SE-30/Chromosorb W, 1.5 m) and characterized by their ^{1}H-NMR spectra and high-resolution mass spectra. In addition, the compounds **7b** (n = 3–6) were prepared independently by flash vacuum thermolysis of **6b** (n = 3–6) at 480°C and 4×10^{-2} mbar: L. W. Jenneskens, L. A. M. Turkenburg, W. H. de Wolf, F. Bickelhaupt, *Recl. Trav. Chim. Pays-Bas*, in press. 5 mmol of **3** or **4** and 6 mmol of the carbene precursor were also used for the other carbene additions [8–10] from Table 1.
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2,5,7,10-Tetrakis(trimethylsilyl)-1,6-methano[10]annulene, a Fluxional Valence Tautomer with Cyclopolyolefin Structure**

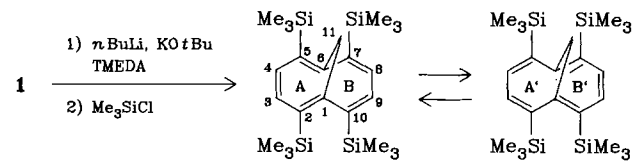
By *Richard Neidlein,* Wolfgang Wirth, Alfred Gieren, Viktor Lamm,* and *Thomas Hübner*

Dedicated to Professor Rolf Huisgen on the occasion of his 65th birthday

1,6-Methano[10]annulene **1** has an aromatic structure with a Hückel 10π-electron system in the perimeter.[1,2] Depending on the substituents, isolable valence tautomers



can occur; thus, the derivative **2** with dicyano-substituted methano-bridge and having a norcaradiene crystal structure has already been reported.[3]



3

The compound 2,5,7,10-Tetrakis(trimethylsilyl)-1,6-methano[10]annulene **3** has been shown by an X-ray structure analysis to be the first cycloheptatriene/cycloheptadiene valence isomer with a cyclopolyolefin structure. If **1** is lithiated in the presence of tetramethylenediamine (TMEDA) and potassium *tert*-butoxide and subsequently trimethylsilylated, **3** can be isolated in 6% yield as colorless crystals.

One of the two equivalent resonance structures representing the aromatic character of 1,6-methano[10]annulene is present as valence tautomer in **3**. In solution at room temperature, a fluctuation between single and double bonding takes place. This manifests itself in the appearance of only one signal in the ^{1}H-NMR spectrum for the perimeter protons and only one signal in the ^{13}C-NMR spectrum for the perimeter carbon atoms 2, 5, 7, and 10. At lower temperatures, a diminution in the fluctuation leads to a broadening, and, below 155 K, a doubling of the proton signals is observed.

The molecule **3** (Fig. 1)[4] has a well-fulfilled non-crystallographic mirror plane through the bridge carbon atom C11 and the midpoints of the C3–C4 and C8–C9 bonds. The tendency of the bulky trimethylsilyl groups in the "*peri*" positions to make way for each other not only determines the bonding behavior and conformation of the molecule but also removes the aromaticity of 1,6-methano[10]annulene. In the [10]annulene perimeter of **3**, there are alternating single and double bonds, as in a cycloolefin. The single bonds have a length of 1.45–1.47 Å, while the double bonds have a length of 1.35–1.36 Å. The two seven-membered rings do not have the same conformation: the cycloheptatriene ring A has a boat conformation, while the cycloheptadiene ring B has an envelope conformation. In ring B, the silyl-substituted atoms C7 and C10 are noticeably rehybridized from sp^2 to sp^3 (sum of angles: 356.2°). The Si3 and Si4 atoms lie 0.75 Å outside of the plane of the six coplanar C atoms of ring B. The rehybridization of the analogous C-atoms of the boat-shaped ring A is comparatively slight (sum of angles: 358.9°). In both cases, however, steric strain between the "*peri*" silyl groups is reduced by the rehybridization. The silyl groups on ring A, on the one hand, and on ring B, on the other, are located on opposite sides of the [10]annulene ring (Fig. 1b). The aromaticity of the 1,6-methano[10]annulene is removed by the steric effects of the substituents, which lead to a strong torsion about the C6–C7 and the C1–C10 bonds. The torsional angle C5–C6–C7–C8 is −127.5°, the mirror symmetry equivalent angle 126.7°. If the rehybridization at C7 and C10 is still taken into account then the p_z orbitals of these bonds are rotated through 61.4° with respect to each other. The transannular C1–C6 distance is 2.298 Å.

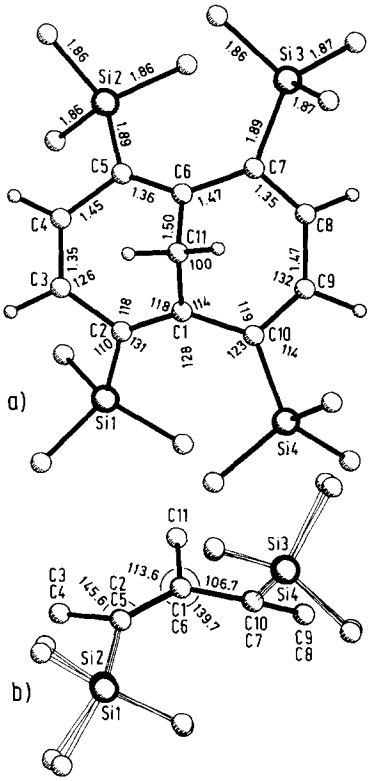


Fig. 1. Molecular structure of **3**. a) Plan view, without H-atoms of the $Si(CH_3)_3$ groups. b) Side view, without H-atoms, with interplanar angles. The given bond lengths [Å] and angles [°] are averaged over the molecular mirror symmetry, and, for clarity, given with one digit less than the least significant one (standard deviations of the individual values: 0.004–0.008 Å and 0.2–0.5°, respectively).

The reversible valence isomerization in solution leads to a mutual transformation of the conformations of the seven-membered rings; this results in the structures being the same.

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Experimental

TMEDA (20 mL) was treated with **1** (5 g, 33 mmol), potassium *tert*-butoxide (1 g), and a 2.5M solution of *n*-butyllithium in hexane (84 mL, 210 mmol). The mixture was heated for 1 h at 50°C and then treated, with ice-cooling, with 25 g (230 mmol) of trimethylsilyl chloride, stirred for a further hour at room temperature, and finally hydrolyzed with dilute hydrochloric acid. Subsequent extraction with ether, drying over anhydrous $MgSO_4$, removal of the solvent, and column-chromatographic purification (silica gel, 30 cm, Ø 3 cm, hexane as eluent) afforded 910 mg (6%) of **3** (colorless crystals, m.p. 128°C).—UV (hexane): λ_{max} (lgε) = 240 (4.15), 320 nm (3.88).—^{1}H NMR (250 MHz, CCl_2F_2/[D$_6$]acetone): 293 K: δ (referred to [D$_6$]acetone) = 0.30 (s, CH_3), 1.53 (s, CH_2), 6.84 (s, H-3,4,8,9). 128 K: δ = 0.11, 0.31 (CH_3), 0.82, 1.66 (CH_2), 6.47, 7.03 (perimeter-H).—^{13}C NMR (62.89 MHz, $CDCl_3$): δ = 1.87 (q, CH_3), 39.7 (t, C-11), 132.4 (d, C-3,4,8,9), 138.3 (s, C-2,5,7,10).

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CAS Registry numbers:
1, 2443-46-1; **3**, 97102-37-9.

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[4] Monoclinic, $P2_1/c$, a = 9.933(4), b = 25.449(7), c = 11.654(4) Å, β = 108.92(3)°, V = 2786.8 Å^3, Z = 4, ρ_{calc} = 1.027 g cm^{-3}; CAD4, $Mo_{K\alpha}$, graphite monochromator, 3251 independent reflections ($I > 2\sigma(I)$), $0° < \theta < 26.5°$, $\omega/2\theta$-scan, direct methods, R = 0.073. Further details of the crystal structure investigation are available on request from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2, on quoting the depository number CSD 51356, the names of the authors, and the full citation of the journal.

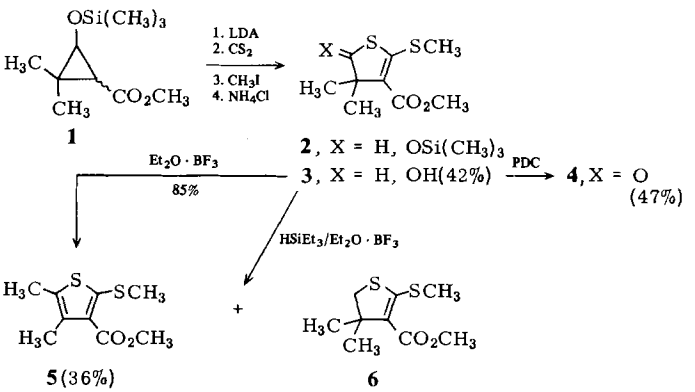
Thiophene Derivatives by Novel Rearrangements of Siloxy-substituted Cyclopropanecarboxylates**

By *Christiane Brückner* and *Hans-Ulrich Reissig**

Dedicated to Professor Rolf Huisgen on the occasion of his 65th birthday

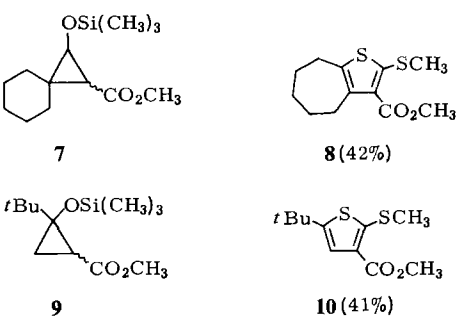
Siloxy-substituted cyclopropanecarboxylates are, as synthetic equivalents of 1,4-dicarbonyl compounds, versatile building blocks for the preparation of heterocycles; after having already used such intermediates for the synthesis of furan,[1] pyrrole,[1c] and pyridazine derivatives,[2] we have now found that the "cyclopropane trick"[3] can also be exploited for a surprisingly easy access to thiophene derivatives.

Generation of the ester enolate by reaction of **1** in tetrahydrofuran (THF) with lithium diisopropylamide (LDA)[4] followed by successive addition of carbon disulfide (1 h, −78°C/3 h, 20°C) and methyl iodide (16 h, 20°C) does not lead to formation of a cyclopropanedithiocarboxylate, as would be expected, but to the dihydrothiophene **2**. We presume that the ring expansion takes place at the stage of the anionic CS_2-adduct. The driving force behind this novel rearrangement[5] could arise from the release of strain in the cyclopropane ring and better stabilization of the negative charge in the ring expanded intermediate.



The siloxy compound **2** can be smoothly desilylated with $Et_3N \cdot 3HF$ (THF, 1 h, 20°C) to the hydroxy compound **3**, which, in turn, can be oxidized with pyridinium dichromate (PDC) (CH_2Cl_2, 3 d, 20°C) to give the thiolactone **4**. On attempting to reduce **3** with $HSiEt_3/Et_2O \cdot BF_3$ (CH_2Cl_2, 1 h, 0°C/3 h, 20°C)[6] to the dihydrothiophene derivative **6**, not only **6** but also the 3-thiophenecarboxylate **5** was formed (**6** : **5** ≈ 1 : 3). Treatment of **3** (or **2**) with $Et_2O \cdot BF_3$ (CH_2Cl_2, 30 min, 0°C/3 h, 20°C) provides exclusively **5** in high yield (overall yield **1** → **5**: 36%). The formation of **5** can be explained in terms of ionization by the Lewis acid, Wagner-Meerwein migration of a methyl group, and deprotonation with aromatization. The bicycle **8** is formed in a completely analogous way from **7** (overall yield in three steps: 42%). Two ring expansion steps (**3** → **5**, **6** → **7**) lead from a spirocyclic to an annelated ring system.

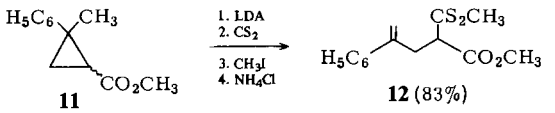
The example **9** shows that siloxycyclopropanes unsubstituted in position 3 are also capable of forming thiophene derivatives. Deprotonation of **9**, addition of CS_2 and MeI, and treatment of the crude product with catalytic amounts of CF_3CO_2H (3 h, 20°C) leads directly to **10** [overall yield (not optimized): 41%].



In the absence of a trimethylsiloxy group on the cyclopropane ring, another reaction takes place: in an analogous procedure, **11** affords the ring-opened dithio ester **12**.[7]

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11 12 (83%)

The SCH_3-group in the 2-position in 3-thiophenecarboxylates ought to be substitutable;[8] hence, new possibilities are opened up for the synthesis of highly-substituted thiophene derivatives.[9,10]

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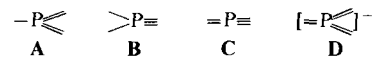
CAS Registry numbers:
1, 77903-45-8; **2**, 96914-02-2; **3**, 96914-03-3; **4**, 96914-04-4; **5**, 96914-05-5; **6**, 96914-06-6; **7**, 82884-41-1; **8**, 96928-67-5; **9**, 77903-42-5; **10**, 96914-07-7; **10** (silylated precursor), 96914-09-9; **11**, 40474-22-4; **12**, 96914-08-8.

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[7] Possibly a homo-1,5-sigmatropic hydrogen shift and subsequent prototropy are involved. Cf. D. E. McGreer, N. W. K. Chin, *Can. J. Chem. 46* (1968) 2217.
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[10] All the new compounds isolated (purified by Kugelrohr distillation and recrystallization) gave satisfactory elemental analyses and correct spectra. **3**: m.p. 126–127°C; ^{1}H NMR (90 MHz, $CDCl_3$): $\delta = 5.00$ (s, 1H, 5-H), 3.71 (s, 3H, CO_2CH_3), 2.86 (s, 1H, OH), 2.41 (s, 3H, SCH_3), 1.38, 1.22 (2s, each 3H, $2CH_3$); IR (CCl_4): $\nu = 3580$ (OH), 1705 cm^{-1} (CO_2CH_3). **4**: m.p. 68–69°C; ^{1}H NMR ($CDCl_3$): $\delta = 3.78$ (s, 3H, CO_2CH_3), 2.50 (s, 3H, SCH_3), 1.45 (s, 6H, $2CH_3$). **5**: m.p. 66–67°C; ^{1}H NMR ($CDCl_3$): $\delta = 3.72$ (s, 3H, CO_2CH_3), 2.39 (s, 3H, SCH_3), 2.13, 2.19 (2s, each 3H, $2CH_3$). IR (CCl_4): $\nu = 1710$ cm^{-1} (CO_2CH_3). **12**: b.p. 150°C/0.02 torr; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.30$ (m, 5H, C_6H_5), 5.26, 5.08 (2s, each 1H, $=CH_2$), 4.29 (t, $J = 7.0$ Hz, 1H, CH), 3.61 (s, 3H, CO_2CH_3), 3.42, 3.19 (2dd, $J = 7.0$, 14.5 Hz, each 1H, CH_2), 2.56 (s, 3H, CS_2CH_3); IR (CCl_4): $\nu = 1745$ (C=O), 1630 cm^{-1} (C=C).

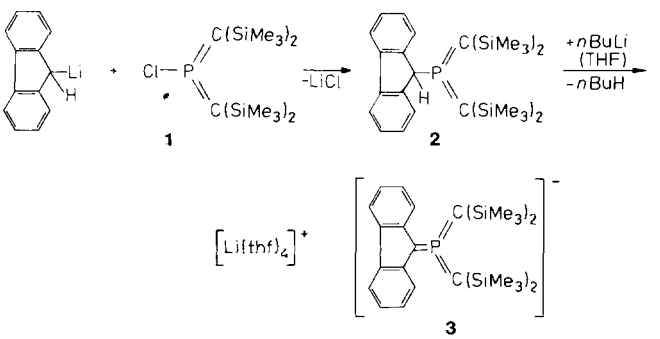
The First Tris(methylene)phosphate Ion $[P(=C<)_3]^-$ **

By *Rolf Appel,* Elisabeth Gaitzsch,* and *Falk Knoch*

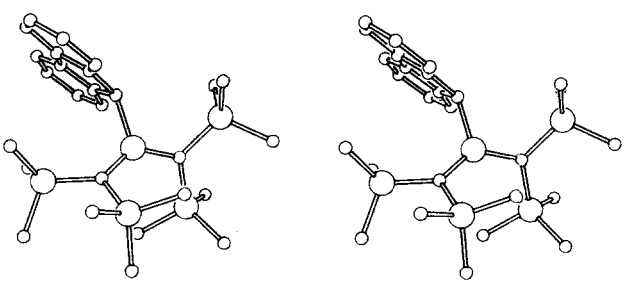
Pentavalent phosphorus has mainly the coordination numbers 4, 5, and 6. Compounds in which P^V is coordinated by only three or two ligands have only become known in recent years. Currently, they are being intensively investigated. Recent examples of such systems, which are characterized by double or triple bonds, exhibit the structure types **A**,[1] **B**,[2] and **C**.[3] We report here the first synthesis of a salt of the anion type **D**.



The *P*-chlorobis(methylene)phosphorane **1**,[4] the starting material, is first converted into the bis(methylene)phosphorane **2**[5] by reaction with fluorenyllithium. **2** is converted into the corresponding anion **3** by treatment with *n*BuLi or lithium dimethylamide in tetrahydrofuran (THF). According to the X-ray structure determination and spectroscopic data in solution, **3** can be described as a discrete anion with fourfold THF-coordinated lithium[7] as counterion in the solid state and in solution.[6]



The following structural parameters—particularly in comparison with those of the neutral compound **2**—justify the characterization of **3** as tris(methylene)phosphate: The fluorenyl C9-P distance (167 pm) is shorter in **3** than in **2**, corresponding to a double bond. The $P{=}C(SiMe_3)_2$ bond



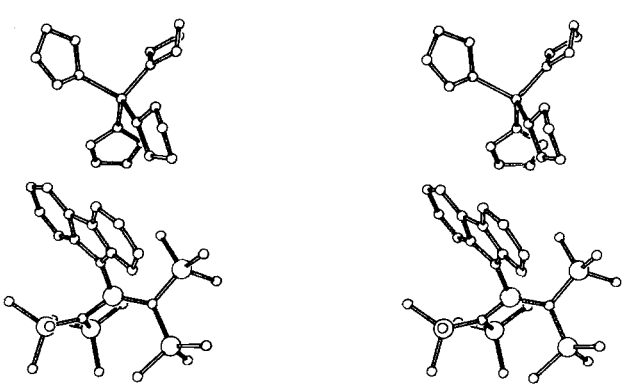


Fig. 1. Stereograph of the structure of **2** (above) and of Li(thf)$_4$ **3** (below).

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[**] Low-Coordinated Phosphorus Compounds, Part 39.—Part 38: R. Appel, W. Schuhn, F. Knoch, *Angew. Chem. 97* (1985) 421; *Angew. Chem. Int. Ed. Engl. 24* (1985) 420.

lengths remain essentially the same on going from **2** (mean 166 pm) to **3** (169 pm); the angle $(SiMe_3)_2C{=}P{-}C(SiMe_3)_2$ is decreased by 6° due to the introduction of the third double bond. The central PC_3 group is planar and the CPC angles are almost identical. The three double-bonded C atoms with their substituents surround the central phosphorus atom in a propeller-like manner (sp^2 hybridization). These results do not allow conclusions to be drawn about the ylene or ylide character of the three PC double bonds. Phosphorus may be bonded similarly to the sulfur in tris(imino)sulfur compounds.[8]

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CAS Registry numbers:
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[1] a) E. Niecke, W. Flick, *Angew. Chem. 86* (1974) 128; *Angew. Chem. Int. Ed. Engl. 13* (1974) 134; b) O. J. Scherer, N. Kuhn, *J. Organomet. Chem. 78* (1974) C 17; c) *Angew. Chem. 86* (1974) 899; *Angew. Chem. Int. Ed. Engl. 13* (1974) 811; d) E. Niecke, O. J. Scherer, *Nachr. Chem. Tech. Lab. 23* (1975) 395; e) E. Niecke, D. A. Wildbredt, *Angew. Chem. 90* (1978) 209; *Angew. Chem. Int. Ed. Engl. 17* (1978) 199; f) *J. Chem. Soc. Chem. Commun. 1981*, 72; g) R. Appel, J. Peters, A. Westerhaus, *Angew. Chem. 94* (1982) 76; *Angew. Chem. Int. Ed. Engl. 21* (1982) 80; h) R. Appel, F. Knoch, H. Kunze, *ibid. 95* (1983) 1008 and *22* (1983) 1004; i) J. Navech, J. P. Majoral, R. Kraemer, *Tetrahedron Lett. 24* (1983) 5885; j) M. Yoshifuji, K. Shibayama, W. Inamoto, *Chem. Lett. 1984*, 603; k) M. Caira, R. H. Neilson, W. H. Watson, P. Wisian-Neilson, Ze-Min Xie, *Organometallics 1983*, 1406; *J. Chem. Soc. Chem. Commun. 1984*, 698.

[2] G. Bertrand, *J. Am. Chem. Soc. 106* (1984) 6008.

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[4] R. Appel, K. H. Dunker, E. Gaitzsch, T. Gaitzsch, *Z. Chem. 24* (1984) 384.

[5] Experimental procedure: Fluorene (1.6 g, 10 mmol) was dissolved in 40 mL of THF. The stirred solution was treated at room temperature with 6.25 mL of a 15% solution of *n*BuLi in hexane (10 mmol). After 30 min, a solution of **1** (3.83 g, 10 mmol) in 20 mL of THF was added in portions. After a further 60 min, the solvent was removed in vacuum and the residue dissolved in pentane. The precipitated LiCl was filtered off and the product crystallized from pentane. Yield: 4.7 g (92%). M.p. = 175°C (correct elemental analysis). b) Significant NMR data: ^{31}P NMR (C_6D_6, H_3PO_4 ext.): $\delta = 173.2$ (d, $^2J(PH) = 19.6$ Hz); ^1H NMR ($CDCl_3$, TMS int.): $\delta = 5.1$ (d, $^2J(PH) = 19.5$ Hz, fluorenyl C9–H); $^{13}C\{^1H\}$ NMR ([D_8]THF, TMS ext.): $\delta = 60.65$ (d, $J(PC) = 31.35$ Hz, fluorenyl C9), 77.48 (d, $J(PC) = 38.17$ Hz, $PC(SiMe_3)_2$), 94.91 (d, $J(PC) = 42.91$ Hz, $PC(SiMe_3)_2$); c) X-ray structure data of **2**: Pbca, $a = 1015.1(3)$, $b = 1878.1(6)$, $c = 3325.1(10)$ pm, $V = 6339.1 \times 10^6$ pm^3, $\rho_{calc.} = 1.08$ g/cm^3, $Z = 8$. Direct methods (SHELXTL), 2154 reflections, $R = 0.076$, $R_w = 0.050$. Geometry: planar arrangement around the P atom, PC_3 plane twisted 68° with respect to the fluorenyl plane, sum of angles at fluorenyl C9 340.0°, CPC angle (methylene group) 129.9(3)°. Distances [pm]: P=C 165–167(1), P–C 183(1) [6c].

[6] a) Experimental procedure: **2** (5.12 g, 10 mmol) was dissolved in 40 mL of THF and treated with 6.25 mL of a 15% solution of *n*BuLi in hexane (10 mmol). After stirring for 3 h at room temperature, the solvent was removed in vacuo and the product recrystallized from ether. Yield: 3.63 g (45%). M.p. = 130°C (decomp.) (correct elemental analysis). b) Significant NMR data: ^{31}P NMR (C_6D_6, H_3PO_4 ext.): $\delta = 152$ (s); $^{13}C\{^1H\}$ NMR ([D_8]THF, TMS ext.): $\delta = 65.34$ (d, $J(PC) = 51.53$ Hz, $PC(SiMe_3)_2$), 98.52 (d, $J(PC) = 114.25$ Hz, fluorenyl C9). c) X-ray structure data of $Li(thf)_4$ **3**: Pbca, $a = 1844.2(8)$, $b = 2338.7(6)$, $c = 2394.7(17)$ pm, $V = 10328.6 \times 10^6$ pm^3, $\rho_{calc.} = 1.04$ g/cm^3, $Z = 8$. Direct methods (SHELXTL), 1912 reflections, $R = 0.139$, $R_w = 0.131$. Refinement beyond this R value was not possible since only weakly reflecting crystals were obtained from the substance; moreover, the strong thermal motion in the THF molecules could not be prevented by measurement in a cold stream of N_2. Geometry: PC_3 group and fluorenyl C9 geometry planar, PC_3 group twisted 134° with respect to the fluorenyl plane, $(SiMe_3)_2C{=}P{-}C(SiMe_3)_2$ angle 124(1)°. Distances [pm]: $P{=}C(SiMe_3)_2$ 169(2), P=C(fluorenyl 167(1)). Further details of the crystal structure investigation may be obtained on request from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2, by quoting the depository number CSD 51283, the names of the authors, and the journal citation.

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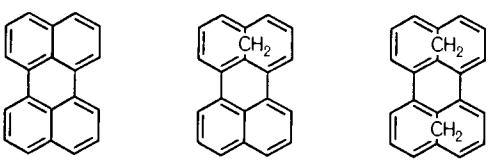
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syn- and *anti*-Bishomoperylene

By *Emanuel Vogel,* Klaus-Dieter Sturm, Aderson de Farias Dias, Johann Lex, Hans Schmickler,* and *Fred Wudl**

Dedicated to Professor Günther Wilke on the occasion of his 60th birthday

Perylene **1** has gained importance as a key molecule in the construction of organic solids exhibiting unconventional properties. The radical-cation salts of **1** and some other low molecular arenes, which are to be regarded as charge transfer complexes, qualify as organic metals,[1] while perylene-3,4:9,10-bis(dicarboximides) are pigments[2] that have recently been shown to be versatile fluorescent dyes.[3] The hitherto hypothetical polyperylene (poly-*peri*-naphthalene) is of interest since, according to theoretical calculations, it ought to exhibit metallic conductivity without requiring the presence of a dopant.[4] Arene-radical salts and perylene pigments have in common that their macroscopic properties are associated with a stacked arrangement of the arene moieties in the molecular crystals—thus enabling charge transfer or intermolecular π-electron interactions.[5]



1 **2** **3a**: *syn* **3b**: *anti*

In the light of these findings it seemed attractive to us to include the homoperylenes (derived from **1**), i.e. monohomoperylene **2** and the *syn-anti* isomeric bishomoperylenes **3a** and **3b** (and their analogues with hetero-atom bridges), in research studies on organic solids.

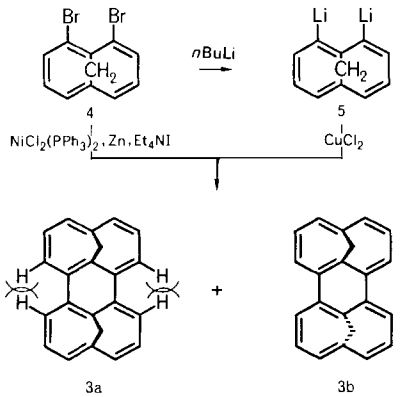
The question as to what extent the molecular geometry of homoperylenes still permits stacking in the crystal due to intermolecular electronic interactions is of special interest in this respect. We now report on the synthesis of the stereoisomeric bishomoperylenes **3a** and **3b**.

Reductive coupling of 2,10-dibromo-1,6-methano[10]annulene **4**[6] with triphenylphosphane-nickel(0) complexes generated in situ seemed to be the most promising strategy for a facile entry to **3a** and/or **3b**. However, the use of methods[7] customarily resorted to for such couplings led to formation of very complex reaction mixtures. In view of the ready metalation of **4** with butyllithium to give 2,10-dilithium-1,6-methano[10]annulene **5**[6] it therefore seemed worthwhile to investigate the oxidative coupling of **5** with copper(II) chloride.[8]

For the coupling reaction, a solution of **5**—prepared from **4** (3 g, 10 mmol) and a 2 M solution of butyllithium in ether (10 mL)—was added to a cooled suspension of anhy-

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drous $CuCl_2$ (2.7 g, 20 mmol) in ether (300 mL) at −78 °C. The deep-brown mixture was stirred for 6 h at −78 °C and 1 h at room temperature. Chromatographic work-up on alumina (Woelm, activity III, neutral) with chloroform-hexane (1:3) afforded a hydrocarbon which crystallized from dichloromethane as orange-colored platelets, m.p. 250–252 °C (decomp.), yield 25–30%. Physical investigations of the compound showed the presence of *anti*-bishomoperylene **3b** as the only isomer.

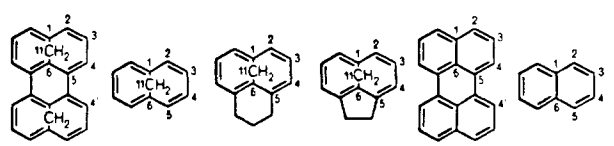
The ^{1}H-NMR spectrum of **3b**, which shows an ABX system at low field for the annulene protons and a singlet at high field for the bridge protons, is similarly related to that of 1,6-methano[10]annulene **6** as the spectrum of perylene **1** is to that of naphthalene **7** (see Table 1). That the signals of H-4 (X part of the ABX system)—analogously to the situation in the perylene spectrum—are shifted to lower field compared to those of H-2 and H-3 (AB part) is ascribed primarily to non-bonding interactions[9] between H-4 and H-4', similarly as in the case of **1**. Since this steric effect is distinctly more pronounced in **3a** than in **3b**, the position of the H-4 resonance signals—a knowledge of both stereoisomers prerequisite—permits an assignment of configuration, which, due to the symmetries of **3a** and **3b**, is not possible by other NMR-spectroscopic means.

The existence of **3b** as annulene valence tautomer is supported not only by the ^{1}H-NMR and ^{13}C-NMR spectra (Tables 1 and 2) but also by the finding that the dihydrohomophenalene **8**,[10] which can serve as a model for **3a**/**3b** with regard to the *peri*-bridging, is fully consistent with 1,6-methano[10]annulene **6** so far as the NMR parameters that can be used for a comparison are concerned (see Table 1). In the case of homoacenaphthene **9**,[11] on the other hand, the relatively short *peri*-bridge appears to confer some weight on the norcaradiene valence tautomer.

The UV/VIS spectrum of **3b** may be qualitatively interpreted in terms of a bathochromically shifted perylene spectrum. For the longest wave band (L_a band), which could correspond to a HOMO-LUMO transition, the red shift is relatively slight (ca. 15 nm), but sufficient to give **3b** a vivid orange color.

The presence of the *anti*-isomer **3b**, with a center of inversion, was confirmed by an X-ray structure analysis[12] (Fig. 1). The geometry of the 1,6-methano[10]annulene halves of the molecule shows no unusual alterations compared to **6**; this seems understandable, since the formation of the C^5–$C^{5'}$ and C^7–$C^{7'}$ bonds is almost strain-free if relatively weak non-bonding H–H interactions are disregarded. The central six-membered ring in **3b** is strikingly similar to that in **1** regarding the C–C bond lengths,[13] but

Table 1. ^{1}H-NMR parameters—chemical shifts (δ values) and coupling constants [Hz]—of **3a**, **3b**, and reference compounds (from 300-MHz spectra, in CD_2Cl_2) [a].



Cpd.	H-2	H-3	H-4	H-11	J(2,3)	J(3,4)	$^1J(^{13}C\text{-}11,^1H)$
3a	7.11	7.09	7.61	0.48	8.81	10.05	141.8
3b	7.02	7.02	7.31	0.51	8.81	9.68	143.3
6	7.27	6.95	6.95	−0.51	8.97	9.19	142.7
8	7.28	7.00	6.91	−0.42	9.02	8.96	141.5
9	7.07	6.89	6.64	0.43	9.55	8.82	146.2
1	7.69	7.49	8.20		8.23	7.55	
7	7.87	7.50	7.50		8.28	6.85	

[a] For easier comparison, the compounds are numbered in analogy to 1,6-methano[10]annulene **6**.

Table 2. Some spectral data of **3a** and **3b**.

3a: ^{13}C NMR (75.5 MHz, CD_2Cl_2): δ = 137.01 (C-5), 128.63 (C-3), 126.26 (C-2), 123.57 (C-4), 119.34 and 111.09 (C-1, 6), 34.78 (C-11); MS (75 eV): *m/z* 280 (M^+, 85%), 279 (M^+ − H, 82), 264 (M^+ − CH_2, 100), 252 (M^+ − $2CH_2$, 26); IR (CsI): 3034, 2946, 1889, 1520, 757 cm^{-1}; UV/VIS (cyclohexane): λ_{max} = 223 nm (ε = 50700), 263 (16700), 301 (24400), 468 (17800) sh, 476 (18500)

3b: ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 139.21 (C-5), 127.70 (C-3), 124.83 (C-2), 121.20 (C-4), 116.13 and 113.47 (C-1, 6), 36.32 (C-11); MS (70 eV): *m/z* 280 (M^+, 45%), 279 (M^+ − H, 53), 264 (M^+ − CH_2, 77), 252 (M^+ − $2CH_2$, 31), 132 (100); IR (KBr): 3041, 2967, 1904, 1532, 764 cm^{-1}; UV/VIS (cyclohexane): λ_{max} = 228 nm (ε = 64500), 258 (32600) sh, 268 (36300), 290 (34700), 310 (8750) sh, 440 (21500)

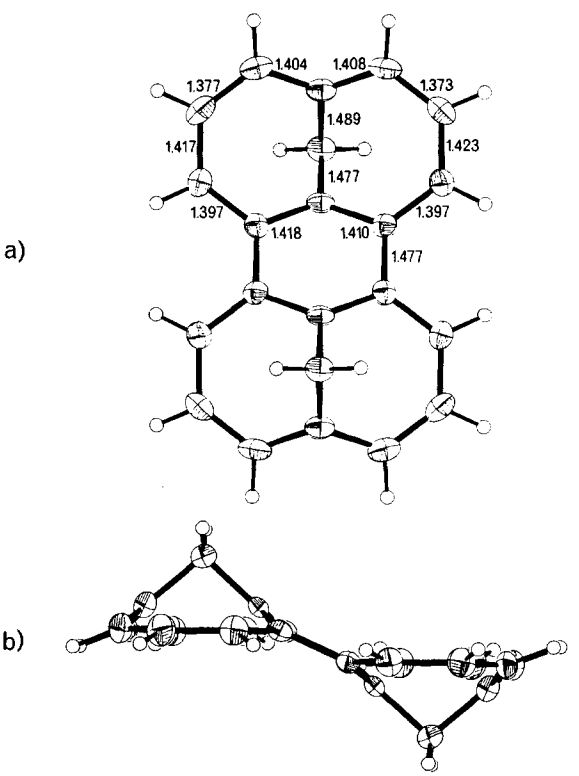


Fig. 1. Molecular structure of *anti*-bishomoperylene **3b**. Bridge-bond angle: 96.7°, transannular C–C distance in the 1,6-methano[10]annulene moieties (C^1–C^6): 2.216 Å. a) Plan view, bond lengths [Å] in the centrosymmetric molecule; b) side view.

differs from the latter in that it has a flat chair conformation. The median planes of the two [10]annulene rings in **3b** are at a slightly different level (difference ca. 0.6 Å) which can be explained in terms of the geometry of **6**.[14]

In the meantime, it has been shown that the *syn*-isomer **3a** (*syn/anti*-isomeric ratio 1:4) is also formed in the oxidative coupling of **5**. **3a** initially escaped detection, because it polymerized on the carrier material during chromatography. The isolation of **3a** has now been made possible by the surprising finding that the dibromide **4**, on reaction with $NiCl_2(PPh_3)_2$, zinc, and tetraethylammonium iodide in tetrahydrofuran[15] (1 h at 50°C) forms *syn*- and *anti*-bishomoperylene in the ratio of 4:3. After chromatographic separation on silica gel (hexane), **3a** is recrystallized from ethanol to give fine, red crystals [decomp. above 200°C; yield 7%]. **3b** is obtained in 18% yield via this route.

3a was identified mainly by its ^{1}H-NMR spectrum, since this is almost identical to the spectrum of **3b**, except for the resonance signals of H-4, H-4′ and H-8, H-8′, which, as expected, are shifted further downfield (by 0.3 ppm) (see Table 1).

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CAS Registry numbers:
3a, 96412-62-3; **3b**, 96479-48-0; **4**, 5896-04-8; **5**, 96412-63-4.

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[12] Crystal data of **3b**: monoclinic, space group C2/c, $a=15.495(1)$, $b=4.504(1)$, $c=23.148(4)$ Å, $\beta=117.29(1)°$, $Z=4$; 715 reflections, $R=0.051$. Further details of the crystal structure investigation are available on request from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2, on quoting the depository number CSD 51405, the names of the authors, and the full citation of the journal.

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3,8-Methanoaza[10]annulene (Homoisoquinoline)

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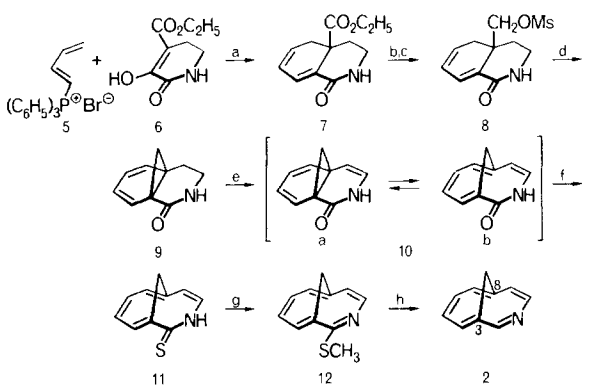
2,7-Methanoaza[10]annulene **1** and 3,8-methanoaza[10]annulene **2**, the two bridged aza[10]annulenes formally derived from the Hückel-arene 1,6-methano[10]annulene, can, on the one hand be regarded as 10π-homologues of pyridine and, on the other, as homoquinoline and homoisoquinoline, respectively. This characterization definitely applies to **1**,[1] first described in 1978: It is a stable aromatic compound, which, in many of its properties, is reminiscent of pyridine or quinoline **3**. Several derivatives of **2** are known,[1a,2] but all attempts to synthesize the parent heterocycle have hitherto failed. The presumption consequently fostered, that **2** is less stable than **1**, finds support from theoretical considerations. According to semiempirical MNDOC and ab initio calculations[3] **2** has an enthalpy of formation (ΔH_f^0) 5 kcal/mol lower than that of **1**, whereas isoquinoline **4** is only slightly energetically less favored than quinoline **3** ($\Delta\Delta H_f^0 = 1.1$ kcal/mol).



1 2 3 4

We have now succeeded in synthesizing **2**. The isomers **1** and **2** very closely resemble each other in many respects, yet at the same time exhibit some remarkable differences.

The expectation that **2** could be prepared analogously to **1** did not materialize. It was only by an unconventional route involving **10** as strategic intermediate that the target compound yielded to synthesis (Scheme 1).



Scheme 1. a) Diazabicyclo[5.4.0]undecene (DBU), tetrahydrofuran (THF), RT, 5 h; b) diisobutylaluminum hydride (DIBAH), CH_2Cl_2, −78°C, 5 h; c) MsCl, NEt_3, CH_2Cl_2, RT, 3 h; d) DBU, THF, reflux, 12 h; e) di-*tert*-butyl peroxalate, C_6H_6, RT, 5 h; f) Lawesson reagent, C_6H_6, reflux, 30 min; g) trimethyloxonium tetrafluoroborate, CH_2Cl_2, K_2CO_3, RT, 1 h; h) 1 mmol **12**, 20 mL 75% C_2H_5OH, 1–1.5 mL Raney nickel (suspension in C_2H_5OH), RT, ca. 15 min (see text).

Reaction of the readily accessible pyridone derivative **6**[4] with butadienyltriphenylphosphonium bromide **5**[5] in

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the presence of DBU led, via successive terminal nucleophilic addition and intramolecular Wittig reaction, to formation of the bicyclic ester **7** [m.p. 162–164°C (from benzene); yield 65%]. Selective reduction of the ester group of **7** with DIBAH furnished the corresponding alcohol, which was converted, as crude product, into the mesylate **8** [m.p. 144–146°C (from methanol); yield 67% referred to **7**]. Consistent with the theoretically established rule that kinetically controlled alkylations of enolate ions of conjugatively unsaturated carbonyl compounds preferentially occur at the α-position rather than at the vinylogous positions,[6] reaction of **8** with DBU afforded the tricycle **9** [m.p. 109–111°C (from ether/pentane 10:1); yield 70–75%], which, according to the chemical shifts and coupling constants of the CH_2-bridge protons ($^2J_{H,H}=4.8$ Hz; $^1J_{^{13}C,H}=165$ Hz), is present solely as the norcaradiene valence tautomer. The conversion of **9** into **10** [existent as **10a** and/or **10b**], i.e. the dehydrogenation of a lactam to an enelactam with the double bond adjacent to the nitrogen, appears to be without precedent in the literature.[7] This crucial step was realized by a radical reaction employing di-*tert*-butyl peroxalate[8] as the agent. The chromatographically isolated (silica gel, pentane/ethyl acetate 2:1) **10** [yellow needles, m.p. 90–92°C (first from acetonitrile, then from hexane/dichloromethane 8:1); yield 5–10%], shows changes in the coupling constants of the bridge protons compared to **9** ($^2J_{H,H}=7.2$ Hz; $^1J_{^{13}C,H}=155$ Hz), from which, in combination with other NMR findings, it can be concluded that it is present as the fluxional norcaradiene-cycloheptatriene system **10a/10b**. After exploratory experiments had shown that the 2-azabicyclo[4.4.1]undeca-4,6,8,10-tetraene-3-one[1] isomeric with **10b** (3-azabicyclo-[4.4.1]undeca-4,6,8,10-tetraene-2-one) can be converted without problem into **1** by the reaction sequence of thiolactam formation, *S*-methylation, and desulfurization, the same procedure was used for **10**. Whereas **10** on reaction with Lawesson reagent readily underwent replacement of oxygen by sulfur to give **11** [orange needles, m.p. 158°C (decomp.) (from acetonitrile); yield 65%], and **11** could be routinely methylated with trimethyloxonium tetrafluoroborate to give **12** [yellow liquid, b.p. 50°C/4×10^{-5} mbar; yield 72%], the desulfurization of **12** with Raney nickel yielded the desired **2** only under strictly controlled conditions. It was found expedient to treat **12** with Raney nickel (activity grade W2)[9] in ethanol at room temperature until ca. 50% conversion was achieved. After chromatography on silica gel (pentane/ether 2:1) and distillation at 4×10^{-5} mbar (receiver cooled to −78°C), 3,8-methanoaza[10]annulene (3-azabicyclo[4.4.1]undeca-2,4,6,8,10-pentaene) **2** was obtained as a bright yellow liquid. In striking contrast to **1**, compound **2** rapidly polymerizes even in the absence of air.—The spectroscopic data of the new compounds are listed in Table 1.

Proof of the structure of **2** is based on the spectra as well as on the X-ray structure analysis of the methanesulfonyl derivative **13**. Particularly informative is the ^{1}H-NMR spectrum [300 MHz (CCl_4, CD_2Cl_2): $\delta=-0.18$ and -0.01 (AX system, $^2J=8.56$ Hz, 2H, H-11a and H-11b[10]), 7.01 (1H, H-5), 7.12 (1H, H-6), 7.31 (1H, H-7), 7.45 (1H, H-4) (ABCD system, $^3J_{H\text{-}4,H\text{-}5}=9.10$ Hz, $^3J_{H\text{-}5,H\text{-}6}=9.01$ Hz, $^3J_{H\text{-}6,H\text{-}7}=9.13$ Hz), 7.04 (1H, H-9), 8.19 (1H, H-10) (AX system, $^3J_{H\text{-}9,H\text{-}10}=6.40$ Hz), 8.43 (s, 1H, H-2)]. The data are consistent with **2** having aromatic character, like the stable isomer **1**, even though its instability would rather suggest an olefinic molecule.[11] As in the spectrum of **1**, the resonances of the annulene and bridge protons appear at relatively low and high field, respectively, while the vicinal H,H couplings are found to be nearly equal. The absorption pattern of the annulene protons of **2** is qualitatively the same as that of the corresponding isoquinoline protons, but, as in the case of the **1/3** pair, the signals appear on average ca. 0.5 ppm further upfield.

Table 1. Some spectral data of the new compounds.

2 [a]: ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta=34.10$, 112.77, 113.68, 120.74, 126.74, 128.69, 129.27, 129.37, 143.58, 149.75; MS (75 eV): *m/z* 143 (M^+, 100%), 115 (M^+-H_2CN, 86); IR (CH_3CN): 3030, 2960, 1579, 1523, 1446 cm^{-1}

7: ^{1}H NMR (300 MHz, CD_2Cl_2): $\delta=1.22$ (t, 3H), 1.95 (m, 1H), 2.17–2.24 (m, 2H), 2.96 (m, 1H), 3.29 (m, 2H), 4.14 (m, 2H), 6.04 (m, 1H), 6.14 (m, 1H), 6.83 (br. s, 1H), 7.11 (d, 1H); MS (70 eV): *m/z* 221 (M^+, <1%), 148 ($M^+-COOEt$, 89), 105 ($M^+-COOEt-HNCO$, 100); IR (KBr): 3182, 1720, 1676 (C=O) cm^{-1}; UV/VIS (MeOH): $\lambda_{max}=285$ nm ($\varepsilon=8500$)

8: ^{1}H NMR (300 MHz, CD_2Cl_2): $\delta=1.80$ (m, 1H), 2.17–2.25 (m, 2H), 2.61 (dd, 1H), 2.99 (s, 3H), 3.34 (m, 1H), 3.56 (m, 1H), 4.12 (s, 2H), 6.06 (m, 1H), 6.17 (m, 1H), 6.58 (br. s, 1H), 7.13 (d, 1H); MS (70 eV): *m/z* 258 (M^+ + H(^{32}S), <1%), 148 (M^+-CH_2OMs, 30), 105 ($M^+-CH_2OMs-HNCO$, 100); IR (KBr): 3300, 1663, 1650 (C=O), 1352, 1172 (SO_2) cm^{-1}; UV/VIS (MeOH): $\lambda_{max}=208$ nm ($\varepsilon=4790$), 268 (2570)

9: ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=0.14$ and 2.38 (AB, 2H, $^2J=4.8$ Hz), 1.94 (m, 1H), 2.26 (m, 1H), 3.13 (m, 2H), 5.82–6.01 (m, 3H), 6.76 (d, 1H), 6.85 (br. s, 1H); MS (70 eV): *m/z* 161 (M^+, 96%), 105 ($M^+-C_2H_2ON$, 100); IR (KBr): 3286, 3191, 1657 (C=O) cm^{-1}; UV/VIS (MeOH): $\lambda_{max}=208$ nm ($\varepsilon=4800$), 268 (2550)

10: ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=0.27$ and 2.16 (AX, 2H, $^2J=7.2$ Hz), 5.81 (d, 1H), 6.00 (dd, 1H), 6.37 (dd, 1H), 6.49 (t, 1H), 6.58 (t, 1H), 7.02 (d, 1H), 8.35 (br. s, 1H); MS (70 eV): *m/z* 159 (M^+, 100%); IR (KBr): 3225, 1647, 1614 (C=O) cm^{-1}; UV/VIS (cyclohexane): $\lambda_{max}=226$ nm ($\varepsilon=12300$), 245 (8130) sh, 268 (5130) sh, 300 (2090) sh, 348 (910)

11: ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=0.14$ and 2.09 (AX, 2H, $^2J=9.75$ Hz), 6.32–7.23 (m, 5H), 7.69 (d, 1H), 10.80 (br. s, 1H); MS (70 eV): *m/z* 175 (M^+ (^{32}S), 100%); IR (CsI): 3153, 1602 cm^{-1}; UV/VIS (cyclohexane): $\lambda_{max}=232$ nm ($\varepsilon=21200$), 315 (10900), 395 (7100)

12: ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=-0.32$ and 0.83 (AX, 2H, $^2J=9.06$ Hz), 2.54 (s, 3H), 6.89 (d, 1H), 7.01–7.22 (m, 3H), 7.54 (d, 1H), 7.67 (d, 1H); MS (70 eV): *m/z* 189 (M^+ (^{32}S), 15%), 115 (M^+-SCH_3-HCN, 100); IR (film): 3032, 2929, 1572, 1532 cm^{-1}; UV/VIS (cyclohexane): $\lambda_{max}=235$ nm ($\varepsilon=21770$), 290 (6130) sh, 330 (5700), 390 (1300) sh

13: ^{1}H NMR (300 MHz, CD_2Cl_2): $\delta=-0.29$ and -0.06 (AX, 2H, $^2J=9.31$ Hz), 3.21 (s, 3H), 7.24 (t, 1H), 7.31 (t, 1H), 7.48 (d, 1H), 7.51 (d, 1H), 8.26 (d, 1H), 8.28 (d, 1H); MS (70 eV): *m/z* 221 (M^+ (^{32}S), 7%), 115 ($M^+-SO_2CH_3-HCN$, 100); IR (CsI): 3010, 2932, 1313, 1133 (SO_2) cm^{-1}; UV/VIS (CH_3CN): $\lambda_{max}=240$ nm ($\varepsilon=22000$), 263 (17800) sh, 320 (3800), 363 (1500) sh

2·HCl: ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=-0.01$ and 0.29 (AX, 2H, $^2J=9.6$ Hz), 7.30 (t, 1H), 7.40 (t, 1H), 7.63 (d, 1H), 7.87 (d, 1H), 7.93 (d, 1H), 8.17 (t, 1H), 9.13 (d, 1H), 16.65 (br. s, 1H); IR (KBr): 3013, 2713, 1602 cm^{-1}; UV-VIS (0.1 N HCl): $\lambda_{max}=250$ nm ($\varepsilon=23940$), 260 (21840) sh, 310 (3140), 372 (2840)

[a] ^{1}H NMR and UV/VIS see text.

The UV/VIS spectrum of **2** [(cyclohexane): $\lambda_{max}=240$ nm ($\varepsilon=22500$), 260 (sh, 8900), 310 (2000), 375 (650)[12]] is comparable with that of **1**. It corresponds in its type to that of 1,6-methano[10]annulene and thus provides a further argument in favor of **2** being regarded as an aromatic system.

Even before **2** had been synthesized, its basicity was already the subject of theoretical calculations, for it was found that **1** ($pK_a=3.20$) is significantly more weakly basic than pyridine and quinoline ($pK_a=5.23$ and 4.92, respectively).[1] If the theoretically determined values for the electron densities in the region of the lone pair on nitrogen in **1**–**4**[13] are correlated with the pK_a values of **1**, **3**, and **4**, a pK_a value of 4.8 ± 0.1 can be predicted for **2**, i.e., **2** should be more basic than its isomer **1**.

We have now been able to confirm this prediction; a pK_a value of 4.7 has been determined experimentally for **2**

(isoquinoline **4**: $pK_a = 5.14$). On reaction with HCl in ether, **2** readily forms a hydrochloride [dark yellow crystals, m.p. 160°C (decomp.) (from acetonitrile)].

The reason for the relatively weak basicity of **1** lies in the stereoelectronic conditions prevailing in the molecule. The lone pair orbital on the nitrogen and the 2pπ orbital on the neighboring bridgehead carbon atom deviate in their alignment pronouncedly from orthogonality so that the lone pair electrons can, to a certain extent, delocalize into the aza[10]annulene ring.[14]

The aromaticity of **2** deduced from the spectra is further substantiated by the X-ray structure analysis of the crystalline 2-methanesulfonyl-3,8-methanoaza[10]annulene **13** [bright yellow platelets, m.p. 86°C (from ether); yield 58%] obtained from **12** by oxidation with potassium peroxomonosulfate ("Oxon")[15] in dichloromethane in the presence of [18]crown-6.[16] As shown in Figure 1, the

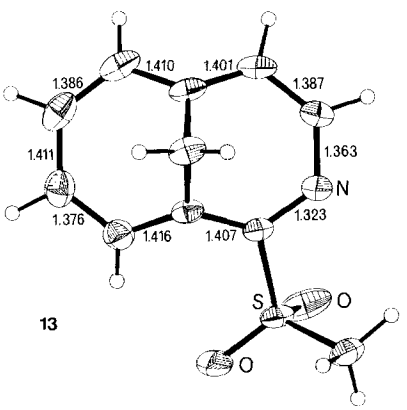


Fig. 1. Molecular structure of **13** in the crystal. Selected bond lengths [Å].

aza[10]annulene ring of **13** exhibits C–C and C–N bond lengths that correspond to those found in heteroarenes. The stretching of the $N-C^{10}$ bond compared to that of the $N-C^{2}$ bond is understandable, when one considers that the $C^{3}-C^{4}$ bond and the oppositely situated $C^{8}-C^{9}$ bond in 1,6-methano[10]annulene are relatively long.[17] Interestingly, the transannular C–C distance ($C^{3}-C^{8}$: 2.222 Å; bridge-bond angle 97°) in **13** is shorter than in 1,6-methano[10]annulene ($C^{1}-C^{6}$: 2.235 Å; 97.6°);[17] the same holds for the 3-bromo derivative of **1** ($C^{2}-C^{7}$: 2.202 Å; 95.5°) analyzed by *Simonetta et al.*[18] The introduction of a nitrogen atom into the peripheral ring of the 1,6-methano[10]annulene system (particularly at the α-position) thus appears to favor the homoconjugative transannular interaction. Consequently, there is in fact some justification for alternatively considering the aza[10]annulenes **1** and **2** as homoquinoline and homoisoquinoline, respectively.

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2, 64183-85-3; **2**·HCl, 96363-73-4; **5**, 21310-07-6; **6**, 21472-88-8; **7**, 96363-65-4; **7** (alcohol), 96363-66-5; **8**, 96363-67-6; **9**, 96363-68-7; **10**, 96363-69-8; **11**, 96363-70-1; **12**, 96363-71-2; **13**, 96363-72-3.

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[10] H-11a is the proton above the carbocyclic segment; the assignment of the two bridge protons is based on long-range couplings.

[11] Investigation of the ^{13}C-NMR spectrum of **2** for temperature-dependence gave no indication of the norcaradiene valence isomer (see also [2e]).

[12] Due to the sensitivity of **2**, the limit of error of the extinction coefficients of the UV/VIS spectrum is relatively high (± 15%).

[13] The position of the lone pair on the nitrogen was determined via the Laplace concentration of the electron-density distribution $\rho(r)$: D. Cremer, E. Kraka, *Angew. Chem. 96* (1984) 612; *Angew. Chem. Int. Ed. Engl. 23* (1984) 627; *Croat. Chem. Acta 57* (1984) 1265. The densities ρ calculated at the lone pair positions are 4.002(1), 4.152(2), 4.162(3), and 4.180(4) e $Å^{-3}$.

[14] The remarkable finding that, other than in naphthalene, the α-ring protons in 1,6-methano[10]annulene are no less than two to three pK_a units more acidic than the β-ring protons is explained in the same way; W. A. Böll, *Tetrahedron Lett. 1968*, 2595.

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[16] Crystal data of **13**: triclinic, space group $P\bar{1}$, $a = 7.940(1)$, $b = 8.360(1)$, $c = 8.619(1)$ Å, $\alpha = 86.28(1)$, $\beta = 64.32(1)$, $\gamma = 86.71(1)°$, $Z = 2$; 2006 reflections, $R = 0.045$. Further details of the crystal structure investigation are available on request from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2, on quoting the depository number CSD 51406, the names of the authors, and the full citation of the journal.

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Synthesis of Seven-Membered Rings by $[(_\sigma 2 + _\pi 2) + _\pi 2]$ Cycloaddition to Homodienes**

By *Rainer Herges* and *Ivar Ugi**

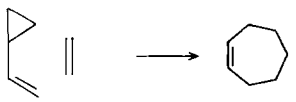
Dedicated to Professor Rolf Huisgen on the occasion of his 65th birthday

Most thermally allowed pericyclic reactions, such as the Diels-Alder reaction, the electrocyclic reactions of hexatrienes, the [1,5] sigmatropic shift, and the Cope rearrangement, proceed via an aromatic six-center transition state.[1, 2] According to our studies using the artificial intelligence program IGOR,[4] one of the twelve possible types of reactions[3] with six carbon atoms as reaction centers that should be realizable, the $[(_\sigma 2 + _\pi 2) + _\pi 2]$ cycloaddition [Reaction (a)], has not been investigated in detail. In fact,

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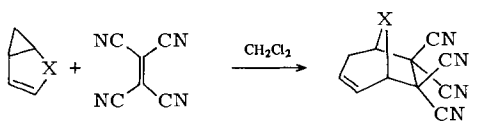
[**] This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.

only four examples are known,[5-8] one of which[7] could not be reproduced by other investigators.[9-11] This reaction is related to the Diels-Alder reaction, one of the double bonds of the diene being replaced by a single bond. The most well known analogous reaction is the ene reaction, which, however, has a hydrogen atom as a component of the four centers.



(a)

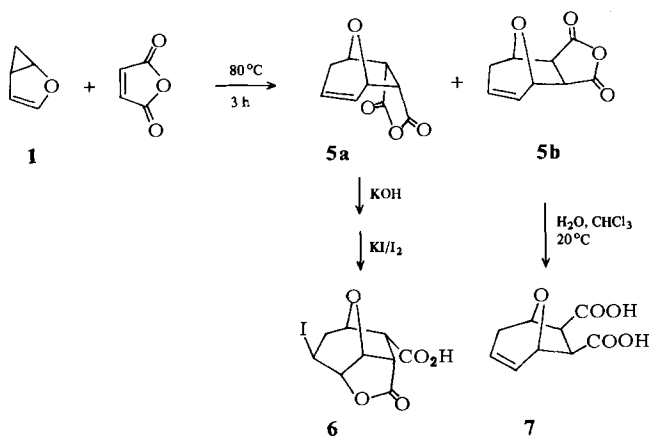
Homofuran **1** and homothiophene **2**, which are almost as reactive toward dienophiles as furan, have proved to be suitable dienes. They react quantitatively with tetracyanoethylene (TCNE) at 20°C in a few minutes to give the corresponding [3.2.1] bicyclic compounds **3** and **4**, respectively (activation parameters of the reaction of **3**: $\Delta H^{+} = 54.0 \pm 0.81$ kJ/mol, $\Delta S^{+} = 110.9 \pm 1.7$ J mol^{-1} K^{-1}). The course of the reaction can be easily monitored by following the change in the color of the reaction mixture; the initially formed charge-transfer complex is deep red for homofuran and blue for homothiophene.



1, X = O
2, X = S

3, X = O
4, X = S

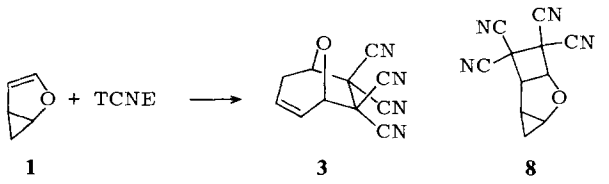
Homofuran (like furan[12]) reacts with maleic anhydride to give the *endo* and *exo* cycloadducts **5a** and **5b**, respectively, in a ratio of 1 : 1. They can be easily separated after hydrolysis to give **6** and **7**, respectively. The activation parameters, determined by ^{1}H-NMR spectroscopy, are $\Delta H^{+} = 58.6 \pm 3$ kJ/mol and $\Delta S^{+} = -165.3 \pm 37$ J mol^{-1} K^{-1}. Only the *exo* isomer **5b** reacts with water to give the dicarboxylic acid **7**. After hydrolysis and iodolactonization, the *endo* isomer **5a** affords **6**.[13]



1 **5a** **5b**

6 **7**

In polar solvents, homofuran reacts with TCNE not only to give **3**, but also to give the $[\pi 2 + \pi 2]$ cycloadduct **8**. The product ratio is very strongly dependent on the solvent[14] (Scheme 1).



1 **3** **8**

CH_2Cl_2	100	:	0
THF	43	:	57
acetone	37	:	63
acetonitrile	23	:	77

Scheme 1.

Since, to a first approximation, two irreversible parallel reactions are involved, the reaction rates and activation parameters can be determined separately for each reaction. Whereas the activation energy of the $[(\sigma 2 + \pi 2) + \pi 2]$ cycloaddition in very strongly polar acetonitrile is almost identical to that in CH_2Cl_2, the rate of the $[\pi 2 + \pi 2]$ cycloaddition in acetonitrile is just measureable. On going from CH_2Cl_2 to acetonitrile, the rate increases by at least a factor of 1000.

1 + TCNE $\xrightarrow{\text{acetonitrile}}$	**3**	+	**8**
$\Delta H^{+} =$	57.3 ± 0.8		29.3 ± 0.4 kJ/mol
$\Delta S^{+} =$	-110.5 ± 2		-195.0 ± 2 J mol^{-1} K^{-1}

Similar results are obtained for the addition of TCNE to homothiophene. In chloroform, exclusively the [4+2] cycloadduct is formed; in acetonitrile, the [2+2] cycloadduct is formed in 83% yield. In this case, the different yields are also attributable only to the change in the rate of the [2+2] cycloaddition, the [4+2] cycloaddition not being affected by solvent polarity. The activation entropies of the $[(\sigma 2 + \pi 2) + \pi 2]$ cycloaddition of TCNE (-54 J mol^{-1} K^{-1}) and of maleic anhydride (-165 J mol^{-1} K^{-1}) to homofuran are approximately the same order of magnitude as those of other pericyclic bimolecular reactions—e.g., the ene reaction ($\Delta S^{+} = -134$ J mol^{-1} K^{-1}),[15] the Diels-Alder reaction (-146 J mol^{-1} K^{-1}),[16] and the [1,3] dipolar cycloaddition (-105 to -150 J mol^{-1} K^{-1}).[17] The very negative activation entropy supports an ordered transition state and at least does not rule out a concerted mechanism. The small influence of solvent polarity on the reaction rate is also in accordance with a concerted $[(\sigma 2 + \pi 2) + \pi 2]$ cycloaddition. The increase of the activation energy with increasing solvent polarity even renders a mechanism with a polar intermediate unlikely.

Most vinylcyclopropane systems react with strong dienophiles with formation of the [2+2] cycloadduct, rearrangement of the initially formed dipole,[18] or reaction of the dipole with the solvent.[19] In order for the $[(\sigma 2 + \pi 2) + \pi 2]$ cycloaddition to be successful, additional strain in the cyclopropane ring[6,8] or activation of the cyclopropane bond via a heteroatom appears to be necessary.

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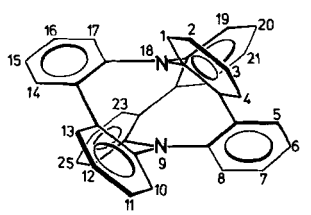
CAS Registry numbers:
1, 6664-26-2; **2**, 6573-95-1; **3**, 96913-80-3; **4**, 96913-81-4; **5a**, 96997-10-3; **5b**, 96997-11-4; **6**, 96913-82-5; **7**, 96928-63-1; **8**, 96928-64-2; maleic anhydride, 108-31-6; TCNE, 670-54-2.

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A Triphenylamine Double-Decker**

By *Franz A. Neugebauer** and *Sigrid Kuhnhäuser*

Bicyclic diamines are perfect models for intramolecular n(σ)-electron interactions.[1] We report here on the synthesis and spectroscopic properties of the double layered triphenylamine 9,18-dihydro-9,18-[2,2']biphenylotetrabenzo-[*b,d,g,i*][1,6]diazecine **1**.



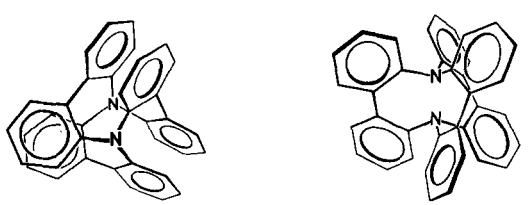


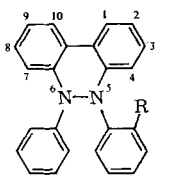
Fig. 1. Conformations of the triphenylamine **1**. Top: planar. Bottom left: out,out. Bottom right: in,in.

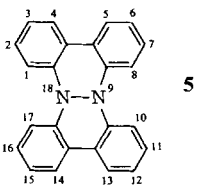
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Addition of phenyllithium to benzo[*c*]cinnoline and subsequent reaction with 1-fluoro-2-nitrobenzene led to formation of 5,6-dihydro-5-(2-nitrophenyl)-6-phenylbenzo[*c*]-cinnoline **2** (35%, m.p. 241°C), which was converted by catalytic hydrogenation (Raney nickel, 3 equivalents of H_2) into the corresponding amine **3** (84%, m.p. 201–202°C). Diazotization of **3** and subsequent thermal decomposition yielded, surprisingly smoothly, benzo[*c*]benzo[3,4]cinnolino[1,2-*a*]cinnoline **5** (53%, yellow needles, m.p. 194–195°C).[2] Immediate reduction of the diazonium salt of **3** in phosphinic acid[3] afforded 5,6-dihydro-5,6-diphenylbenzo[*c*]cinnoline **4** (80%, m.p. 160–161°C). **4** and **5** are derivatives of tetraphenylhydrazine in which *N,N'*-phenyl residues are coupled at one or both sides in the *o*-position.

2, R = NO_2
3, R = NH_2
4, R = H



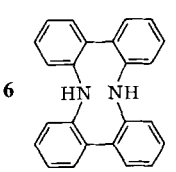


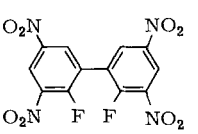
5

The central N–N bond in **5** can be opened by catalytic hydrogenation (Raney nickel, H_2) to give 9,18-dihydrotetrabenzo[*b,d,g,i*][1,6]diazecine **6** (60%, colorless needles, m.p. 268–269°C[4]). **6** is sensitive to oxidation and is dehydrogenated by oxygen in the presence of bases to give, inter alia, the starting compound **5** again.

Twofold reaction of the dilithium compound of **6** with the activated 2,2'-difluorobiphenyl **7** led to formation of the 19,21,24,26-tetranitro derivative of the desired compound **1** [17%, orange crystals, m.p. > 330°C; MS: *m/z* 664 ($M^{\oplus}$, 100%)]. Catalytic hydrogenation (Raney nickel, 12 equivalents of H_2) afforded the corresponding tetraamino compound [MS: *m/z* 544 ($M^{\oplus}$, 100%)], extremely sensitive to oxidation, which was immediately diazotized in phosphinic acid and reduced to **1**[3] [8%, bright pink crystals, m.p. > 330°C; MS: *m/z* 484 ($M^{\oplus}$, 100%), *m/2z* 242 (14%)].[5]

6



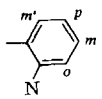


7

The proton resonances of **5** lie in the arene region and show typical chemical shifts corresponding to the substitution. In the case of **1** and **6**, on the other hand, upfield shifts of ca. $\Delta\delta = 0.2$–1 ppm are observed for three sets of protons (Table 1). These protons are apparently located within the shielding region of aromatic systems above or below the protons. According to model considerations, the conformation of the inner ten-membered ring of **6** is highly flexible. Of the four phenylene moieties, alternatingly each pair of oppositely situated rings can approach each other, and, as in a [3.3]paracyclophane, eventually lie one above the other. The extreme case of this arrangement is found for all six phenylene rings in the *out,out*-arrangement of **1**, for which considerably larger upfield shifts in

the ^{1}H-NMR spectrum are to be expected than in the case of **6**. Since the chemical shifts of **1** and **6** differ only very slightly, an *out,out*-arrangement is highly improbable in the case of **1**. The alternative *in,in*-form is already highly improbable because of repulsion between the lone electron pairs. The ^{1}H-NMR spectrum is also not reconcilable with such an arrangement, since, as in the case of **5**, the proton resonances should then appear in the usual arene region. The ^{1}H-NMR data of **1** agree best with an almost planar propeller-like arrangement of the phenyl moieties at the nitrogen atoms, as is known in the case of triarylamines.[6] The threefold *o,o'*-coupling of two such oriented triphenylamine moieties would result in a triphenylamine double decker (**1**, planar), with a N···N distance of ca. 2.5 Å.

Table 1. Chemical shifts of the protons in the phenylene segment.



	o	*m*	*p*	*m'*
5	6.77	7.2–7.3	7.2–7.3	7.90
6	6.73	7.01	6.87	7.08
1	6.63	6.79	6.91	6.97

The dication with *m/2z* 242 (14%) is observed in the mass spectrum of **1**. Its constitution can correspond to an *in,in*-arrangement with a N–N σ bond. In comparison to triphenylamine [dioxane, $\lambda_{max_1}=299$ nm ($\lg\varepsilon=4.41$)], **1** shows an electron spectrum shifted markedly to longer wavelength [dioxane, 357 nm (4.21)], which we ascribe to the extended conjugation of the system. **1** is very sensitive to oxidation and immediately forms a deep-violet, extremely persistent radical cation. Studies on its properties and those of the radical cations $\mathbf{4}^{\oplus\ominus}$ and $\mathbf{5}^{\oplus\ominus}$ are currently under way.

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CAS Registry numbers:
1, 96807-12-4; **1** (tetranitro deriv.), 96807-19-1; **1** (tetraamino deriv.), 96807-20-4; **2**, 96807-13-5; **3**, 96807-14-6; **4**, 96807-15-7; **5**, 96807-16-8; **6**, 96807-17-9; 6·2Li, 96807-18-0; **7**, 315-81-1; phenyllithium, 591-51-5; benzo[*c*]cinnoline, 230-17-1; 1-fluoro-2-nitrobenzene, 1493-27-2.

[1] R. W. Alder, R. B. Sessions in S. Patai (Ed.): *Chemistry of Functional Groups. Supplement F, Part 2*, Wiley, Chichester 1982, pp. 763–804.
[2] MS: *m/z* 332 ($M^{\oplus}$, 100%); ^{1}H NMR [360 MHz, [D$_6$]dimethyl sulfoxide (DMSO)]: $\delta=6.77$ (dd, $^3J(1,2)=7.2$, $^4J(1,3)=1.8$ Hz; 1,8,10,17-H), 7.90 (dd, $^3J(3,4)=6.7$, $^4J(2,4)=2.3$ Hz; 4,5,13,14-H), 7.21–7.27 (m; 2,3,6,7, 11,12,15,16-H).
[3] Reductive NH_2-elimination according to: D. C. Iffland, H. Siegel, *J. Am. Chem. Soc. 80* (1958) 1947.
[4] MS: *m/z* 334 ($M^{\oplus}$, 100%), *m/2z* 167 (30%); ^{1}H NMR (360 MHz, CD_2Cl_2): $\delta=6.73$ (br. d, $^3J(1,2)=7.9$ Hz; 1,8,10,17-H), 6.87 (ddd, $^3J(2,3)=7.3$, $^3J(3,4)=7.6$, $^4J(1,3)=1.2$ Hz; 3,6,12,15-H), 7.01 (ddd, $^4J(2,4)=1.5$ Hz; 2,7,11,16-H), 7.08 (dd; 4,5,13,14-H). ([D$_6$]DMSO): $\delta=7.62$ (s; 2NH).
[5] ^{1}H NMR (360 MHz, [D$_6$]DMSO): $\delta=6.63$ (d, $^3J(1,2)=7.9$ Hz; 1,8,10,17,19,26-H), 6.79 (dd; $^3J(2,3)\approx7.3$, $^3J(3,4)=7.7$ Hz; 3,6,12,15,21,24-H), 6.91 (dd; 2,7,11,16,20,25-H), 6.97 (d; 4,5,13,14,22,23-H).
[6] S. L. Reynolds, R. P. Scaringe, *Cryst. Struct. Commun. 11* (1982) 1129; R. P. Scaringe, private communication.

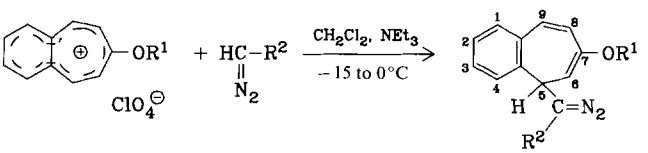
Intramolecular [4+3]-Cycloaddition to 5-Diazomethyl-5*H*-benzocycloheptenes—a Step in a New Benzosemibullvalene Synthesis**

By *Manfred Böhshar, Heinrich Heydt, Gerhard Maas, Helmut Gümbel,* and *Manfred Regitz**

Dedicated to Professor Rolf Huisgen on the occasion of his 65th birthday

The preparative significance of aliphatic diazo compounds lies partly in their ability to undergo [3+2]-cycloaddition.[1] In addition, examples of intramolecular [2+1]-cycloaddition are known in which the terminal nitrogen adds like a nitrene to a CC double bond.[2] The intramolecular [4+3]-cycloaddition of the title compound **3** represents a new type of cycloaddition involving unsaturated diazo compounds; this reaction makes possible a new synthesis of benzosemibullvalenes.

The starting materials are the 7-alkoxy-5-diazomethyl-5*H*-benzocycloheptenes **3a–d**, which are obtained in 35–60% yields via electrophilic diazoalkane substitution[3] of **2a, b** by the 7-alkoxybenzocycloheptenylium perchlorates **1a, b**.[4] Only **3c** (orange oil) and **3d** (yellow crystals, m.p. 78 °C) can be purified via chromatography on silica gel with ethyl acetate; under such conditions, **3a, b** isomerize to **5a, b**.

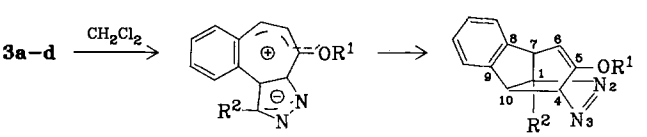


1 **2** **3**

	R^1	R^2
1a + 2a → 3a	CH_3	$PO(C_6H_5)_2$
1a + 2b → 3b	CH_3	$PO(OCH_3)_2$
1b + 2a → 3c	CH_2–C≡CH	$PO(C_6H_5)_2$
1b + 2b → 3d	CH_2–C≡CH	$PO(OCH_3)_2$

3a–d exhibit strong diazo stretching vibration bands in the IR spectra (KBr or film, $\nu=2070-2090$ cm^{-1}); according to the ^{1}H-NMR spectra of **3a–d**,[5] C-5 of **1** is the reaction center.

The diazo compounds **3a–d** are only stable at −20 °C for longer periods of time. In dichloromethane at 20 °C, they undergo intramolecular [4+3]-cycloaddition of the diazo dipole to the 1,3-butadiene moiety of the seven-membered ring within a few hours (**3a, b**) or days (**3c, d**)



4a–d **5a–d**

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[**] In estigations on diazo compounds and azides, Part 64. This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie. Part 63: T. Allspach, H. Gümbel, M. Regitz, *J. Organomet. Chem.*, in press.

to give quantitatively the azo isomers **5a—d**. Such additions are formally of the [4π+4π]-type, concerted reactions of this kind being thermally not allowed; to the best of our knowledge, they have been unknown up to now.[6]

Even though the solvent has only a modest effect on the rate of cycloaddition [**3d** → **5d**: $k = 3.0 \times 10^{-6}$ (C_6D_6), 1.26×10^{-5} (CD_3CN), 2.1×10^{-5} s^{-1} (CD_3OD), ^{1}H-NMR spectroscopy], we assume that the reaction proceeds in two steps via the betaine **4**, which is stabilized by the donor groups in the cationic part of the molecule and the acceptor groups in the anionic part. In the absence of donor groups (**3**, Br in place of OR^1), the isomerization does not occur.

In the IR spectra of **5a-d**, the diazo vibration of **3a-d** is replaced by the −N=N− absorption (1505—1520 cm^{-1}); in the ^{1}H- and ^{13}C-NMR spectra, only one olefinic hydrogen atom and two olefinic carbon atoms, respectively, can be detected (Table 1). An X-ray structure determination was carried out for **5d** (Fig. 1).[7]

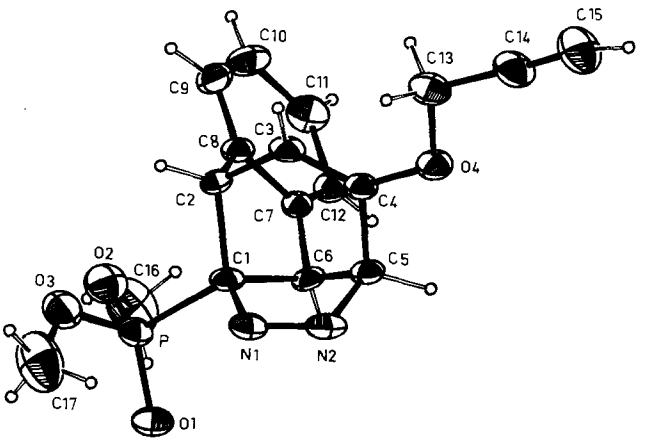


Fig. 1. ORTEP diagram of **5d** [7]. The ellipsoids of vibration correspond to 38% probability.

Table 1. Melting points and characteristic NMR data for the diazatricyclodecatrienes **5a-d**.

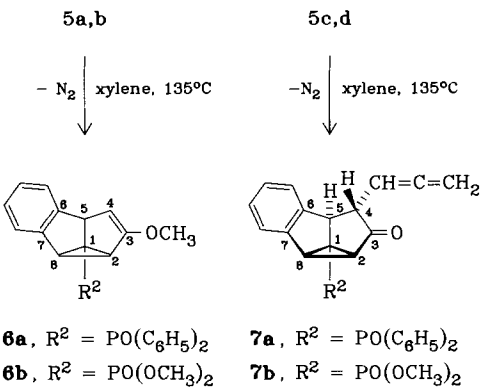
Cpd.	Decomp. point [°C]	^{1}HNMR (200 MHz, $CDCl_3$, δ values, J in Hz) 4-H (^3J(4-H/10-H), ^4J(4-H/6-H), ^4J(P/4-H))	6-H (^3J(6-H/7-H), ^4J(6-H/4-H), ^4J(P/6-H))	7-H (^3J(7-H/6-H), ^3J(P/7-H))	10-H (^3J(10-H/4-H), ^3J(P/10-H))
5a	135–137	5.06 (5.6, 2.3, -)	4.74 (6.3, 2.3, 4.8)	3.83 (6.3, 6.6)	3.87 (5.6, 8.2)
5b	84–86	5.12 (5.7, 2.4, 1.3)	4.72 (6.1, 2.4, 3.4)	3.88 (6.1, 6.3)	3.96 (5.7, 10.0)
5c	136–138	5.07 [a] (4.5, 1.8, -)	4.85 [a] (m) [b]	3.86 [a] (m) [b]	
5d	123–125	5.15 (5.7, 2.4, 1.3)	4.84 (6.2, 2.4, 3.3)	3.87 (6.2, 8.0)	3.97 [c] (5.7, 10.3)

Cpd.	^{13}C-NMR (50.28 MHz, $CDCl_3$, δ values, J in Hz) C-1 (^1J(P/C))	C-4 (^1J(H/C), ^3J(P/C))	C-5	C-6 (^1J(H/C), ^3J(P/C))	C-7 (^1J(H/C))	C-8/C-9	C-10 (^1J(H/C))
5a	104.9 (84.5)	101.1 (168.9, 10.0)	134.2	84.2 (153.3, 7.7)	44.2 (146.7)	148.7, 155.6	55.4 (142.8)
5b	104.3 (171.5)	100.3 (162.9, 12.1)	134.4	84.2 (152.5, 10.8)	43.7 (149.0)	148.8, 155.0	55.0 (144.1)
5c	104.6 (84.3)	103.2 (168.0, 9.8)	133.9	83.7 (164.0, 8.1)	44.1 (147.6)	148.1, 153.2	55.4 (143.3)
5d	104.0 (173.9)	102.3 (168.4, 12.4)	134.1	83.7 (159.0, 10.8)	43.5 (149.1)	148.1, 152.6	55.1 (144.7)

[a] 90-MHz spectrum. [b] Signal not resolved. [c] In addition, ^4J(10-H/7-H) ≈ 0.8 Hz; the coupling only causes broadening of the 7-H signal.

When **5a, b** is refluxed in xylene for 10–15 min, N_2 is eliminated and the benzosemibullvalenes **6a, b** (100%) are formed. For **5c, d**, moreover, a hetero-Cope rearrangement takes place in the propargyl enol ether moiety of the molecule; the 4-propadienyl-3,4-dihydrobenzosemibullvalen-3-ones **7a, b** (60 and 85%, respectively) are thereby formed.

The rearrangement can be recognized by the CO (**7a, b**: 1750 and 1730 cm^{-1}, respectively) and allene bands (**7a, b**: 1970 and 1945 cm^{-1}, respectively) in the IR spectra.



6a, $R^2 = PO(C_6H_5)_2$ **7a**, $R^2 = PO(C_6H_5)_2$

6b, $R^2 = PO(OCH_3)_2$ **7b**, $R^2 = PO(OCH_3)_2$

The NMR data of **6** and **7** confirm the structure of the tricyclic systems.[8] The *exo* arrangement of the propadienyl residues in **7a, b** is evidenced indirectly in the finding that 5-H (necessarily in the *exo* position) is not coupled with 4-H (dihedral angle ≈90°).

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1a, 96618-03-0; **1b**, 96617-92-4; **2a**, 5353-66-2; **2b**, 27491-70-9; **3a**, 96617-93-5; **3b**, 96617-94-6; **3c**, 96617-95-7; **3d**, 96617-96-8; **4a**, 96618-04-1; **4b**, 96618-05-2; **4c**, 96618-06-3; **3d**, 96618-07-4; **5a**, 96617-97-9; **5b**, 96633-20-4; **5c**, 96617-98-0; **5d**, 96633-21-5; **6a**, 96617-99-1; **6b**, 96618-00-7; **7a**, 96618-01-8; **7b**, 96618-02-9.

[1] Review: M. Regitz, H. Heydt in A. Padwa: *1,3-Dipolar Cycloaddition Chemistry, Vol. 1*, Wiley, New York 1984, p. 393 ff.
[2] Y. Nishizawa, T. Miyashi, T. Mukai, *J. Am. Chem. Soc. 102* (1980) 1176; A. Padwa, A. Rodriguez, *Tetrahedron Lett. 22* (1981) 187.
[3] Review: J. Fink, M. Regitz, *Synthesis*, in press.
[4] Analogous reactions of 7-bromobenzocycloheptenylium bromide: M. Böhshar, H. Heydt, M. Regitz, *Chem. Ber. 117* (1984) 3093.
[5] **3a—d**, ^{1}H NMR ($CDCl_3$): δ = 4.03—4.34 (dd, ^3J(H/H) = 7.5—8.7 Hz, ^3J(P/H) = 6.0—6.6 Hz, 5-H), 4.93—5.10 (dd, ^3J(H/H) = 7.5—8.7 Hz, ^4J(H/H) = 1.5—2.1 Hz, 6 H), 6.57—6.69 (AB system, J(A/B) = 12.0—12.6 Hz, 8-H/9-H).
[6] J. N. Crabb, R. C. Storr in A. Padwa: *1,3-Dipolar Cycloaddition Chemistry, Vol. 2*, Wiley, New York 1984, p. 545.
[7] **5d**: monoclinic, $a = 8.131(2)$, $b = 12.852(3)$, $c = 15.857(4)$ Å, $\beta = 94.21(2)$, $P2_1/n$, $Z = 4$, $\rho_{calcd} = 1.383$ g cm^{-3}. Data collection: Enraf-Nonius CAD4 diffractometer, 2024 independent reflections with $2.0 \le \theta \le 22.0°$, $Mo_{K\alpha}$ radiation. Refinement: $R = 0.051$, $R = \Sigma\Delta^2 F / \Sigma F_0^2 = 0.052$ (1685 reflections with $I \ge 2\sigma(I)$), unit weights, non-H-atoms with anisotropic temperature factors, H-atoms refined isotropically, methyl H-atoms not refined.

Further details of the crystal structure investigation are available on request from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2, on quoting the depository number CSD 51 249, the names of the authors, and the journal citation.

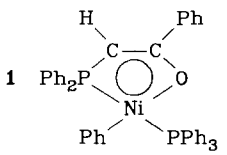
[8] For example, **6a**: colorless crystals, m.p. = 71 °C (ethyl acetate/ether): ^{1}H-NMR (200 MHz, $CDCl_3$): δ = 2.96 (ddd, 1H, ^3J(H/H) = 7.1, ^3J(P/H) = 11.48, ^4J(H/H) = 0.75 Hz, 2-H), 3.40 (s, 3H, OMe), 3.45 (dd, 1H, ^3J(H/H) = 7.1, ^3J(P/H) = 10.7 Hz, 8-H), 3.91 (dd, 1H, ^3J(H/H) = 2.3, ^3J(P/H) = 10.3 Hz, 5-H), 4.41 (br. s, 1H, 4-H), 6.90—7.85 (m, 14H, arene-H); ^{13}C-NMR ($CDCl_3$): δ = 39.62 (dd, ^1J(C/H) = 170.7, ^2J(P/C) = 1.9 Hz, C-2), 40.72 (d, ^1J(C/H) = 171.0 Hz, C-8), 51.62 (dd, ^1J(C/H) = 135.0, ^2J(P/C) = 6.7 Hz, C-5), 52.40 (d, ^1J(P/C) = 99.0 Hz, C-1), 57.27 (q, ^1J(C/H) = 143.7 Hz, CH_3), 101.30 (dd, ^1J(C/H) = 168.2, ^3J(P/C) = 4.5 Hz, C-4), 120.69—132.71 (arene-C), 136.04 (s, C-3), 151.47, 152.70 (each s, C-6/C-7). — **7a**: colorless crystals, m.p. = 173 °C (decomp.) (ethyl acetate/ether); ^{1}H-NMR (200 MHz, $CDCl_3$): δ = 2.76 (dd, 1H, ^3J(H/H) = 9.0, ^3J(P/H) = 9.1 Hz, 2-H), 2.84 (m, 1H, 4-H), 3.14 (dd, 1H, ^3J(H/H) = 9.0, ^3J(P/H) = 9.3 Hz, 8-H), 3.93 (d, 1H, ^3J(P/H) = 8.3 Hz, 5-H), 4.74 (dd, 2H, ^4J(H/H) = 6.6, ^5J(H/H) = 2.7 Hz, allene-CH_2), 5.14 (pseudo-q, 1H, ^4J(H/H) = ^5J(H/H) = 6.6 Hz, allene-CH), 7.05—7.85 (m, 14H, arene-H); ^{13}C-NMR ($CDCl_3$): δ = 42.14, 42.27 (each d, ^1J(C/H) = 175 Hz, C-2/C-8), 48.38 (d, ^1J(P/C) = 100.0 Hz, C-1), 51.25 (dd, ^1J(C/H) = 147.0, ^2J(P/C) = 5.2 Hz, C-5), 65.8 (d, ^1J(C/H) = 141.5 Hz, C-4), 77.3 (t, ^1J(C/H) = 172 Hz, allene-CH_2), 87.21 (d, ^1J(C/H) = 172.0 Hz, allene-CH), 123.69—132.57 (arene-C), 138.28 (s, C-6), 146.61 (d, ^3J(P/C) = 4.2 Hz, C-7), 207.56 (s, allene-C), 209.05 (s, C-3).

Highly Active Ylide-Nickel Catalysts for the Polymerization of Ethylene

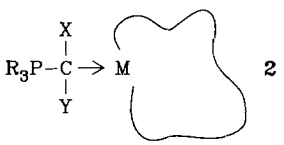
By *K. Alexander Ostoja Starzewski** and *Josef Witte*

Dedicated to Professor Rolf Huisgen on the occasion of his 65th birthday

Ylides are characterized by extremely low first ionization energies and ylide C-atom ^{13}C-NMR signals that are shifted strongly upfield; this is due to a high-energy occupied MO, usually the HOMO that is strongly localized on the ylide C atom.[1]

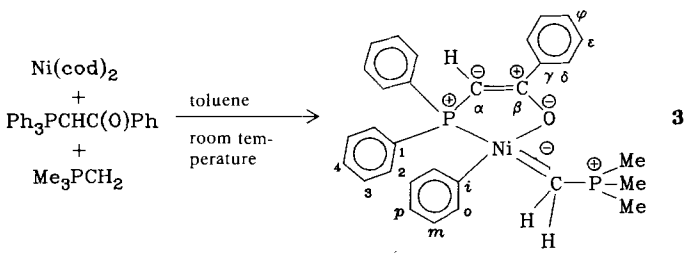


1



2

The reaction of the stabilized ylide benzoylmethylenetriphenylphosphorane with Ni(0) in the presence of triphenylphosphane leads to the oligomerization catalyst **1**, which catalyzes the reaction of 6000 moles of ethylene per mole of complex at 50 bar and 50 °C.[2] The ylide ligand is practically no longer present in **1**. Complexes such as **2**,[3,4] in which the ylide ligand remains largely intact, are of interest concerning their properties as polymerization catalysts, but in this respect had not been studied up to now.



3

cod: cyclooctadiene

We have now found that the reaction of bis(cyclooctadiene)nickel(0) with benzoylmethylenetriphenylphosphorane and trimethylmethylenephosphorane in toluene yields a highly active homogeneous catalyst for the polymerization of ethylene. The spectroscopic data for this catalyst are in accord with the structure **3**, which formally arises via oxidative addition of the Ph_3P group of the stabilized ylide and nucleophilic attack of the carbonyl oxygen atom and of Me_3PCH_2 on Ni. The reaction can be followed by ^{31}P-NMR spectroscopy. After a few minutes, a product has formed that exhibits two doublets (J = 7 Hz) in the ^{1}H-decoupled ^{31}P-NMR spectrum (Fig. 1a); the assignment of the signals was made by analyzing the undecoupled spectrum (Fig. 1b). Concentration of the solution affords a yellow solid whose elemental analysis is in accord with the composition of **3**.

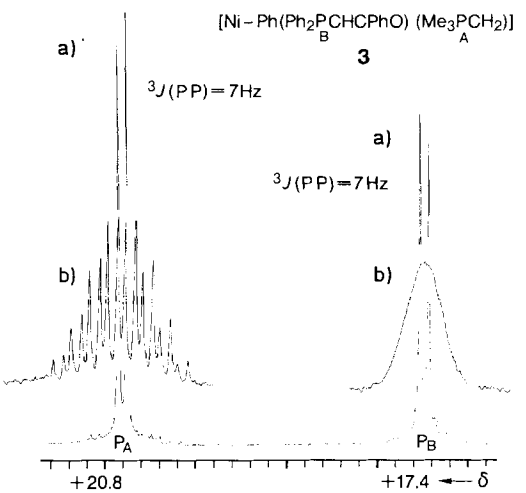


Fig. 1. ^{31}P-NMR spectrum of the ylide complex **3** ([D_6]benzene, room temperature). a) Broad-band ^{1}H-decoupling; b) undecoupled.

3 is stable up to ca. 90 °C in toluene (NMR). Above 130 °C, $M^{\oplus}$ as well as characteristic fragments are observed in the mass spectrum.[5] In the ^{1}H-NMR spectrum of **3**, the resonances of the methylene protons are shifted downfield by nickel complexation (δ = 0.65 in the complex; δ = −0.78 in the free ylide[6]). The double doublet structure (13.1/5.4 Hz)[7] is explained by interaction of the two protons with two different P atoms. The ^2J(PH) coupling in the carbonyl-stabilized ligand is < 0.5 Hz; such small values are typical for free and complexed phosphanes.

The high-resolution room-temperature ^{13}C{^{1}H}-NMR spectrum exhibits sixteen resonances—as expected for **3**—which are partly split due to ^{31}P-^{13}C couplings (Table 1). The Ni-bound ylide C atom is the most strongly shielded C atom of the molecule (δ = 7.2). Noticeable in this case, too, is the double doublet splitting. By comparison with other ylide-metal complexes,[1f,8] the smaller 31-Hz coupling can be assigned to ^1J. We ascribe the 64-Hz coupling to the special *trans* arrangement of ylide and phosphane ligands on square-planar-coordinated nickel. ^1J(CH) (129 Hz, from the undecoupled ^{13}C-NMR spectrum) supports a pyramidalization of the ylide C atom[1d,f,8] due to coordination to the Ni atom. The position of the signals of *o*- and *p*-C atoms on the Ni-bound phenyl group (Table 1) is charac-

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Table 1. ^{13}C-NMR data [a—d] for **3**. Coupling constants in Hz.

	Intact ylide ligand			Ni—Ph group			
	Me	CH_2		C-*i*	C-*o*	C-*m*	C-*p*
$\delta^{13}C$	14.5 (15.4)	7.2 (7.3)	$\delta^{13}C$	156.5 (156.1)	125.4 (125.2)	[c] (128.9)	120.7 (120.3)
^1J(PC)	54 (55)	31 (31)	$^2J(PC)_{cis}$ [e]	31 (31)	[d] ([d])	[c] ([d])	[d] ([d])
$^2J(PC)_{trans}$ [e]	— (—)	64 (65)	^1J(CH)	—	154	[c]	157
^1J(CH)	130	129					

	PO chelate ligand									
	C-4	C-3	C-2	C-1	C-α	C-β	C-γ	C-δ	C-ε	C-φ
$\delta^{13}C$	139.1 (138.8)	[c] (128.0)	133.0 (132.8)	136.3 (135.9)	78.9 (78.9)	182.5 (182.1)	140.5 (139.9)	[c] (127.2)	[c] (128.1)	[c] (128.0)
^nJ(PC)	3 (4)	[c] (3)	16 (10)	44 (42)	52 (52)	26 (25)	13 (13)	[c] ([d])	[c] ([d])	[c] ([d])
^1J(CH)	153	[c]	161	—	163	—	—	[c]	[c]	[c]

[a] 10^{-1} M in C_6D_6/TMS int. [b] 10^{-1} M in CD_2Cl_2/TMS int., values in brackets. [c] Solvent signals overlap. [d] Not resolved. [e] Square-planar coordinated nickel.

teristic for a phenyl group that is bound to an electron-rich center (benzyl Grignard compound,[9] benzylidenephosphorane[11]). C-α is still trigonal planar after complexation according to ^1J(CH) (163 Hz).

The double bond in **3** is strongly polarized. The C-α atom, which bears a partial negative charge, exhibits a signal ($\delta = 78.9$) that is shifted upfield relative to those of "normal" sp^2-hybridized C atoms ($\delta = 128$). The signal of C-β is correspondingly strongly shifted downfield ($\delta =$ 182.5). In comparison, the values for benzoylmethylenetriphenylphosphorane are $\delta = 50$ and 185, respectively.[10]

The ylide complex **3** catalyzes the oligomerization of ethylene at 10 bar and 90 °C with an activity of ca. 0.5×10^5 moles of ethylene per mole of **3**. The polyethylene so formed has a higher molecular weight than that obtained with **1**. We have also synthesized the ylide complexes **4** and examined their ability to catalyze the polymerization of ethylene. We have observed, among other things, the marked effect of substituents on the activity of the catalyst. The activity increases in changing the chelate ligand from formyl to acetyl and finally to benzoyl (**4a**—**c**). The activity of the catalyst can also be influenced by variation of the intact ylide ligand; this is shown by the complexes **4d**—**f**, whose activity increases with decreasing first ionization energy of the ylide (IE_1 of $Me_3PCH_2 = 6.81$, of $Ph_3PCH_2 = 6.62$, of Me_3PCHPh as a model for the ylide ligand in **4f** = 6.19 eV). Accordingly, the metal-ylide bond determines the positions of the highest occupied molecular orbitals, which are metal-d- and metal-C-localized, and thereby the catalyst's (re)activity.

[NiPh(*Ph$_2$PCHCHO*)(Me$_3$PCH$_2$)] **4a**

[NiPh(*Ph$_2$PCHCMeO*)(Me$_3$PCH$_2$)] **4b**

[NiPh(*Ph$_2$PCHCPhO*)(Me$_3$PCH$_2$)] **4c**

[NiPh(Ph$_2$PCHCMeO)(*Me$_3$PCH$_2$*)] **4d**

[NiPh(Ph$_2$PCHCMeO)(*Ph$_3$PCH$_2$*)] **4e**

[NiPh(Ph$_2$PCHCMeO)(*iPr$_3$PCHPh*)] **4f**

Experimental Procedure

3: Bis(cyclooctadiene)nickel(0) (13.75 g, 50 mmol) in ca. 250 mL of anhydrous N_2-saturated toluene is mixed under inert gas with 19.02 g (50 mmol) of benzoylmethylenetriphenylphosphorane and 4.50 g (50 mmol) of trimethylmethylenephosphorane. A dark yellowish brown solution is formed upon intense stirring and is then heated for ca. 1 h at 40 to 60 °C. After subsequent Schlenk filtration, the solution is evaporated under vacuum to half its volume. Upon cooling to 0 to −20 °C, an initial fraction of yellow crystals forms, which is isolated by Schlenk filtration, washed with hexane, and dried under vacuum. The filtrate is then treated similarly, affording the pure nickel-ylide complex in 90% yield already in the first three crystalline fractions. Impure fractions can be purified by recrystallization, e.g., from toluene/hexane. M.p. = 117—120 °C (decomp.). ^{1}H-NMR (CD_2Cl_2, TMS int.): $\delta = 0.65$ (dd, ^2J(PH) = 13.1, ^3J(PH) = 5.4 Hz, 2 H), 1.56 (d, ^2J(PH) = 13.9 Hz, 9 H), 4.93 (br., ^2J(PH) < 0.5 Hz, 1 H), 6.56—7.83 (m, 20 H).

Polymerization of ethylene with **4f** as catalyst: **4f** (2 mmol) in 250 mL of toluene is injected into an autoclave containing 4 L of toluene at 80 °C under a constant pressure of 10 bar of ethylene parallel to the consumption of ethylene (multipulse injection), air and water being excluded. After ca. 1 h, the autoclave is allowed to cool down, the pressure released, and the solid polyethylene (PE) isolated. In the filtrate, $(C_2H_4)_n$ for n = 2 to ca. 20 can be identified by gas chromatography. The amount of oligomers is determined by solvent evaporation (rotary evaporator), the low-boiling fractions being ignored. The polymer consists of monoolefins having over 90% terminal double bonds and high linearity (ratio $-CH_3/-CH=CH_2 \approx 1$ by IR spectroscopy). Total yield: 1366 g (5% oligomers); catalyst activity: 24393 moles of ethylene converted per mole of nickel; m.p. of the PE ≈ 116 °C; intrinsic viscosity of the PE in tetralin at 120 °C: 0.11 dL/g.

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CAS registry numbers:
4f, 90569-21-4; $Ph_3PCHCPhO$, 859-65-4; Me_3PCH_2, 14580-91-7; $(C_2H_4)_n$ homopolymer, 9002-88-4; $Ni(cod)_2$, 33221-58-8.

[1] a) K. A. Ostoja Starzewski, H. tom Dieck, K. D. Franz, F. Hohmann, *J. Organomet. Chem. 42* (1972) C35; b) K. A. Ostoja Starzewski, H. tom Dieck, H. Bock, *J. Organomet. Chem. 65* (1974) 311; c) K. A. Ostoja Starzewski, H. Bock, H. tom Dieck, *Angew. Chem. 87* (1975) 197; *Angew. Chem. Int. Ed. Engl. 14* (1975) 173; d) K. A. Ostoja Starzewski, M. Feigel, *J. Organomet. Chem. 93* (1975) C20; e) K. A. Ostoja Starzewski, W. Richter, H. Schmidbaur, *Chem. Ber. 109* (1976) 473; f) K. A. Ostoja Starzewski, H. tom Dieck, *Phosphorus 6* (1976) 177; g) K. A. Ostoja Starzewski, H. Bock, *J. Am. Chem. Soc. 98* (1976) 8486; h) E. E. Astrup, A. M. Bouzga, K. A. Ostoja Starzewski, *J. Mol. Struct. 51* (1979) 51; i) K. A. Ostoja Starzewski, H. tom Dieck, *Inorg. Chem. 18* (1979) 3307; j) K. A. Ostoja Starzewski, M. Feigel, J. Rieser, *Phosphorus Sulfur 18* (1983) 448.

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[4] W. C. Kaska, *Coord. Chem. Rev. 48* (1983) 1; see [1a, f, i].
[5] For ^{58}Ni: *m/z* 528 ($M^{\oplus}$), 438 [Ni(Ph$_3$PCHCPhO)$^{\oplus}$], 91 [Me$_3$PCH$_2$·H$^{\oplus}$], 77 [C$_6$H$_5^{\oplus}$].
[6] H. Schmidbaur, W. Buchner, D. Scheutzow, *Chem. Ber. 106* (1973) 1251.
[7] The PH coupling constants of the trimethylmethylenephosphorane ligands in **3** have the same sign according to selective homodecoupling experiments. Their values, −13.2 (P–CH$_3$) and −13.1 Hz (P–CH$_2$), are characteristic for a tetracoordinated phosphorus that is bonded to an approximately sp^3-hybridized carbon atom.
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[10] a) G. Fronza, P. Bravo, C. Ticozzi, *J. Organomet. Chem. 157* (1978) 299; b) T. A. Albright, M. D. Gordon, W. J. Freeman, E. E. Schweizer, *J. Am. Chem. Soc. 98* (1976) 6249.

[(η^5-C$_5$Me$_5$)CrO$_2$]$_2$— A Dinuclear Oxo-Complex of Chromium(v)**

By *Max Herberhold,* Walter Kremnitz, Abbas Razavi, H. Schöllhorn,* and *Ulf Thewalt**

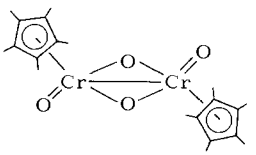
The photoinduced oxidation of [Cp*Re(CO)$_3$] to [Cp*ReO$_3$] **8**[1–4] has demonstrated that cyclopentadienyl ligands (η^5-C$_5$H$_5$ (Cp), η^5-C$_5$Me$_5$ (Cp*)) can tolerate both low as well as high oxidation states of a metal. Oxygen attack ought to be favored if the metal in the low oxidation state bears strong acceptor ligands. We have therefore investigated the oxidation of the nitrosyl complexes **1a–c** with oxygen.

On stirring an oxygen-saturated solution of **1a** in toluene (without irradiation), a red dinuclear complex **2**[5] is slowly formed, the structure of which has been elucidated by X-ray crystallography (Fig. 1). In the complex **2**, chromium does not attain its highest possible oxidation number, +6; nevertheless, the formal oxidation state of +5 is two oxidation states higher than in the antiferromagnetic tetranuclear pseudocubane cluster [CpCrO]$_4$,[6–8] prepared by mild oxidation of CrCp$_2$ in organic solvents[6,7] and likewise characterized by an X-ray structure analysis.[7]

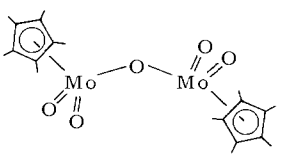
In contrast to **1a**, the molybdenum complex **1b** is oxidized by oxygen to a yellow dinuclear complex **3**,[5] which, according to its IR spectrum (ν(Mo=O) 908 and 879 cm^{-1}), contains two *cis*-oriented terminal oxo-ligands per metal atom, i.e. the characteristic unit [Mo$_2$O$_5$]$^{2+}$ with molybdenum in the oxidation state +6. No simple oxo-complex has been isolated from **1c** under comparable conditions.

Table 1 contains characteristic data of the new oxo-complexes **2** and **3** and of some reference compounds. **2** and **3** are diamagnetic. In the ^{13}C-NMR spectrum, the signal of the Cp* ring atoms is shifted by $\Delta\delta \approx 15$ ppm downfield as a result of the oxidation of the nitrosyl complexes **1a** and **b**; the methyl groups, however, are barely influenced. In the IR spectrum, the very strong absorptions of the terminal oxo-ligands appear in the region 850—950 cm^{-1}.

[Cp*M(CO)$_2$NO] **1**; **a**: M = Cr; **b**: M = Mo; **c**: M = W



2



3

[(CpMoO)$_2$(μ-O)$_2$] **4**

[(CpMoO$_2$)$_2$(μ-O)] **5**

[{CpCr(NSiMe$_3$)}$_2$(μ-NSiMe$_3$)$_2$] **6**

[CpCr(μ$_3$-O)]$_4$ **7**

[Cp*ReO$_3$] **8**

[(Cp*ReO)$_2$(μ-O)$_2$] **9**

[{(L)MoO}$_2$(μ-O)$_2$]$^{2+}$
10, L = 1,4,7-triazacyclononane

Dinuclear oxo-complexes of chromium(v) were hitherto unknown. On the other hand, some oxo-complexes have been isolated in the oxidation of cyclopentadienylmolybdenum compounds;[9] these include, inter alia, the brown molybdenum(v) complex **4** analogous to **2**,[9,10] and the bright-yellow molybdenum(vi) complex **5** analogous to **3**[9] (Table 1).

An X-ray structure analysis[11] of **2** reveals a centrosymmetric molecule with a planar Cr$_2$O$_2$ four-membered ring, the chromium atoms of which have a distorted tetrahedral environment (Fig. 1). The two Cp*-rings and the two terminal oxo-ligands are each arranged *trans* to each other. In contrast, both in the structurally similar complex **6**[12] as well as in **4**[10] the five-membered rings are in the *cis* posi-

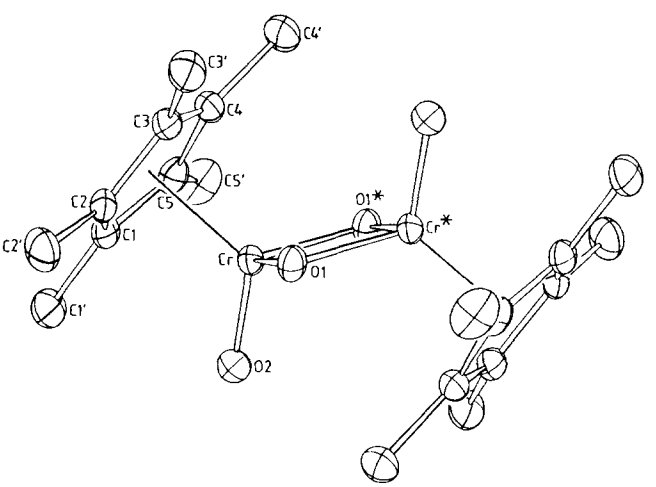


Fig. 1. Molecular structure of **2** in the crystal. Selected bond lengths [pm] and angles [°]: Cr–Cr* 250.5(1), Cr–O1 181.7(4), Cr–O1* 181.3(4), Cr–O2 159.4(3), Cr–Z 193.1(6), O1–Cr–O1* 92.7(2), O1–Cr–O2 106.4(2), O1*–Cr–O2 107.3(2), Cr–O1–Cr* 87.3(2). Z = center of the five-membered ring. Atoms marked with an asterisk are centrosymmetrically related to the corresponding unmarked atom.

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[**] This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.

Table 1. Spectroscopic and X-ray structural data of the oxo-complexes **2** and **3** and some reference compounds.

	IR [cm^{-1}]		NMR (δ-values)		X-ray structure analysis [pm]		
	ν(M=O)	ν(M–O–M)	^{1}H	^{13}C	M=O	M–O(–M)	M–M
1a			1.81 [b]	10.2 [b] 103.2			
1b			2.07 [b]	10.7 [b] 107.3			
2	910 [a]	715	1.81 [b]	10.2 [b] 118.6	159.4(3)	181.7(4) 181.3(5)	250.5(1)
3	908 [a] 879	755 (br)	1.97 [b]	10.6 [b] 121.7			
4 [9, 10]	925 [c] 901	710			169.5 170.2	193.2 194.8	260.2
5 [9]	930, 920 [c] 898, 850	770			170.2	194.8	
6 [12]	—				164.1 [d] 165.1	181(2), 192(2) [d] 182(3), 199(3)	256.9(4)
7 [7]	—					193.7 av.	270.2(6) to 290.0(6)
8 [1, 3]	909 [a] 878		2.08 [e]	10.2 [f] 120.4		≈ 175 [3]	
9 [1, 2]	930 [a]	634 614	2.03 [g]				

[a] KBr. [b] [D$_6$]acetone. [c] C_4Cl_6 and Nujol mulls. [d] Cr=N and Cr–N(–Cr) distances, see [12]. [e] CD_2Cl_2, –80 °C. [f] $CDCl_3$. [g] CD_2Cl_2, 28 °C.

tion on the same side of the non-planar four-membered ring. In the case of the molybdenum(v) cation **10** both the *cis*- as well as the *trans*-form could be structurally characterized;[13] the *trans*-isomer can be converted irreversibly into the thermodynamically more stable *cis*-isomer.[14] The chromium-chromium distance and the Cr=O distances in **2** are remarkably short.

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CAS Registry numbers:
1a, 34808-36-1; **1b**, 51213-19-5; **2**, 96689-32-6; **3**, 96689-33-7; Cr, 7440-47-3.

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[5] Procedures: **2**: A solution of **1a** (273 mg, 1 mmol) in 50 mL of toluene (or ether) was saturated with O_2-gas and stirred in the presence of air for 2–4 h until the IR spectra (ν(CO) region) showed that no more **1a** was present. The solution was evaporated to dryness at room temperature and the brown residue was chromatographed on silica gel TLC-plates (Merck TLC 60 GF_{254}, pentane/THF (10:2)). Recrystallization from THF/pentane gave red crystals of **2**, which are insoluble in H_2O, sparingly soluble in pentane, but readily soluble in polar organic solvents. Yield: 90–110 mg (41–50%).—**3**: The O_2-saturated solution of **1b** (160 mg, 0.5 mmol) in toluene (30 mL), after five hours' stirring and subsequent thin-layer chromatography of the residue, furnished a yellow powder that crystallized from pentane/THF at –30 °C in the form of yellow needles. Yield 110 mg (40%). FD-MS: *m/z* 542 (w.r.t. ^{96}Mo; M^+).
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[11] $P\bar{1}$, $Z=1$, $a=827.0(2)$, $b=857.5(2)$, $c=927.5(4)$ pm, $\alpha=98.78(4)$, $\beta=108.14(2)$, $\gamma=117.77(3)^\circ$, $V=517.2\times10^6$ pm^3, $\rho_{exp}=1.41$ (in $CHBr_3$/hexane), $\rho_{calc}=1.408$ g/cm^{-3}; $Mo_{K\alpha}$ radiation, graphite monochromator $\theta/2\theta$scan; 1703 independent reflections ($2\theta<50^\circ$) with $I>\sigma(I)$; Lp- but no absorption correction ($\mu=10.1$ cm^{-1}); H atoms not considered; $R=0.067$, $R_w(F)=0.076$. Further details of the crystal structure investigation are available on request from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2, on quoting the depository number CSD 51445, the names of the authors, and the full citation of the journal.
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Bis(dihydro-1,2-azaborolyl)tin—a Novel Boron-Nitrogen Stannocene**

By *Günter Schmid,* Dagmar Zaika,* and *Roland Boese*

Dihydro-1,2-azaborolyl ligands provide transition metals with a more diverse range of electronic possibilities than the isoelectronic cyclopentadienyl(Cp) systems. In addition to η^5-coordination, η^4- and η^3-coordination are observed.[1] Corresponding to its electron configuration, the metal seeks stronger contact to the acceptor atom boron, to the donor atom nitrogen, to the C_3 allyl moiety, or equally to all five ring atoms. Interestingly, in the stannocenes that have been synthesized and structurally investigated in the last few years, relatively marked deviations from the η^5 arrangement of the Cp ligands have been found. Moreover, the Cp rings are usually not coplanar but rather are at an angle with respect to each other.

With the synthesis of bis(1-*tert*-butyl-2,3-dimethyldihydro-1,2-azaborolyl)tin **1**, we have succeeded for the first time in binding a main group metal to a dihydro-1,2-azaborolyl ligand (apart from Li in 1-*tert*-butyl-2,3-dimethyl-

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[**] Azaborolinyl Complexes, Part 19. This work was supported by the Fonds der Chemischen Industrie. Comment on the nomenclature: the traditional name "azaborolinyl" has been replaced by "dihydroazaborolyl" according to IUPAC rule RB-1.2 (*Pure Appl. Chem. 55* (1983) 409).—Part 18: G. Schmid, G. Barbenheim, R. Boese, *Z. Naturforsch. B*, in press.

dihydro-1,2-azaborolyl, **2**). **1** has enabled us to study the behavior of the metal with respect to its preferred coordination site and to make comparisons with stannocenes.

The reaction of **2** with $SnCl_2$ at $-45°C$ in tetrahydrofuran (THF) afforded orange-yellow **1** in 49% yield; **1** decomposes above $-20°C$ with formation of tin.[2] The molecular structure of the BN/NB isomer[3] (Fig. 1) shows

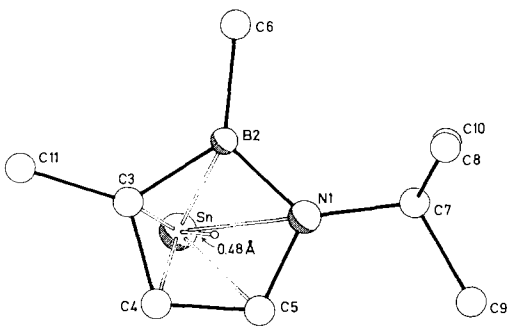


Fig. 1. Crystal structure of **1**. Selected bond lengths [Å]: Sn–C3 2.489(9), Sn–C4 2.592(10), Sn–B2 2.742(10), Sn–C5 2.810(10), Sn–N1 2.917(9), N1–B2 1.480(7), B2–C3 1.511(7), C3–C4 1.422(6), C4–C5 1.377(8), N1–C5 1.399(4).

planar rings lying at an angle with respect to each other and thus resembles most of the stannocenes studied so far.[4–7] Only in the sterically highly hindered $[(Ph_5C_5)_2Sn]$ are the rings arranged in a coplanar fashion.[8] The molecule exhibits C_2 symmetry, which is due to the crystallographic axis in $0/Y/0.25$.

The angle of aperture between the two rings in **1** is 46.5°, thus lying between the corresponding angles in stannocene (55°)[4] and decamethylstannocene (36°).[5] According to MO calculations, the angled structure is energetically favorable (energy minimum at 60°) compared with the coplanar geometry.[5] Figure 2 shows the displacement

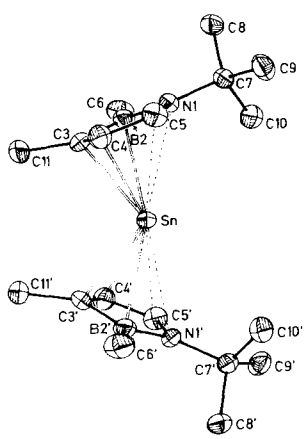


Fig. 2. Displacement of the tin atom from the ring center in **1**.

of tin from the center of the ring by 0.48 Å in the direction of the atoms C3 and C4. Accordingly, the Sn–C5 and Sn–N1 distances, 2.810 and 2.917 Å, respectively, are unusually long. This observation is in accord with the bonding relationships in stannocenes or stannocene-like complexes, in which marked differences in the Sn–C bond angles also exist: 2.56–2.85 Å in **3**,[4] 2.59–2.74 Å in **4**,[5] or 2.53–2.81 Å in **5**.[6] In the boron-containing complexes **6**[9] and **7**[10] the tin atoms are clearly displaced from the center of the ring in the direction of the boron atoms.

$[(C_5H_5)_2Sn]$ **3** $[(C_5Me_5)_2Sn]$ **4** $[\{C_5H_4(iPr_2N)\}_2Sn]$ **5**

$[\{CpCo(C_3B_2R_5)\}_2Sn]$ **6** $[(C_2Me_2B_9H_9)SnL]$ **7**

Whereas metal-boron bonds in transition-metal complexes result in upfield shifts of the ^{11}B-NMR signals compared with those in the free ligands, a shift downfield from $\delta = 24.5$ (in **2**) to $\delta = 31.5$ is observed for **1**. This is due to the reduced ability of main group metals to engage in back-bonding because of a lack of available d electrons.

As is the case for the dihydro-1,2-azaborolyl complexes with transition metals, the two expected diastereomers of **1** can be observed by ^{1}H-NMR spectroscopy; their formation is due to the prochiral character of the rings. The proton signals of the diastereomers have an intensity ratio of ca. 10:1. It is not yet known whether the enrichment of one of the forms occurs only during the course of the work-up, or, instead, whether one isomer is already formed preferentially during the formation of the complexes. In the case of the transition-metal complexes, an isomer ratio of ca. 1:1 is usually found. Possibly, the special bonding and structure relationships play a role in the example discussed here. The ^{1}H-NMR signals lie in the expected ranges, the ring protons H4 and H5 each appearing as a doublet due to the mutual coupling.

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1, 96745-78-7; **2**, 96706-55-7; **8**, 96706-56-8; 1-*tert*-butyl-2-methyl-1*H*-2,3-dihydro-1,2-azaborolyllithium, 84356-32-1.

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[2] Experimental procedure: 1-*tert*-Butyl-2,3-dimethyl-1*H*-2,3-dihydro-1,2-azaborole **8**: 1-*tert*-butyl-2-methyl-1*H*-2,3-dihydro-1,2-azaborolyllithium (8.55 g, 59.8 mmol) [11] was dissolved in 90 mL of THF and treated dropwise at $-50°C$ with a solution of iodomethane (8.49 g, 59.8 mmol) in pentane. The solution was warmed slowly to room temperature and stirred for 1 h. LiI was separated by suction filtration through a sintered-glass filter. Distillation at 163–165°C afforded 6.86 g (75.9%) of colorless **8**. ^{1}H NMR (200 MHz, [D$_6$]benzene): $\delta = 0.69$ (s, 3H, BCH_3), 1.15 (d, $J \approx 7$–8 Hz, 3H, CCH_3), 1.16 (s, 9H, $C(CH_3)_3$), 1.78 (m, 1H, H3), 5.41 (dd, $J = 4$ Hz, $J = 2$ Hz, 1H, H4), 6.47 (dd, $J = 4$ Hz, $J = 2$ Hz, 1H, H5); ^{11}B NMR (200 MHz, [D$_6$]benzene): $\delta \approx 50.8 \pm 1$; ^{13}C{^{1}H} NMR (200 MHz, [D$_6$]benzene): $\delta = 0.8$ (br. s, BCH_3), 13.01 (s, CCH_3), 31.35 (s, $C(CH_3)_3$), 35.6 (br. s, C3), 53.52 (s, $C(CH_3)_3$), 118.21 (s, C4), 136.4 (s, C5). Correct C–H–N analysis. **2**: Similarly to the synthesis of other dihydroazaborolyllithium salts from lithium tetramethylpiperidide and **8** [11]. Yield: 76.0%. ^{1}H NMR (200 MHz, [D$_8$]THF): $\delta = 0.47$ (s, 3H, BCH_3), 1.34 (s, 9H, $C(CH_3)_3$), 1.82 (s, 3H, CCH_3), 5.54 (d, $J = 2.7$ Hz, 1H, H4), 5.73 (d, $J = 2.7$ Hz, 1H, H5); ^{11}B NMR (200 MHz, [D$_8$]THF): $\delta = 24.5 \pm 1$; ^{13}C{^{1}H} NMR (200 MHz, [D$_8$]THF): $\delta = 0.6$ (br. s, BCH_3), 15.25 (s, CCH_3), 32.56 (s, $C(CH_3)_3$), 53.64 (s, $C(CH_3)_3$), 103.28 (s, C4), 113.31 (s, C5). The signal for C3 cannot be observed due to the neighboring boron atom. Correct C–H–N–Li analysis. **1**: Anhydrous $SnCl_2$ (0.74 g, 3.9 mmol) in 25 mL of THF was slowly added dropwise to a solution of **2** (1.23 g, 7.8 mmol). After 1 h, the solvent was removed without heating. The residue was treated with 20 mL of cold pentane. Filtration through a sintered-glass filter cooled with dry ice afforded an orange-yellow solution. The solvent was removed at $-20°C$. Repeated washing with pentane at $-20°C$ and subsequent drying in vacuum yielded 0.79 g (48.6%) of analytically pure **1** as a mixture of diastereomers, which was stored at $-78°C$. According to the ^{1}H NMR spectrum, the sample contains both diastereomers in a ratio of 10 (**a**):1 (**b**). Assignment of **a** and **b** to the BN/BN- or BN/NB isomer was not achieved since a preparative separation was not possible. ^{1}H NMR (200 MHz, [D$_8$]toluene, $-40°C$): δ = (**a**) 1.02, (**b**) covered by $C(CH_3)_3$, (s, 6H, BCH_3), 1.10 (1.16) (s, 18H, $C(CH_3)_3$), 2.28 (2.42) (s, 6H, CCH_3), 5.39 (5.52) (d, $J = 3$ Hz, 2H, H4), 6.80 (6.70) (d, $J = 3$ Hz, 2H, H5); ^{11}B NMR

(200 MHz, [D$_8$]toluene, -40°C): $\delta = 31.5 \pm 1$ (**a** = **b**); ^{13}C{^{1}H} NMR (200 MHz, [D$_8$]toluene, -40°C): δ = (**a**) 13.41 (s, CCH_3), 31.22 (s, $C(CH_3)$), 54.22 (s, $C(CH_3)_3$), 103.89 (s, C4), 117.94 (s, C5). The signals for C3 and C6 cannot be observed due to their position next to the boron atom. Owing to the poor signal-to-noise ratio, the ^{13}C-NMR signals of **b** can no longer be observed. Correct C–H–N–Sn analysis.

[3] In the BN/NB isomer, the same sides of the rings are coordinated to tin; in the BN/BN isomer, different sides. BN/NB **1** (-120°C): from pentane at low temperature: C2/c; $Z = 4$; $a = 20.972(4)$, $b = 9.266(2)$, $c = 18.137(5)$ Å; $\beta = 144.01(1)$°; $V = 2071.2(9)$ Å^3; $\rho_{calcd.} = 1.34$ g/cm^3; $3° \leq 2\theta \leq 60°$ ($Mo_{K\alpha}$, $\lambda = 0.71069$ Å, graphite monochromator), $\mu = 12.4$ cm^{-1}; 2469 independent intensities, 2320 with $F \geq 3.5\sigma(F)$. Structure solution using Patterson and difference Fourier methods, refinement according to the block cascade method with SHELXTL. The hydrogen atoms of the CH_3 groups were refined as "riding groups" and the ring hydrogen atoms were obtained from a difference Fourier synthesis and refined to $R = 0.066$. Further details of the crystal structure investigation are available on request from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2, by quoting the depository number CSD 51413, the names of the authors, and the journal citation.

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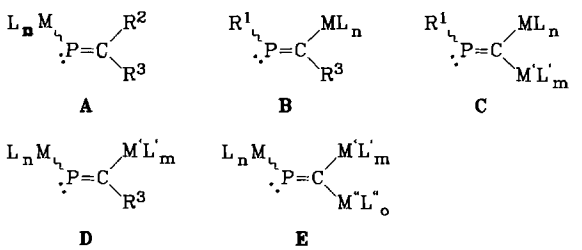
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Z-[(η^5-C_5H_5)(CO)$_2$Fe–P=C(OSiMe$_3$)(*t*Bu)], a Phosphaalkenyl-Complex with FeP Single Bond**

By *Lothar Weber,* Klaus Reizig, Roland Boese,* and *Michael Polk*

Multiple-bond systems with elements of higher periods ($n \geq 3$) are of current interest, not only from the preparative and the theoretical point of view,[1] but also with regard to the ligand properties of compounds containing such structural units.[1e,2] Thus, for example, η^1- and η^2-complexes of phosphaalkenes and phosphaalkynes have recently been the subject of intensive studies; phosphaalkenes can be terminal or bridging ligands.[3] All phosphaalkene complexes reported so far contain an intact $R^1P{=}CR^2R^3$ structural unit.

In principle, it should be possible to replace the R^1, R^2 and R^3 groups of a phosphaalkene by transition metal-complex fragments to give complexes of the type **A**—**E**.



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We recently reported the synthesis and structure of rhenium complexes of type **B**,[4] while *Cowley* et al. have described the first phosphavinylidene complex **4**.[5] In this communication we present for the first time a phosphaalkenyl complex of iron, which represents a complex of type **A**.

The synthetic strategy chosen here is an extension of that developed by *Becker* for the synthesis of phosphaalkenes from disilylphosphanes and pivoloyl chloride[6] to the disilylphosphidoiron complex **1**.[7] The complex **1** reacts with pivaloyl chloride to give the brown title compound **3**.[8] No intermediate, such as, e.g., **2**, could be detected in the reaction between -70°C and 22°C by ^{31}P-NMR spectroscopy.

$$[(\eta^5\text{-}C_5H_5)(CO)_2FeP(SiMe_3)_2] \xrightarrow[-Me_3SiCl]{+t\text{BuC(O)Cl}}$$

1

$$[(\eta^5\text{-}C_5H_5)(CO)_2FeP(SiMe_3)\{C(O)t\text{Bu}\}] \longrightarrow$$

2

$$[(\eta^5\text{-}C_5H_5)(CO)_2FeP{=}C(OSiMe_3)(t\text{Bu})]$$

3

$$[(\eta^5\text{-}C_5H_5)(CO)_2Mo{=}P{=}C(SiMe_3)_2]$$

4

The constitution and configuration of the isolated complex **3** were confirmed by elemental analysis and spectroscopic methods.[8] The Fe(CO)$_2$-group gives rise to two intense ν(CO) bands in the IR spectrum. The characteristic downfield shifts of the resonances of the (C=P) unit and the M^+ ion in the mass spectrum are reconcilable with the monomeric structure of the complex. The configuration at the P=C bond was ascertained by analysis of the ^{1}H- and ^{13}C-NMR spectra. The protons of the Me_3SiO unit gave rise to a singlet at $\delta = 0.44$, while the resonances of the *tert*-butyl protons appear as a doublet due to coupling with the phosphorus atom. The doublet at $\delta = 4.15$ is assigned to the

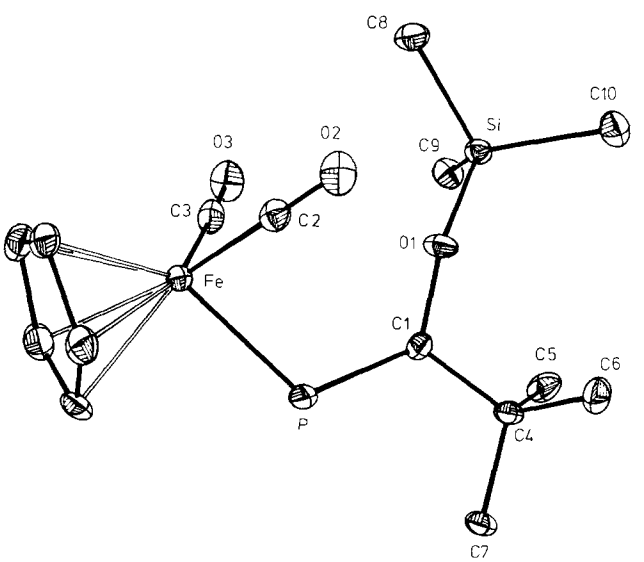


Fig. 1. Crystal structure of **3**. Selected bond lengths [pm] and angles [°]: Fe–P 229.8(1), P–Cl 170.1(4), Cl–O1 136.5(5), Cl–C4 152.9(6), Fe–C2 175.3(5), Fe–C3 178.3(5), C2–O2 115.1(6), C3–O3 110.8(7), Fe–C(ring) 211.2(3) to 211.9(3). C2–Fe–P 86.2(1), P–Fe–C3 88.8(2), C2–Fe–C3 96.5(2), Fe–P–Cl 113.8(2), P–Cl–O1 123.9(3), P–C1–C4 120.5(3), O1–C1–C4 115.3(4), C1–O1–Si 144.7(3).

cyclopentadienyl ligand. On the basis of reference data,[9] and the fact that couplings to moieties which are oriented in the eclipsed position with respect to the free electron pair of the phosphorus atom are larger, a *Z*-configuration must be assumed for **3**. This finding is confirmed by the X-ray structure analysis of **3** at −162°C (Fig. 1).[10] The P=C bond length (170.1(4) pm) lies in the range (168 to 172 pm) characteristic for phosphaalkenes.[11] The iron atom lies in a plane with the atoms P, C1 and O1 and is linked to the phosphorus via a single bond (229.8(1) pm). The C1–O1 distance (136.5(5) pm) is markedly shorter than the length calculated for a C(sp^2)O single bond (141 pm).[12] The angle at the phosphorus is 113.8(2)°, while that at O1 is considerably widened (144.7(3)°). Complex **3** differs from the phosphavinyl complex **4** in that the lone pair on the phosphorus is not required for electronic saturation of the metal; hence, **3** can be regarded as a transition metal-substituted phosphaalkene or as an η^1(Fe–P)-phosphaalkenyl complex.

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CAS Registry numbers:
1, 76586-94-2; **3**, 96729-32-7; pivaloyl chloride, 3282-30-2.

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[8] Experimental: **3**: A solution of pivaloyl chloride (0.849 g, 7.05 mmol) in 100 mL of tetrahydrofuran (THF) was added dropwise in 1 h at 35°C to a solution of **1** (2.496 g, 7.05 mmol) in a mixture of pentane (25 mL) and THF (75 mL). After removal of the solvent, the oily, brown residue was extracted with ca. 50 mL of pentane. The filtered pentane extract was evaporated to ca. 20 mL and allowed to stand at −78°C for 24 h. A precipitate settled out. The mother liquor was drawn off with a pipette and the precipitate was recrystallized from a little pentane at −25°C. This furnished 0.590 g (23%) of brownish-red crystalline **3**, m.p. 61°C.—^{1}H NMR (200 MHz, C_6D_6, 22°C): δ = 0.44 (s, 9H, OSi(Me$_3$)$_3$), 1.43 (d, ^4J(PH) = 2.2 Hz, 9H, *t*Bu), 4.15 (d, ^3J(PH) = 2.2 Hz, 5H, C_5H_5).—^{13}C{^{1}H} NMR (C_6D_6, 22°C): δ = 2.8 (s, OSiMe$_3$), 31.1 (d, ^2J(PC) = 14.7 Hz, C(CH$_3$)$_3$), 45.4 (d, ^1J(PC) = 23.6 Hz, *C*(CH$_3$)$_3$), 86.0 (d, ^2J(PC) = 3.8 Hz, C_5H_5), 213.5 (d, ^1J(PC) = 95.7 Hz, P=C), 215.4 (s, Fe–C≡O).—^{31}P{^{1}H} NMR (C_6D_6, 22°C): δ = 215.2.—IR (cyclopentane): 2018 s, 1963s cm^{-1} (ν(CO)).—EI-MS (Varian MAT 312, 70 eV, 70°C): 366 (M^+), 338 (M^+ − CO), 310 (M^+ − 2CO), 238 [(C_5H_5)FeP(H)C(O)*t*Bu$^+$], 210 [(C_5H_5)FeP(H)(*t*Bu)$^+$], 195 [(C_5H_5)FeP(H)[C(CH$_3$)$_2$]$^+$], 73 (SiMe$_3^+$), 57 (*t*Bu$^+$), 56 (Fe$^+$).

[9] G. Becker, O. Mundt, G. Uhl, *Z. Anorg. Allg. Chem. 517* (1984) 89.

[10] Space group: $P2_1/n$; a = 673.4(2), b = 3147.6(10), c = 842.1(4) pm, β = 97.91(3)°, V = 1.7694(11) × 10^9 pm^3; Z = 4, R = 0.061. Further details of the crystal structure investigation are available on request from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2, on quoting the depository number CSD 51374, the authors names, and the full citation of the journal.

[11] a) R. Appel, V. Barth, F. Knoch, *Chem. Ber. 116* (1983) 938; b) R. Appel, M. Halstenberg, F. Knoch, H. Kunze, *ibid. 115* (1982) 2371; c) B. Bak, N. A. Kristiansen, H. Svanholt, *Acta Chem. Scand. A 36* (1982) 1; d) R. Appel, F. Knoch, B. Laubach, R. Sievers, *Chem. Ber. 116* (1983) 1873; e) G. Becker, O. Mundt, *Z. Anorg. Allg. Chem. 443* (1978) 53; f) T. A. van der Knaap, T. C. Klebach, F. Visser, F. Bickelhaupt, P. Ros, E. J. Baerends, C. H. Stam, M. Konijn, *Tetrahedron 40* (1984) 765.

[12] U. Schubert, H. Fischer, P. Hofmann, K. Weiss, K. H. Dötz, F. R. Kreissl: *Transition Metal Carbene Complexes*, Verlag Chemie, Weinheim 1983, p. 77.

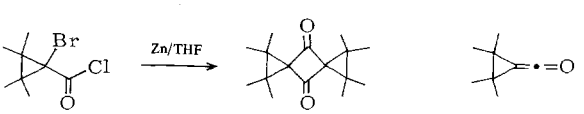
Novel Carbonylcyclopropane Dimers and Trimers—Free Ketenes or Organometallic Intermediates?**

By *Jan-Michael Wulff* and *H. M. R. Hoffmann**

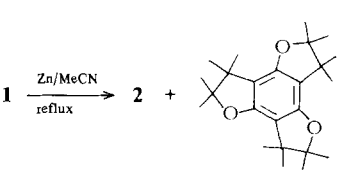
We have previously reported on the preparation of dispiro[2.1.2.1]octane-4,8-diones via dehalogenation of 1-bromocyclopropanecarbonyl chlorides with zinc in tetrahydrofuran (THF), e.g. **1** → **2**.[1]

We have now investigated other 1-bromocyclopropanecarbonyl chlorides and also expanded the experimental conditions for dehalogenation, by using magnesium in addition to zinc as a reducing agent and acetonitrile in addition to tetrahydrofuran as a solvent.

For example, when magnesium was added to **1** in THF and the reaction solution was scanned by IR after 5 min, the band of the acid chloride **1** (1780 cm^{-1}) and that of **2** (1708 cm^{-1}) were visible in a ratio of 1:1 in addition to a new absorption at 2115 cm^{-1}, which we assign to the cumulated system of double bonds of the free carbonylcyclopropane **3**.[2] This band had an intensity of ca. 10% with respect to the dominating acid chloride band and had disappeared after ca. 10 min. Hence, permethylated **3** has a considerably longer lifetime than parent carbonylcyclopropane, which stays monomeric at liquid nitrogen temperatures only.[3] Magnesium and THF are also optimum for preparing the cyclic dimer **2** (70–75% isolated yield) from **1**.



With zinc as metal and absolute acetonitrile as solvent not only **2** was formed, but also dodecamethylhexahydrobenzo[1,2-*b*:3,4-*b'*:5,6-*b''*]trifuran **4** (**2**:**4** = 77:23; 56% combined yield).[4]

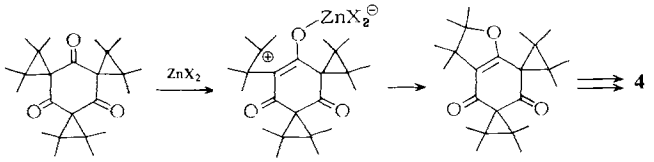


A rational precursor of **4** is the novel trispiro compound **5a**, which, on contact with the zinc halide generated, will

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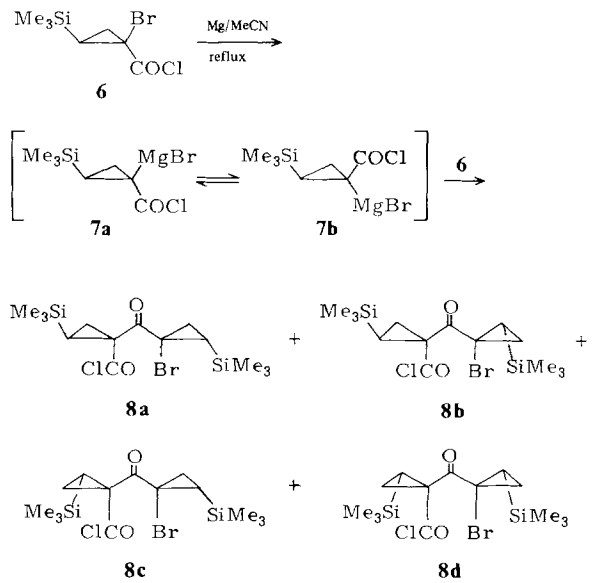
[**] We thank the Fonds der Chemischen Industrie for support of this work.

first form the tertiary homoallylic cation **5b** and eventually the arene **4**.



5a **5b** **5c**

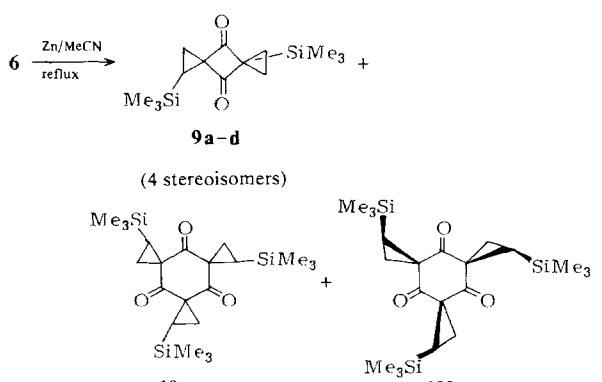
Since 1,3,5-trihydroxybenzene (phloroglucinol) is known to exhibit ketonic properties, we felt that trispirotriketones other than the hypothetical permethylated **5a** might actually be isolable. Surprisingly, dehalogenation of **6**[4] with magnesium in acetonitrile gave the β-ketoacid chlorides **8a–d** as a mixture of four stereoisomers. Dimers of the dispiro[2.1.2.1]octane-4,8-dione type (cf. **9a–d**) were formed only in traces (GC). Attempts to cyclize **8** to **9** with zinc in THF and acetonitrile remained unsuccessful.



6 **7a** **7b** **8a** **8b** **8c** **8d**

However, dehalogenation of **6** with zinc in boiling acetonitrile gave four stereoisomeric dimers, **9a–d**,[5] and two stereoisomeric trimers, **10a**, **b** (60% combined yield; **9** : **10** = 88 : 12; **10a** : **10b** = 2 : 1). After sublimation of the dimers **9a–d** the remaining trimer fraction was separated by chromatography (basic Al_2O_3, pentane/ether = 10 : 1).

The cyclic trimer, formed in only small amounts, could be identified clearly as **10b** by virtue of its C_3 axis. In the 90-MHz and 270-MHz ^{1}H-NMR spectra **10b** showed only *one* Me_3Si signal at $\delta = 0.09$ and only *one* ABM system.[4]



9a–d

(4 stereoisomers)

10a **10b**

The major trimer **10a**[4] had an IR spectrum identical to that of **10b**, showing, inter alia, a carbonyl band at 1670 cm^{-1}.

While there can be little doubt that free carbonylcyclopropanes occur on reaction with magnesium in tetrahydrofuran (cf. **3**), the formation of coupling products such as **8a–d** in acetonitrile is in better agreement with organometallic intermediates such as 1-chloroformylcyclopropyl Grignard compounds **7a**, **b**. Similarly, since the formation of cyclic trimers of the 1,3,5-cyclohexanetrione type (cf. **10a**, **b**) is unknown in conventional ketene chemistry[6] we propose that a corresponding organozinc intermediate is involved in the cyclotrimerization. The hypothetical 1-chloroformylcyclopropylmetal compounds should be both nucleophilic and electrophilic and thus enter into multiple coupling, including polymerization. Their finite existence can be ascribed to several factors, including covalency of the cyclopropylmetal bond, solvation—or lack thereof—of the metal atom and impeded enolate resonance due to developing methylenecyclopropane and carbonylcyclopropane strain.

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1, 81359-22-0; **2**, 81359-25-3; **3**, 96929-29-2; **4**, 96929-30-5; **6**, 96929-31-6; **8a**, 96929-32-7; **8b**, 96997-72-7; **8c**, 96997-73-8; **8d**, 96997-74-9; **9a**, 96929-33-8; **9b**, 96997-75-0; **9c**, 96997-76-1; **9d**, 96997-77-2; **10a**, 97058-15-6; **10b**, 96929-34-9; Mg, 7439-95-4; Zn, 7440-66-6; 1,1-dibromo-2-(trimethylsilyl)cyclopropane, 17544-73-9; *cis*-1-bromo-(trimethylsilyl)cyclopropanecarboxylic acid, 96929-35-0; *trans*-1-bromo-2-(trimethylsilyl)cyclopropanecarboxylic acid, 96929-36-1.

[1] H. M. R. Hoffmann, J. M. Wulff, A. Kütz, R. Wartchow, *Angew. Chem. 94* (1982) 79; *Angew. Chem. Int. Ed. Engl. 21* (1982) 83; *Angew. Chem. Suppl. 1982*, 17.

[2] Carbonylcyclopropane itself shows IR bands at 2125 and 2145 cm^{-1} [3a]. 6-Carbonylbicyclo[3.1.0]hexane shows an IR band at 2126 cm^{-1} [C. Wentrup, G. Gross, A. Maquestiau, R. Flammang, *Angew. Chem. 95* (1983) 551; *Angew. Chem. Int. Ed. Engl. 22* (1983) 542].

[3] a) G. J. Baxter, R. F. C. Brown, F. W. Eastwood, K. J. Harrington, *Tetrahedron Lett. 1975*, 4283; J. L. Ripoll, *Tetrahedron 33* (1977) 389. b) The much greater kinetic stability of di-*tert*-butylketene compared with the parent ketene CH_2CO is well documented: M. S. Newman, A. Arkell, T. Fukunaga, *J. Am. Chem. Soc. 82* (1960) 2498.

[4] **4** has C_{3h} symmetry: IR (KBr): 2980 (m), 2960 (m), 2930 (m), 2870 (w), 1640 (s, C=C), 1340 (s), 1390 (w), 1375 (w), 1365 (m), 1245 (m), 1225 (w), 1170 (m), 1145 (w), 1130 (w), 1065 (vs), 960 (m), 940 (w), 850 (w), 830 (m). ^{1}H-NMR ($CDCl_3$): $\delta = 1.19$ (s, 18H, $6CH_3$), 1.26 (s, 18H, $6CH_3$). ^{13}C-NMR ($CDCl_3$): $\delta = 23.05$ (q, CH_3), 23.17 (q, CH_3), 44.95 (s, Me_2C–C), 91.45 (s, Me_2C–O), 111.08 (s, C=C–O), 153.48 (s, C=C–O).—Preparation of **6**: 1,1-Dibromo-2-trimethylsilylcyclopropane (5.44 g, 20 mmol) (prepared by addition of dibromocarbene to trimethylvinylsilane) was dissolved in THF (100 mL), Et_2O (20 mL), and pentane (20 mL). After addition of 12.5 mL of a 1.6 M solution of *n*-butyllithium (20 mmol) at −125 °C for 15 min, the mixture was stirred for 30 min at −110 °C and carboxylated by treatment with an excess of divided solid CO_2. Work-up gave a mixture (40 : 60, GC) of *exo*-bromo and *endo*-bromocarboxylic acids (1.65 g, 35%). After recrystallization from ether/pentane, 1-bromo-2-trimethylsilylcyclopropanecarboxylic acid (bromine *cis* to Me_3Si group) was isolated as a white solid, m.p. 135 °C, which was converted into **6** by treatment with $SOCl_2$.—**10b**: 90- and 270-MHz ^{1}H NMR, ABM system centered at $\delta = 1.50$, 2.03 and 2.23, with $J(AB) = 1$ Hz, $J(AM) = 10.5$ Hz and $J(BM) = 11.5$ Hz. ^{13}C NMR ($CDCl_3$): $\delta = 203.6$ (s, C=O), 45.8 (s, spiro C), 38.9 (m, CH_2), 32.7 (m, CH), −0.8 (q, $SiMe_3$).—**10a**: ^{1}H NMR (270 MHz, $CDCl_3$): $\delta = 0.075$, 0.079, 0.081 (3s, 27H, $3SiMe_3$), 1.44, 1.49, 1.56 (M part of ABM system, 3H), 1.94, 1.99, 2.06 (A part of ABM system, 3H), 2.11, 2.19, 2.29 (B part of ABM system, 3H); $J(AB) = 1$ Hz, $J(AM) = 10.5$ Hz, $J(BM) = 11.5$ Hz. Due to partial overlapping of signals only 12 of the expected 15 signals were observed in the ^{13}C NMR spectrum: $\delta = 203.6$, 203.5 (2s, C=O, only 2 signals), 45.9, 45.7, 45.6 (3s, spiro C), 38.0, 37.1, 36.7 (3m, CH_2), 33.3, 32.7 (2m, CH, only 2 signals), −0.7, −0.8 (2q, $SiMe_3$, only 2 signals).

[5] The least hindered dimer (Me_3Si groups *anti, trans*) was formed preferentially (57%), the sterically most hindered dimer (Me_3Si groups *syn, cis*) was formed in least amount (3.1%).

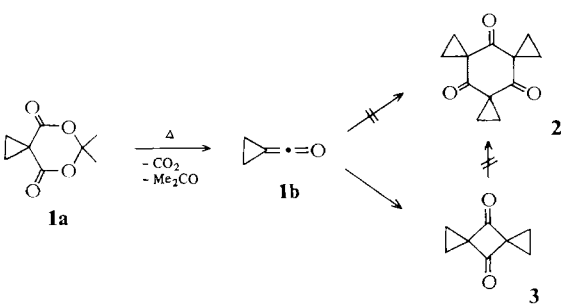
[6] S. Patai (ed.): *The Chemistry of Ketenes, Allenes and Related Compounds, Parts 1 and 2*. Wiley, Chichester 1980; D. Seebach in *Houben-Weyl: Methoden der Organischen Chemie, Vol. 4/4*, Thieme, Stuttgart 1971, p. 174; W. T. Brady, *Tetrahedron 37* (1981) 2949.

Trispiro[2.1.2.1.2.1]dodecane-4,8,12-trione**

By *H. M. R. Hoffmann,* Angela Walenta, Ulrike Eggert,* and *Dietmar Schomburg*

Dedicated to Professor Rolf Huisgen on the occasion of his 65th birthday

The title compound, **2**, is a new, simple, and potentially highly symmetric D_{3h} molecule which merits preparative and theoretical interest. We have confirmed that *free* carbonylcyclopropane, **1b**, which was generated by flash vapor thermolysis (FVT) from **1a** as described by *Brown* et al.,[1] cyclodimerizes to the dispirodiketone **3**.[1] There was no evidence for the formation of **2**.[2a] Similarly, attempts to prepare **2** by treatment of **3** with bases[3] remained unsuccessful.

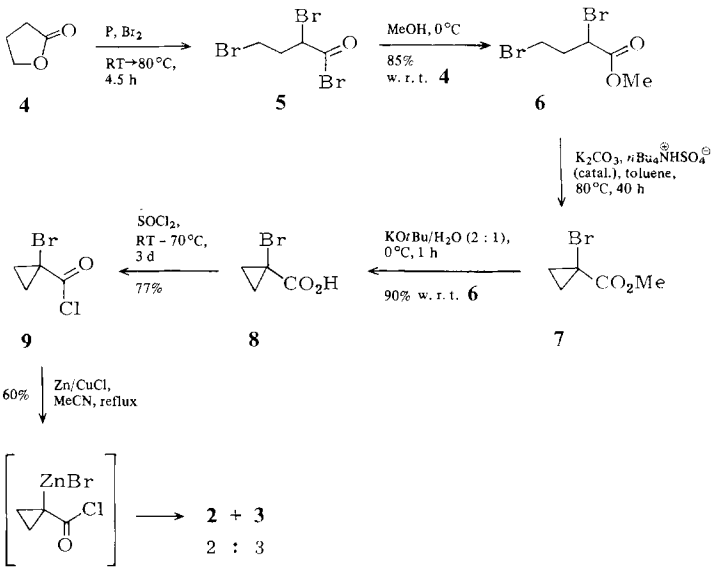


We have suggested that the novel formation of substituted 1,3,5-cyclohexanetriones from potential ketene precursors does not involve traditional ketenes, but rather organometallic intermediates, presumably 1-chloroformylcyclopropylzinc compounds.[2b] Accordingly, an attempt at the direct dehalogenative cyclotrimerization of 1-bromocyclopropanecarbonyl chloride, **9**, was of interest.

The preparation of 1-bromocyclopropanecarboxylic acid, **8**, by α-bromination of cyclopropanecarboxylic acid was not promising.[4] However, **8** could be synthesized readily from γ-butyrolactone, **4**. All the steps in Scheme 1 are simple and give high yields. Typically, 1-bromocyclopropanecarboxylic acid, **8**,[5a] (m.p. 78—80°C) and **9** (b.p. 80°C/~15 torr) were obtained in batches of 83 g and 60 g, respectively.

Earlier, dehalogenation of derivatives of **9** with zinc or magnesium in tetrahydrofuran under a wide variety of experimental conditions gave at best traces (<1%, GC) of cyclic trimer.[2b] However, dehalogenation with zinc-copper couple in dry, boiling acetonitrile furnished **2** and **3** in 61% yield (molar ratio 2:3): 1.9 g of **2** (m.p. 143—145°C) and 1.9 g of **3** after liquid-liquid extraction of the acetonitrile mother liquor with pentane.[6,7] The more lipophilic compound **2** was readily soluble in $CHCl_3$, whereas **3** was more polar and could be separated, e.g. by sublimation.

Our procedure for preparing trispirotriketone **2** is simple and efficient. Similarly to **2**, dione **3** is easily accessible in multigram quantities.



Scheme 1.

The X-ray crystal structure of **2**[8] shows that the presence of the trispirocyclopropane system necessitates a drastic flattening of the six-membered ring, as can be seen clearly from the six ring torsion angles (−10.9, 14.0, −5.0, −7.3, 10.4, −1.1°) and their absolute sum of 48.7°.

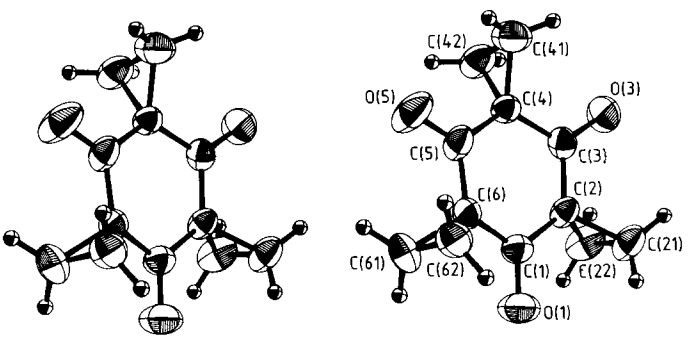
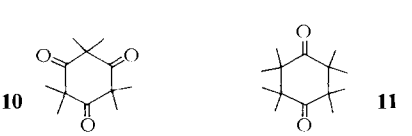


Fig. 1. Stereoview of **2**. Selected mean bond lengths [pm] and angles [°], ranges in brackets: C–C (internal) 147.5 (146.9—148.2), C–C (cyclopropyl, vicinal) 153.2 (151.1—154.4), C–C (cyclopropyl, distal) 144.6 (143.7—145.1), C–O 121.5 (121.4—121.8), C–H 92—99; C–C(O)–C 118.6 (118.4—118.9), C(O)–C–C(O) 120.7 (120.4—120.9), $C(H_2)$–C–$C(H_2)$ 56.3 (56.3—56.4), standard deviations for bond lengths are between 0.2 and 0.4 pm, for bond angles 0.2°.

By comparison, triketone **10** and diketone **11** have completely different geometries. In boat-like **10** the six ring torsion angles sum to 192°[9] and in chair-like **11** to 272.5°.[10] Note also that the six ring torsion angles in cyclohexane, which is slightly flattened, sum to 336°[11] compared with a value of 6 × 60° = 360° for "ideal" cyclohexane. Furthermore, the largest deviation from the least-squares plane of the six-membered ring in **2** is 8.6 pm; O(5) lies practically in the plane, whereas O(1) and O(3) are only 14 and 26 pm below and above the plane, respec-



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[+] X-ray crystal structure analysis.

[**] We thank the Fonds der Chemischen Industrie for continued financial support.

tively. The six internal angles are all within $119.7 \pm 1.2°$ and sum up to 718.1°, compared to 120° and 720° in benzene. Hence the six electrons of the C(21)–C(22), C(41)–C(42), and C(61)–C(62) cyclopropane backbone are well placed for a circumannular, conjugative interaction via the three carbonyl groups.

In this respect it should be mentioned that the distal cyclopropane bonds in **2** (mean value 144.6 pm) belong to the shortest single bonds so far found in cyclopropane ring systems.[12] These bonds, if shortened by interaction with an electron acceptor are usually in the range 145–150 pm, whereas the mean bond length in cyclopropane derivatives, calculated from 115 examples is 150.9(2) pm.[12] The bond lengths in the six-membered ring of trispirotriketone **2** are also very short when compared to the standard C–C bond length of 154 pm or the comparable mean internal C–C length of 152.1 pm in **10**.

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CAS Registry numbers:
2, 96999-00-7; **3**, 59078-46-5; **4**, 96-48-0; **5**, 52412-07-4; **6**, 29547-04-4; **7**, 96999-01-8; **8**, 89544-84-3; **9**, 96999-02-9.

[1] G. J. Baxter, R. F. C. Brown, F. W. Eastwood, K. J. Harrington, *Tetrahedron Lett. 1975*, 4283; see also J. L. Ripoll, *Tetrahedron 33* (1977) 389.

[2] a) C. Sabieraj, unpublished experiments; b) J.-M. Wulff, H. M. R. Hoffmann, *Angew. Chem. 97* (1985) 597; *Angew. Chem. Int. Ed. Engl. 24* (1985) 605.

[3] The base-catalyzed rearrangement of certain non-enolizable 1,3-cyclobutanediones into 1,3,5-cyclohexanetriones has been observed: J. L. E. Erickson, F. E. Collins, Jr., B. L. Owen, *J. Org. Chem. 31* (1966) 480; J. L. E. Erickson, G. C. Kitchens, *ibid. 27* (1962) 460. However, **3** has four spiroactivated methylene carbons, and on treatment with nucleophiles presumably suffers homoconjugate Michael addition.

[4] Cf. H. W. Pinnick, Y. H. Chang, S. C. Foster, M. Govindan, *J. Org. Chem. 45* (1980) 4505; P. M. Warner, D. Le, *ibid. 47* (1982) 893; E. G. E. Jahngen, D. Phillips, R. J. Kobelski, D. M. Demko, *ibid. 48* (1983) 2472; I. Reichelt, H.-U. Reissig, *Chem. Ber. 116* (1983) 3895; *Liebigs Ann. Chem. 1985*, 650; L. A. Paquette, C. Blankenship, G. J. Wells, *J. Am. Chem. Soc. 106* (1984) 6442.

[5] a) Preparation of **8** by another route: J. P. Barnier, G. Rousseau, J. M. Conia, *Synthesis 1983*, 915; P. Bruylants, *Bull. Soc. Chim. Belg. 32* (1923) 358. b) Cf. also L. Fitjer, *Chem. Ber. 115* (1982) 1035; we thank Professor *Fitjer* for a sample of **9**.

[6] Other recent applications of this technique: H. M. R. Hoffmann, K. Haase, *Synthesis 1981*, 715; H. M. R. Hoffmann, L. Iranshahi, *J. Org. Chem. 49* (1984) 1174 and intervening papers.

[7] *Experimental procedure:* A solution of **9** (17.5 g, 95 mmol) in absolute acetonitrile (25 mL) was added dropwise to a suspension of zinc (18.7 g, 0.29 mol) and copper(I) chloride (0.28 g, 2.9 mmol) in acetonitrile (25 mL), previously warmed to 40°C. During addition of **9** the reaction mixture was allowed to reflux. The mixture was refluxed for a further 30 min, allowed to reach room temperature and the products were extracted with pentane. Column filtration (silica gel, pentane) furnished white crystals (3.9 g, 61%) of **2** + **3** (molar ratio **2** : **3** = 2 : 3 by ^{1}H-NMR). The bulk of **3** was removed by sublimation, leaving **2** which was purified by chromatography on silica gel. Spectroscopic data of **2**: IR (KBr): 3120 (w), 3020 (w) (cyclopropane C–H), 1668 (s) (C=O), 1358 (s), 1110 (s) cm^{-1}. ^{1}H-NMR ($CDCl_3$): $\delta = 1.98$ (s). ^{13}C-NMR ($CDCl_3$): $\delta = 29.26$ ($6CH_2$), 40.68 (3 spiro C), 202.22 (3 C=O); $^1J_{C,H} = 169$ Hz.

[8] *X-ray structure analysis:* $P2_1/c$, $a = 8.550(2)$, $b = 15.665(6)$, $c = 8.408(2)$ Å, $\beta = 118.49(3)°$, $\rho_{calc} = 1.370$ g cm^{-3}, 1355 observed of 1746 independent reflections [$I \geq 1.25\sigma(I)$], $R = 0.048$, Syntex-$P2_1$-diffractometer, $Mo_{K\alpha}$ radiation ($\lambda = 0.71069$ Å), $2\theta_{max} = 50°$. Further details of the crystal structure investigation are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW (England).

[9] H. M. R. Hoffmann, M. B. Hursthouse, L. New, *Tetrahedron 37* (1981) 1967.

[10] H. M. R. Hoffmann, M. B. Hursthouse, *J. Am. Chem. Soc. 98* (1976) 7449.

[11] H. R. Buys, H. J. Geise, *Tetrahedron Lett. 1970*, 2991; R. Bucourt, *Top. Stereochem. 8* (1974) 159.

[12] Review: F. H. Allen, *Acta Crystallogr. B 36* (1980) 81.

First 1,4-Dipolar Cycloadditions of 6-Oxo-3,6-dihydro-1-pyrimidinium 4-Olates to Ketenes and Other Carbonyl Compounds**

By *Hans Gotthardt** and *Karl-Heinz Schenk*

Dedicated to Professor Rolf Huisgen on the occasion of his 65th birthday

6-Oxo-3,6-dihydro-1-pyrimidinium 4-olates of type **3** are capable of undergoing [4 + 2]-cycloadditions to certain CC-multiple bond systems,[1] and even to singlet oxygen;[2] such additions have opened up interesting entries to pyridone derivatives and heterobicycles. In contrast, analogous [4 + 2]-cycloadditions of **3** to CO double bonds have so far never been described. We report here on an improved synthesis of **3** and on the first 1,4-dipolar cycloadditions of **3** to ketenes, formaldehyde, hexafluoroacetone, and mesoxalates. These reactions lead to the formation of novel stable primary adducts in high yields.

The synthesis of compounds **3a**, **b**[3] unsubstituted in position 5 has hitherto only been accomplished by reaction of the amidines **2** with carbon suboxide. The preparation of carbon suboxide from malonic acid, however, is somewhat expensive and yields of only 10–20% are obtained.[4] More advantageous is the synthesis of **3a**, **b** via modification of the known method[5] of heating a dry equimolar mixture of **2** and bis(2,4,6-trichlorophenyl) malonate **1** to 140–170°C/< 0.01 torr, whereby the liberated 2,4,6-trichlorophenol is immediately distilled off from the melt. Recrystallization of the melt from ethanol affords **3a** or **3b**. The new compounds **3c–e** (Table 1) and **7**[6] are obtained analogously from **2** or **6**, respectively, and bis(2,4,6-trichlorophenyl) methylmalonate **1**.

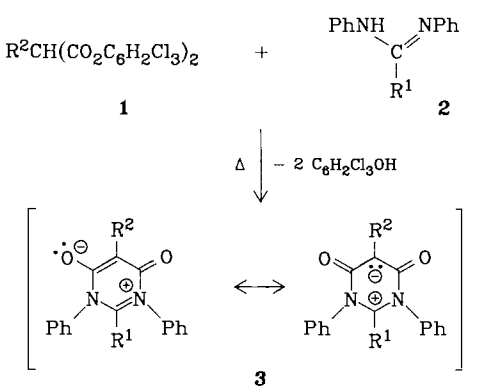


Table 1. 6-Oxo-1,3-diphenyl-3,6-dihydro-1-pyrimidinium 4-olates **3** from bis(2,4,6-trichlorophenyl) malonates **1** and *N,N'*-diphenylamidines **2**.

3	R^1	R^2	Yield [%]	M.p. [°C] [a]	IR (KBr) ν(C=O) [cm^{-1}]
a [b]	Me	H	79 (71)	248–249 (260–261)	
b [b]	Ph	H	65 (76)	255–257 (255–257)	
c	H	Me	71	229–230	1670
d	Me	Me	98	286–287	1655
e	Ph	Me	78	291–292	1678, 1640

[a] Decomposition. [b] Data quoted in the literature [3] given in brackets.

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When **3a** is allowed to react with diphenylketene (molar ratio 1 : 1.27) in acetonitrile at 20°C, colorless needles of **4a** crystallize out whose structure and composition are consistent with the elemental analysis and spectroscopic data.[7] The mode of addition of the ketene in **4a** follows quite clearly from the ^{13}C-NMR spectrum, which shows the resonances of C-1 and C-4 at $\delta = 101.11$ and 58.24, respectively. The opposite mode of addition would lead to bonding of the oxygen with the unsubstituted C-atom, and the ^{13}C-resonance would then be shifted downfield to $\delta = 84.80$.[2] In an analogous way, **3b** and diphenyl ketene or dimethyl ketene afford, after crystallization from ethyl acetate/hexane, **4b** and **4c**,[7] respectively (Table 2).

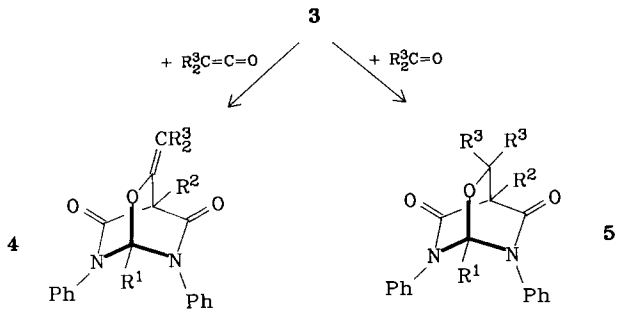


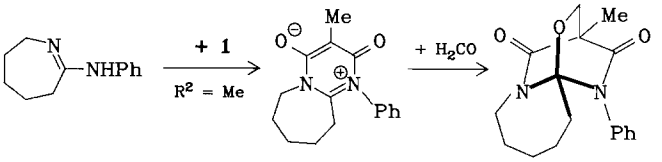
Table 2. 6,7-Diphenyl-2-oxa-6,7-diazabicyclo[2.2.2]octane-5,8-diones **4** and **5** as primary adducts from **3** and carbonyl compounds.

	R^1	R^2	R^3	Yield [%]	M.p. [°C]
4a	Me	H	Ph	74	173.5—174.5 [a]
4b	Ph	H	Ph	88	191—193 [a]
4c	Ph	H	Me	93	174—177 [a]
5a	Ph	H	H	83	175—177
5b	H	Me	H	99	176.5—177
5c	Me	Me	H	68	224—225 [a]
5d	Me	Me	CF_3	87	286—287 [a, b]
5e	H	Me	CO_2Et	88	130—131
5f	Ph	Me	CO_2Et	74	149.5—150 [a]

[a] Decomposition. [b] On heating, decomposes into hexafluoroacetone and **3b**, recognized by its melting point.

The solvent has very little influence on the rate constant k_2 of the cycloaddition of **3a** to diphenyl ketene; k_2 shows an inverse dependence on the solvent polarity, as indicated by the ratio k_2(dioxane)/k_2(acetonitrile) = 2.5. This suggests a diminution in charge in the transition state and is consistent with a concerted mechanism. Analogous inverse solvent dependencies of the same order of magnitude have also been observed in the [3 + 2]-cycloadditions of the sydnones to alkynes,[8] whereas the k_2 values in the multistep [2 + 2]-cycloadditions of tetracyanoethene, which proceed via dipolar intermediates, increase with increasing solvent polarity by factors of up to 63 000.[9]

The 1,4-dipolar cycloadditions of **3a**, **b** to the CO-double bond of ketenes are remarkable, since reaction of ketenes with 1,3-dienes usually yields cyclobutanone derivatives according to a [$_\pi$2$_s$ + $_\pi$2$_a$] process, with the CC double bond of the ketene functioning as antarafacial component.[10, 11] Since the concerted [4 + 2]-cycloadditions of 1,3-dienes to the ketene CC double bond are thermally forbidden as a [$_\pi$4$_s$ + $_\pi$2$_a$] process according to the rules of conservation of orbital symmetry,[11] ketenes apparently do not react with the CC double bond, but specifically and regioselectively with the CO double bond of **3a**, **b** in the sense of a thermally allowed [$_\pi$4$_s$ + $_\pi$2$_s$]-cycloaddition to give the sterically more demanding adducts **4a–c**.



6 **7** **8**

Even formaldehyde—generated in situ from paraformaldehyde by depolymerization at 110°C—reacts with **3b–d** or **7** regiospecifically to give the adducts **5a–c** and **8**,[12] while hexafluoroacetone already combines with **3d** at 0°C to give **5d**.[13] Furthermore, diethyl mesoxalate cycloadds to **3c**, **e** at 110°C with formation of **5e**, **f**.[14] The uniform regiochemistry in the adducts **5** follows from the ^{13}C-NMR spectra.

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1a, 15781-70-1; **1c**, 15781-71-2; **2a**, 621-09-0; **2b**, 2556-46-9; **2c**, 622-15-1; **3a**, 33821-87-3; **3b**, 33821-84-0; **3c**, 96807-23-7; **3d**, 61201-42-1; **3e**, 61201-43-2; **4a**, 96807-24-8; **4b**, 96807-25-9; **4c**, 96807-26-0; **5a**, 96807-27-1; **5b**, 96807-28-2; **5c**, 96807-29-3; **5d**, 96807-30-6; **5e**, 96807-31-7; **5f**, 96807-32-8; **6**, 4903-40-6; **7**, 96807-33-9; **8**, 96807-34-0; $Ph_2C{=}C{=}O$, 525-064; $Me_2C{=}C{=}O$, 598-26-5; H_2CO, 50-00-0; $(F_3C)_2CO$, 684-16-2; $(EtOCO)_2CO$, 609-09-6.

[1] Review: W. Friedrichsen, T. Kappe, A. Böttcher, *Heterocycles 19* (1982) 1083.
[2] H. Gotthardt, K.-H. Schenk, *Tetrahedron Lett. 24* (1983) 4669.
[3] K. T. Potts, M. Šorm, *J. Org. Chem. 37* (1972) 1422.
[4] A. Stock, H. Stoltzenberg, *Ber. Dtsch. Chem. Ges. 50* (1917) 498.
[5] T. Kappe, W. Lube, *Monatsh. Chem. 102* (1971) 781.
[6] **7**: 81%, m.p. 232—233°C (decomp.); IR (KBr): $\nu = 1645$ cm^{-1} (C=O).
[7] **4a**: IR (KBr): $\nu = 1729$, 1695 (C=O), 1646 cm^{-1} (C=C); ^{1}H NMR (90 MHz, $CDCl_3$, TMS): $\delta = 1.39$ (s, Me), 4.77 (s, 4-H), 7.13—7.60 (m, 4 Ph); ^{13}C{^{1}H} NMR ($CDCl_3$): $\delta = 22.05$ (Me), 58.24 (C-4), 101.11 (C-1), 164.88 (2 C=O) and further signals.—**4c**: ^{1}H NMR ($CDCl_3$): $\delta = 1.88$ (s, Me), 2.02 (s, Me), 4.85 (s, 4-H), 6.65-7.28 (m, 3 Ph).
[8] R. Huisgen, H. Gotthardt, *Chem. Ber. 101* (1968) 1059.
[9] R. Huisgen, *Acc. Chem. Res. 10* (1977) 117.
[10] Cf., e.g.: R. Huisgen, P. Otto, *Tetrahedron Lett. 1968*, 4491; D. Borrmann in Houben-Weyl-Müller: *Methoden der organischen Chemie, Vol. VII/4*, 4th ed., Thieme, Stuttgart 1968, p. 53.
[11] R. B. Woodward, R. Hoffmann, *Angew. Chem. 81* (1969) 797; *Angew. Chem. Int. Ed. Engl. 8* (1969) 781.
[12] **5a**: IR (KBr): $\nu = 1731$, 1699 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$): $\delta = 4.05$ (t, $J = 1.65$ Hz, CH_2–CH), 4.60 (d, $J = 1.65$ Hz, CH_2–CH), 6.73—7.27 (m, 3 Ph); MS (70 eV): m/z 370 (M^+, 4%).—**5b**: ^{1}H-NMR ($CDCl_3$): $\delta = 1.51$ (s, Me), 4.02 (s, CH_2), 6.52 (s, 1-H), 7.30 (mc, 2 Ph).—**5c**: ^{1}H NMR ($CDCl_3$): $\delta = 1.23$ (s, Me), 1.52 (s, Me), 4.13 (s, CH_2), 7.12-7.62 (m, 2 Ph); ^{13}C{^{1}H} NMR ($CDCl_3$): $\delta = 9.69$ (Me), 22.62 (Me), 52.13 (C-4), 67.73 (C-3), 99.12 (C-1), 169.23 (2 C=O) and further signals.—**8**: 89%, m.p. = 149.5–151°C; ^{1}H NMR ($CDCl_3$): $\delta = 1.10$–2.10 (m, 8 H), 1.43 (s, Me), 2.82-3.10 (m, NCH), 3.91 (s, OCH_2), 4.26-4.50 (m, NCH), 6.90–7.43 (m, Ph).
[13] **5d**: IR (KBr): $\nu = 1745$, 1718, 1709 cm^{-1} (C=O); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.39$ (s, Me), 1.78 (s, Me), 7.16-7.58 (m, 2 Ph); ^{13}C{^{1}H} NMR ($CDCl_3$): $\delta = 9.04$ (Me), 22.28 (Me), 55.63 (C-4), 99.30 (C-1), 122.03 (q, $J_{CF} = 291.4$ Hz, $2CF_3$), 165.04 (2 C=O) and further signals; MS (70 eV): m/z 458 (M^+, 3%).
[14] **5e**: IR (KBr): $\nu = 1768$, 1745, 1712 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$): $\delta = 1.24$ (t, $J = 7.1$ Hz, CH_2–CH_3), 1.77 (s, Me), 4.31 (q, $J = 7.1$ Hz, CH_2–CH_3), 6.67 (s, 1 H), 7.41 (mc, 2 Ph); ^{13}C{^{1}H} NMR ($CDCl_3$): $\delta = 9.79$ (Me), 13.80 (2 Me), 58.45 (C-4), 63.12 ($2OCH_2$), 81.36 (C-3), 94.45 (C-1), 164.19 (2 C=O), 165.19 (2 C=O) and further signals; MS (70 eV): m/z 452 (M^+, 35%).

1,1- and 1,*o*-Dilithioallyl Phenyl Sulfone: Synthesis, Geminal Cycloalkylation, and Lithium-Titanium Exchange**

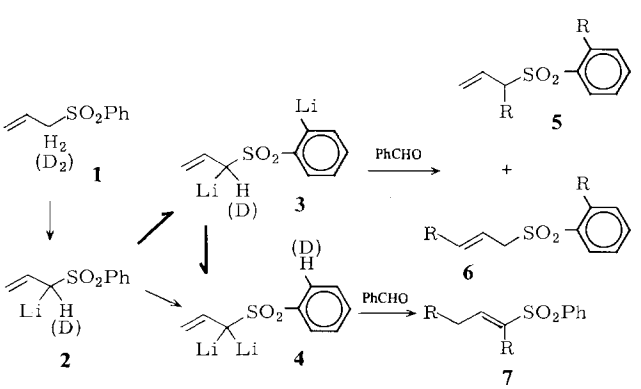
By *Jürgen Vollhardt, Hans-Joachim Gais,** and *Karl L. Lukas*

Ab initio calculations for monomeric 1,1- and 1,3-dilithiopropene gave as an energy minimum an unusual doubly lithium-bridged structure, characterized by *Streitwieser* et al.[1] as an "ion triplet of two lithium cations and a propenylidene dianion." 1,1-Dilithiopropenes containing a sulfonyl group in the 1-position, which is capable of complexing lithium and which is preparatively useful in a variety of ways, are of great interest with regard to their structure in solution and in the crystal as well as their synthetic potential. We describe here the synthesis of 1,1-dilithioallyl phenyl sulfone **4**, the first compound of this type, and that of its isomer **3** as well as their geminal cycloalkylation and lithium-titanium exchange.

The second lithiation of 1-lithioallyl phenyl sulfone **2**, prepared from phenyl 2-propenyl sulfone **1**, proceeds in a remarkable fashion: in tetrahydrofuran (THF) at low temperatures, one equivalent of *n*BuLi metalates **2** in the position *ortho* to the sulfonyl group[2] to give **3** in a kinetically controlled reaction with high selectivity; metalation in the 1-position to give **4** occurs as well. The selectivity decreases with increasing temperature. Upon warming **3** to 50°C in THF, complete transmetalation to the thermodynamically more stable 1,1-dilithio species **4** takes place. The metalation of **2** and the transmetalation of **3** can be followed by ^{1}H-NMR spectroscopy.

In THF at −50°C, **3** reacts with excess benzaldehyde to give the 1,*o*- and 3,*o*-(*E*)-diadducts **5** (74%) and **6** (4%), respectively, while **4** affords the 1,3-(*E*)-diadduct **7** in nearly the same yield (77%).

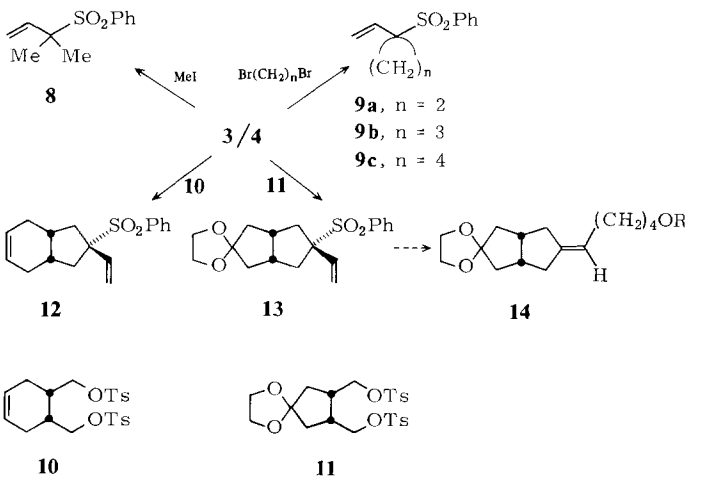
When [1-D_1]-**2** is lithiated, a mixture of [1-D_1]-**3/4** is obtained, which upon warming to 50°C is completely converted into [*o*-D_1]-**4/4** within 2 h; after protonation with HCl/H_2O/THF, [*o*-D_1]-**1/1** is obtained and its composition determined by ^{1}H-NMR spectroscopy. At −35°C in THF, **2** is lithiated with 90% selectivity and [1-D_1]-**2** with 97% selectivity by *n*BuLi.[3]



Scheme 1. R = PhCH(OH).

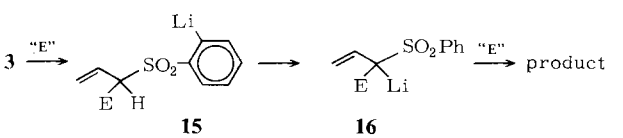
4 is only sparingly soluble in THF and remarkably stable. After 4 h at 50°C, deuteration with DCl/D_2O/THF (0°C) still afforded 82% [1,1-D_2]-**1** (degree of deuteration ≥98%). Interestingly, **4** reacts with CF_3CO_2D in THF (0°C), undergoing both 1,1- and 1,3-dideuteration, to give a 1:1 mixture of [1,1-D_2]-phenyl 2-propenyl sulfone ([1,1-D_2]-**1**) and [1,3-D_2]-phenyl 1-propenyl sulfone (*E*:*Z* = 17:1) (degree of deuteration ≥95% in each case).

The dialkylation of **4** with methyl iodide (THF, −50°C) proceeds regioselectively (≥98%) to give the 1,1-dimethylallyl sulfone **8** (80%). The same is observed for the cycloalkylation of **4** with 1,ω-dibromoalkanes (THF, 0°C) to give the carbocyclic compounds **9a** (44%), **9b** (80%), and **9c** (89%). By geminal cycloalkylation of **4** with the ditosylates **10** and **11**[4] (THF, 25°C), it is possible to synthesize the new bicyclic compounds **12** (77%, *ds* = 70%) and **13** (82%, *ds* = 90%), respectively, in high yield and with high diastereoselectivity (*ds*); these compounds are geminally disubstituted with a vinyl and a phenylsulfonyl group. **13** could eventually be converted by "γ-substitution" with lithium dialkylcuprates[5] into the 6a-carbaprostacyclin[6] precursor **14** (Scheme 2).



Scheme 2.

Surprisingly, nearly the same results are obtained for the methylation and the cycloalkylation of the 1,*o*-dilithio compound **3**. The initial alkylation of **3** in the 1-position to give the *o*-lithiophenyl sulfone **15** is followed by complete transmetalation to the 1-lithioallyl sulfone **16** (Scheme 3), which affords **8**, **9**, **12**, or **13** upon a second alkylation or upon cycloalkylation.[7]



Scheme 3.

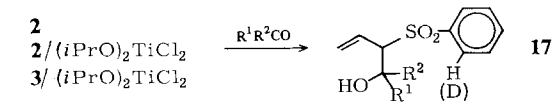
2 reacts regioselectively with benzaldehyde and cyclopentanone (THF, −70°C) to give the 1-adducts **17a** (85%, 1:1 diastereomeric mixture) and **17b** (92%), respectively. Very similar results are obtained when **2** is first converted into the allyltitanium species with one equivalent of $(iPrO)_2TiCl_2$ (THF, −50°C), which is then allowed to react with the carbonyl compound (THF, 0°C): 82% **17a** and

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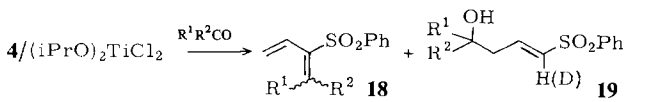
[**] This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.

91% **17b**. The titanation[8] of the 1,*o*-dilithio compound **3** with one equivalent of $(i\mathrm{PrO}_2)\mathrm{TiCl}_2$ (THF, −40°C; color change from orange to red) affords a reactive titanium species, which gives [*o*-D_1]-**17b** (degree of deuteration 85%) in 76% yield upon reaction with cyclopentanone (THF, 0°C) followed by DCl/D_2O work-up.



a: R^1 = Ph, R^2 = H; **b**: $R^1 - R^2$ = $-(CH_2)_4-$

The lithium-titanium exchange is achieved for the 1,1-dilithio species **4** if it is allowed to react with $(i\mathrm{PrO})_2\mathrm{TiCl}_2$ at −70°C in THF and the solution is then warmed to −10°C; a novel organotitanium compound is formed, which until now has only been prepared as a deep red solution. It is deuterated to [1,1-D_2]-**1** (78%, degree of deuteration ≥98%) similarly to **4** with DCl/D_2O; however, in contrast to **4**, it does not react with methyl iodide under the same conditions. With aldehydes (THF, −50°C) and ketones (THF, −50 to 0°C), on the other hand, both the dienes **18** and the 3-adducts **19** are obtained, which, upon trapping with DCl/D_2O, are shown to contain deuterium in the 1-position (e.g., [1-D_1]-**19a**, degree of deuteration 90% (Scheme 4).

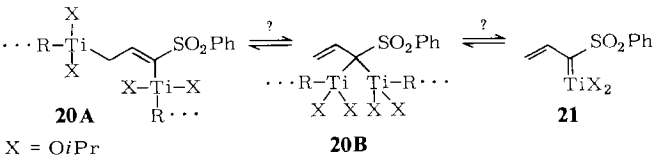


	R^1	R^2	[%]	[%]
a:	Ph	H	5 (*E*)	77 (*E*)
b:	*t*Bu	H	5 (*E*)	68 (*E*)
c:	Cl_3C	H	–	73 (*E*)
d:	Me	H	38 (*E* : *Z* = 3:2)	41 (*E* : *Z* = 9:1)
e:	Ph	Me	48 (*E* : *Z* = 9:1)	31 (*E*)
f:	$-(CH_2)_4-$		73	

Scheme 4.

The fact that sterically hindered aldehydes react with **4**/$(i\mathrm{PrO})_2\mathrm{TiCl}_2$ to form selectively the 3-(*E*)-adducts **19** could be synthetically useful since **2** and **2**/$(i\mathrm{PrO})_2\mathrm{TiCl}_2$ as well as **3**/$(i\mathrm{PrO})_2\mathrm{TiCl}_2$ give selectively the 1-adduct **17**. The reaction of **4**/$(i\mathrm{PrO})_2\mathrm{TiCl}_2$ with cyclopentanone to give the carbonyl olefination product **18f** in good yield is also promising.

The following finding deserves attention in connection with the structure of the titanium species formed by metal exchange on **4**: when one equivalent of lithium diisopropylamide is added at −50°C to the allyltitanium species formed from **2** (one equivalent $(i\mathrm{PrO})_2\mathrm{TiCl}_2$, THF, −50°C) and the mixture warmed to −10°C, a deep red solution (color change from orange to red) is obtained, from which, after addition of benzaldehyde, 34% of the 1-adduct **17a**, 4% of the diene **18a**, and 47% of the 3-adduct **19a** (*E*:*Z* = 3:2) are obtained. The results of the reaction of **4**/$(i\mathrm{PrO})_2\mathrm{TiCl}_2$ with carbonyl compounds can be explained by the presence of a titanium species that contains the partial structures **20A** and **20B**, which are interconvertible;[9] another possibility is the alkylidenetitanium complex **21**.



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1, 16212-05-8; [1,1-D_2]-**1**, 97072-58-7; **2**, 97072-31-6; [1-D_1]-**2**, 97072-59-8; **3**, 97072-32-7; [1-D_1]-**3**, 97072-60-1; **4**, 97072-33-8; [*o*-D_1]-**4**, 97072-61-2; **5**, 97072-34-9; **6**, 97072-35-0; **7**, 97102-06-2; [*o*-D_1]-**7**, 97072-62-3; **8**, 72863-20-8; **9a**, 97072-36-1; **9b**, 97072-43-0; **9c**, 97072-44-1; **10**, 32970-96-0; **11**, 97072-37-2; **12**, 97072-38-3; **13**, 97072-39-4; **14**, 97072-40-7; **17a**, 97072-41-8; **17b**, 97072-42-9; [*o*-D]-**17b**, 97072-65-6; **18a**, 97072-45-2; **18b**, 97072-47-4; (*E*)-**18d**, 97072-50-9; (*Z*)-**18d**, 97072-51-0; (*E*)-**18e**, 97072-54-3; (*Z*)-**18e**, 97072-55-4; **18f**, 97072-57-6; (*E*)-**19a**, 97072-46-3; (*Z*)-**19a**, 97072-66-7; [1-D]-**19a**, 97072-67-8; **19b**, 97072-48-5; **19e**, 97072-49-6; (*E*)-**19d**, 97072-52-1; (*Z*)-**19d**, 97072-53-2; **19e**, 97072-56-5; $(i\text{-Pro})_2\mathrm{TiCl}_2$, 762-99-2; $Br(CH_2)_2Br$, 106-93-4; $Br(CH_2)_3Br$, 109-64-8; $Br(CH_2)_4Br$, 110-52-1; PhCHO, 100-52-7; *t*-BuCHO, 630-19-3; Cl_3CCHO, 75-87-6; MeCHO, 75-07-0; PhCOMe, 98-86-2; (*E*)-[1,3-D_2]-phenyl 1-propenyl sulfone, 97072-63-4; (*Z*)-[1,3-D_2]-phenyl 1-propenyl sulfone, 97072-64-5; cyclopentanone, 120-92-3.

[1] D. Kost, J. Klein, A. Streitwieser, Jr., G. W. Schriver, *Proc. Natl. Acad. Sci. USA 79* (1982) 3922; cf. P. von R. Schleyer, A. J. Kos, *J. Chem. Soc. Chem. Commun. 1982*, 449.
[2] H. W. Gschwend, H. R. Rodriguez, *Org. React. 26* (1979) 1.
[3] The lower *o*-selectivity of the lithiation of **2** in comparison with that of [1-D_1]-**2** could be caused by the isotope effect or, alternatively, it may be only apparent due to transmetalation during the trapping of **3** with benzaldehyde (see Scheme 3).
[4] Synthesis of **11** from *cis*-4-cyclohexene-1,2-dimethanol: H.-J. Gais, *Habilitationsschrift*, Technische Hochschule Darmstadt 1981.
[5] Cf. Y. Masaki, K. Sakuma, K. Kaji, *J. Chem. Soc. Chem. Commun. 1980*, 434.
[6] P. A. Aristoff, *J. Org. Chem. 46* (1981) 1954, and references cited therein.
[7] The deuteration of **3** is also accompanied by transmetalation: [*o*-$D_{0.7}$/1-$D_{1.3}$]-**1** is obtained with CF_3CO_2D and [*o*-$D_{0.4}$/1-$D_{1.6}$]-**1** with DCl/D_2O.
[8] M. T. Reetz, *Top. Curr. Chem. 106* (1982) 1; B. Weidmann, D. Seebach, *Angew. Chem. 95* (1983) 12; *Angew. Chem. Int. Ed. Engl. 22* (1983) 31.
[9] We thank a referee for this suggestion.

Reaction of Homobenzvalene with Tetracyanoethylene; Formation of a Tetracyanodihydrobarbaralane Derivative and a Tetracyanocyclopropane Derivative**

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Dedicated to Professor Rolf Huisgen on the occasion of his 65th birthday

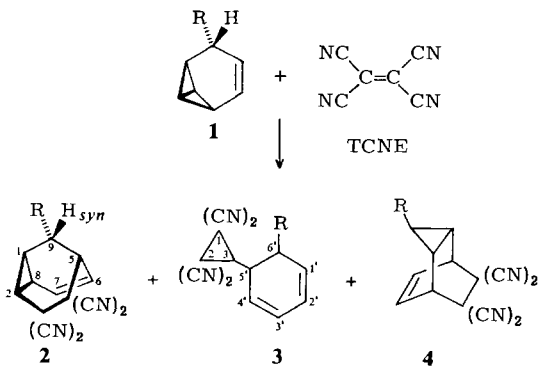
The reactions of tetracyanoethylene (TCNE) and 5,6-dichloro-2,3-dicyano-*p*-benzoquinone with benzvalene recently reported by us constitute the first documented examples of the long sought after one-step 1,4-cycloaddition of an alkene to a vinylcyclopropane.[1a] As a

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$[(\sigma 2_s + \pi 2_s) + \pi 2_s]$ process, this reaction is closely related to the Diels-Alder addition.[1b] However, the TCNE adduct concerned, a dihydrosemibullvalene derivative, is formed in a yield of only a few percent. The major products arise from a zwitterionic intermediate which is formed by addition of TCNE to the benzvalene π-bond.

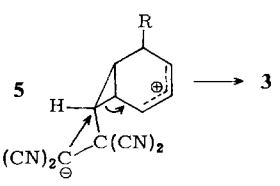
We have now obtained a 5.0 : 1.2 : 1.0 mixture of the 1 : 1 adducts **2a**—**4a** in 43% yield by reaction of homobenzvalene **1a**[2] with TCNE in acetonitrile at −15 to 20°C. **2a** and **3a** were isolated in pure form by extraction and crystallization. Reaction of 5-methylhomobenzvalene **1b**[3a] and TCNE under the same conditions afforded a 10 : 1 mixture of **2b** and **3b** in 50% yield, from which pure **2b** was isolated by recrystallization.[*]



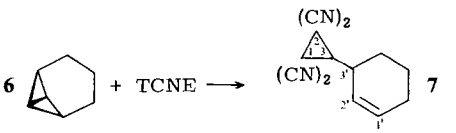
a, R = H; **b**, R = CH_3

The structure of the compounds **2** was deduced from the NMR spectra (Table 1). The ^{13}C-NMR data of **2a**, in particular, indicate the presence of a double bond and a cyclopropane moiety; the H,H-coupling constants rule out other possible combinations of the structural units, e.g. those with the CH_2-group adjacent to the double bond. The structure of **3a** was elucidated by X-ray analysis.[3b] The identity of **4a** was established by comparison of its NMR signals with those of the authentic substance.[4]

Other than in the case of benzvalene,[1a] in the case of homobenzvalene the 1,4-cycloaddition is the main reaction. However, because of the lower symmetry of **1a**, it is not possible to demonstrate the one-step mode of this reaction by labeling with deuterium. If zwitterionic intermediates are taken into consideration, then, because of the localization of the HOMO of **1a**,[5] it must be assumed that TCNE does not attack the double bond but rather the bicyclo[1.1.0]butane system, with rupture of a lateral bond.[6] The species **5** thus formed could then cyclize to **2**. Since, however, the product of the second possible mode of ring closure, namely at the other end of the allyl-cation system, was not found, even though this route would not be disfavored as regards ring strain, and the formation of a five-membered instead of a seven-membered ring would even be favored entropically, we consider the route to **2** via **5** as unlikely and prefer the $[(\sigma 2_s + \pi 2_s) + \pi 2_s]$ process.



On the other hand the formation of **3** from **5** via intramolecular nucleophilic substitution with making and breaking of a cyclopropane bond is plausible. The zwitterion **5a** is possibly also the precursor for **4a**. As such, **5a** would then have to decompose to TCNE and cycloheptatriene, which could then react further to give the known Diels-Alder adduct **4a**.[7] However, the possibility that a radical-ion pair of **1a** and TCNE serves as precursor for cycloheptatriene cannot be ruled out.



In the proposed mechanism for the formation of **3**, the double bond of **1** is inessential; it merely stabilizes the cationic center. Thus, the dihydro derivative of **1**, tricyclo[4.1.0.0^{2,7}]heptane **6**,[6a,8] reacts with TCNE in acetonitrile at 20°C to give the analogue of **3**, compound **7**, as the sole homogeneous product in 38% yield.

If benzvalene and homobenzvalene react with TCNE to give the rearranged products according to the mechanism

Table 1. Some properties of the new compounds [a].

2a: m.p. 189—191°C (from CCl_4). ^{1}H NMR: $\delta = 1.77$ (ddd, $J_{1,9anti} = 1.6$, $J_{5,9anti} = 3.8$, $J_{9,9} = 14.7$ Hz; 9-H_{anti}), 2.25 (m, 8-H), 2.26 (m, 1-H), 2.52 (dd, $J_{1,2} = 7.5$, $J_{2,8} = 8.0$ Hz; 2-H), 2.55 (dtt, $J_{1,9syn} = J_{5,9syn} = 2.5$, $J_{6,9syn} = J_{8,9syn} = 1.2$ Hz; 9-H_{syn}), 3.54 (dddd, $J_{1,5} = 1.3$, $J_{5,6} = 7.0$ Hz; 5-H), 6.16 (ddt, $J_{6,7} = 9.3$, $J_{6,8} = 1.1$ Hz; 6-H), 6.47 (ddd, $J_{1,7} = 1.5$, $J_{7,8} = 4.8$ Hz; 7-H). ^{13}C NMR: $\delta = 14.47$ (d, 173 Hz), 17.74 (d, 171 Hz), 19.41 (d, 169 Hz) (C-1,2,8); 18.97 (t, 133 Hz; C-9); 37.13 (d, 146 Hz; C-5); 37.90, 42.35 (in each case s; C-3,4); 112.10, 112.63, 113.50, 113.68 (in each case s; 4CN); 123.13 (d, 171 Hz), 133.27 (d, 164 Hz) (C-6,7)

2b: m.p. 170—171°C (from CCl_4). ^{1}H NMR: $\delta = 1.01$ (d, $J_{9,CH_3} = 6.6$ Hz; CH_3), 2.15 (≈tt, $J_{1,2} = 7.5$, $J_{1,8} = 8.0$, $J_{1,5} = J_{1,9} = 2.1$ Hz; 1-H); 2.24 (tdt, $J_{2,8} = 8.0$, $J_{7,8} = 6.0$, $J_{6,8} = J_{8,9} = 1.2$ Hz; 8-H), 2.63 (≈t; 2-H), 2.74 (m; 9-H), 3.42 (dt, $J_{5,6} = 7.0$, $J_{5,9} = 2.1$ Hz; 5-H), 5.98 (ddt, $J_{6,7} = 9.3$, $J_{6,9} = 1.1$ Hz; 6-H), 6.52 (dd; 7-H). ^{13}C NMR: $\delta = 17.13$, 21.51, 22.47 (in each case d; C-1,2,8); 17.32 (q; CH_3), 23.27 (d; C-9); 37.72, 44.36 (in each case s; C-3,4); 42.80 (d; C-5); 112.05, 112.61, 113.72 (double signal) (in each case s; 4CN); 120.11, 134.02 (in each case d; C-6,7)

3a: m.p. 195°C (dec., from 2-propanol). ^{1}H NMR: $\delta = 2.44$ (dtdd, $J_{3,5'} = 11.0$, $J_{5',6'cis} = J_{5',6'trans} = 8.5$, $J_{4',5'} = 4.4$, $J_{3',5'} = 1.5$ Hz; 5'-H), 2.61 and 2.67 (in each case dddd, $J_{6',6'} = 17.5$, $J_{1',6'cis} = J_{1',6'trans} = 4.5$, $J_{2,6'} = 1.7$ and 2.0 Hz; 6'-H_2), 3.80 (d; 3-H), 5.98 (dtt, $J_{1',2'} = 9.5$, $J_{1',3'} = J_{1',4'} = 0.8$ Hz; 1'-H), 6.02 (ddt, $J_{3',4'} = 9.5$, $J_{2',4'} = 0.8$ Hz; 4'-H), 6.09 (m; 2'-H), 6.25 (dddd, $J_{2',3'} = 5.2$ Hz; 3'-H). ^{13}C NMR: $\delta = 22.05$, 22.16 (in each case s; C-1,2); 26.56 (t, 129 Hz; C-6'); 33.73 (d, 140 Hz; C-5'); 42.76 (d, 170 Hz; C-3); 109.43, 109.70, 110.81 (double signal) (in each case s; 4CN); 122.59, 125.09, 126.09, 128.60 (in each case d, ca. 165 Hz; C-1'–C-4')

3b: ^{1}H NMR: $\delta = 1.13$ (d, $J_{6,CH_3} = 7.2$ Hz; CH_3), 3.74 (d, $J_{3,5'} = 11.0$ Hz; 3-H); 5.89 (ddq, $J = 9.4$, 5.5, 0.8 Hz), 5.96 (ddm, $J = 9.5$, 5.5 Hz), 6.05 (ddt, $J = 9.5$, 5.1, 0.8 Hz), 6.27 (ddt, $J = 9.4$, 5.2, 0.8 Hz) (1'-H–4'-H); the signals of 5'-H and 6'-H are superposed by signals of **2b**

7: m.p. 176°C (dec., from ethanol). ^{1}H NMR ($CDCl_3$): $\delta = 1.61$—1.88 (m; 3H), 2.07—2.18 (m; 3H), 2.32 (m; 3'-H), 2.66 (d, $J_{3,3'} = 11.4$ Hz; 3-H), 5.61 (dq, $J_{1',2'} = 10.0$ Hz, $J_{2',3'} = J_{2',6'cis} = J_{2',6'trans} = 2.3$ Hz; 2'-H), 6.11 (dtd, $J_{1',6'cis} = J_{1',6'trans} = 3.8$, $J_{1',3'} = 2.0$ Hz; 1'-H). ^{13}C NMR: $\delta = 20.43$, 25.14, 26.70 (in each case t; C-4'–C-6'); 21.90, 21.99 (in each case s; C-1,2); 35.87 (d; C-3'); 44.15 (d; C-3); 109.32, 109.51, 110.71 (double signal) (in each case s; 4CN); 123.81 (d; C-1'); 133.23 (d; C-2').

[a] Elemental analyses and IR and MS spectra of **2a**, **2b**, **3a**, and 7 are consistent with the proposed structures. Solvent for NMR measurements (if not otherwise stated): [D_6]acetone.

[*] The numbering in **3** and **7** do not comply with the IUPAC rules; it merely serves for assignment of the NMR signals (Table 1).

described in ref. [1a] and proposed in this communication then the site of attack of the electrophile would differ in both substrates. This would, in addition to the reaction of thiophenol, in which radical-chain processes take place,[9] be a further case in which regiochemistry is determined by the localization of the HOMOs.[5]

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1a, 35618-58-7; **1b**, 96865-97-3; **2a**, 96865-98-4; **2b**, 96865-99-5; **3a**, 96866-00-1; **3b**, 96866-01-2; **4a**, 16118-23-3; **6**, 287-13-8; **7**, 95866-02-3; TCNE, 670-54-2; 4,5-dibromotricyclo[4.1.0.0^{2,7}]hept-3-ene, 52911-87-2.

[1] a) M. Christl, E. Brunn, F. Lanzendörfer, *J. Am. Chem. Soc. 106* (1984) 373; b) for the reaction of vinylcyclopropanes with TCNE cf. [12] in [1a] and B. König, D. Kaufmann, R. Näder, A. de Meijere, *J. Chem. Soc. Chem. Commun. 1983*, 771.

[2] M. Christl, G. Freitag, G. Brüntrup, *Chem. Ber. 111* (1978) 2320.

[3] a) Prepared by reaction of 4,5-dibromotricyclo[4.1.0.0^{2,7}]hept-3-ene with methyllithium and subsequent reduction with Na in *tert*-butyl alcohol; b) details of the crystal structure investigation are available on request from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2, on quoting the depository number CSD 51268, the names of the authors, and the full citation of the journal.

[4] G. H. Wahl, Jr., *J. Org. Chem. 33* (1968) 2158.

[5] R. Gleiter, *Top. Curr. Chem. 86* (1979) 197.

[6] Cf. reactions of bicyclo[1.1.0]butanes with non-radical electrophiles: a) W. R. Moore, H. R. Ward, R. F. Merritt, *J. Am. Chem. Soc. 83* (1961) 2019; b) K. B. Wiberg, G. Szeimies, *ibid. 92* (1970) 571; c) M. Christl, *Angew. Chem. 93* (1981) 515; *Angew. Chem. Int. Ed. Engl. 20* (1981) 529.

[7] N. W. Jordan, I. W. Elliott, *J. Org. Chem. 27* (1962) 1445.

[8] P. G. Gassman, G. D. Richmond, *J. Am. Chem. Soc. 92* (1970) 2090.

[9] M. Christl, R. Lang, R. Herbert, G. Freitag, *Angew. Chem. 92* (1980) 465; *Angew. Chem. Int. Ed. Engl. 19* (1980) 457.

BOOK REVIEWS

New Pathways for Organic Synthesis. Practical Applications of Transition Metals. By *H. M. Colqhoun, J. Holton, D. J. Thompson* and *M. V. Twigg*. Plenum Press, New York—London 1984. xiv, 454 pp., bound, $ 59.50.—ISBN 0-306-41318-3

A retrospective glance at the Nachrichten aus Chemie, Technik und Laboratorium for 1983 indicates, amongst other things, how vigorously organometallic chemistry is developing. The results from organometallic chemistry fill 16 columns while those of classical organic chemistry only account for 9. The demand for information and teaching material is considerable in this field. Therefore many books have appeared in recent years dealing with organotransition metal chemistry. With few exceptions the disappointed reviewer has laid them aside. This book is one of the exceptions.

Organic molecules or residues bonded to a transition metal often display reactions which do not fit into the classical organic chemical picture. Surprisingly little attention is paid to these new reactions by organic chemists or by the authors of organic chemistry textbooks or laboratory manuals. Starting from this point the authors, four industrial chemists, address themselves to the practical organic chemist and present an extensive collection of catalytic and stoichiometric organic syntheses in which transition metals play a part. The emphasis is—as the authors say in the introduction—on processes which are not possible using classical methods, which are generally applicable, which do not require a great deal of apparatus or much financial outlay and which—where possible—do not deter people by their toxicity. In order to ease the application of the methods described they present in the final chapter brief instructions for the handling of air-sensitive compounds, give instructions for the preparation of 18 important transition metal catalysts and educts and list sources for such compounds.

Between the introduction and the final chapter the material is divided up as follows: Formation of CC bonds (single bond, double bond) (55 p.); Synthesis of carbocyclics (69 p.); Synthesis of heterocyclics (25 p.); Isomerization of alkenes (20 p.); Direct introduction and removal of carbonyl groups (65 p.); Reduction (73 p.); Oxidation (31 p.). The description—product-oriented—is in the Houben-Weyl style, i.e. brief, with formulas reduced to the most important, taking account of stereochemical aspects, giving warning of sources of danger and interspersed with concrete experimental data (in all 147). Only occasional reference is made to theoretical and mechanical details; however, the reader can easily obtain additional information from the carefully chosen references (in all 976).

Since the carbonyl group is the most important functional group in organic chemistry the chapter "Direct introduction and removal of carbonyl groups" is worthy of special interest. On reading this it will become clear to many chemists for the first time that the chemistry of organic carbonyl compounds after its great leap forward in the 19th century has been experiencing a great renaissance since the middle of this century. The chapter on heterocyclics offers the specialist in organotransition metals or heterocyclic chemistry surprising information and an exciting glimpse of a new field. On the other hand criticism must be made of the chapter "Formation of CC bounds". The more recent developments such as the important application of alkyltitanium compounds as alkylation agents with high chemoselectivity, the stereoselective addition reactions of organotransition metal compounds to carbonyl groups or the transition metal-containing reagents for carbonyl olefination are not mentioned (on the other hand, non-oxidative alkene dimerization, cross coupling according to *Kumada*, the McMurry reaction, the Semmelhack method, CC linkage via π-allyl complexes, alkyl cuprate reagents and alkene metathesis are all covered). Such gaps, also to be found in other chapters, and the list of references show that the book was completed some time ago (1978—1980). However, the authors used the intervening period to check the text and formulas carefully.

This book, which is fluently written, may be recommended: a) To the mentally and practically flexible organic chemist searching for new methods of synthesis. b) For use with a textbook containing the theoretical and

practical basics of organotransition metal chemistry (*Collman, Hegedus:* Principles and Applications of Organotransition Metal Chemistry is recommended), to bring university organic chemistry tuition up to date, especially in the practical field—The book deserves to sell, to be improved by its authors by the making good of the gaps which have been mentioned and to be continually updated by the inclusion of new methods.

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Die Bleibelastung des Menschen. By *G. Lehnert* and *D. Szadkowski*. Verlag Chemie, Weinheim 1983. vii, 96 pp., DM 28.00,—ISBN 3-527-26096-X

This booklet describes in 80 pages the important sources of lead uptake (described here as lead burden) and their regulating boundary conditions, the functional changes initiated ("stresses") and the public health measures necessary (in essence tolerance levels). The actual effects of lead and therapeutic questions are only touched on cursorily. The descriptive mode of presentation makes the work suitable for use as an introduction to the field for non-specialists and less useful for medical and toxicological experts. Its value lies in the long list of literature references covering the occurrence and possibilities of uptake of lead from industry, technology, foodstuffs and confections and beverages, in the home and in the air. Daily and annual variations and the possibilities of mobilizing lead in the individual are devoted particular attention. There are no references to guide the interested reader to the larger, more comprehensive monographs on lead and the effects of lead, although they are continually borrowed from both for the text and the diagrams. The MAK for lead is erroneously quoted as 150 $\mu g/m^3$; since 1977 the value has been 100 $\mu g/m^3$.

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Selectivity—A Goal for Synthetic Efficiency. Workshop Conferences Hoechst. Vol. 14. Edited by *W. Bartmann* and *B. M. Trost*. Verlag Chemie, Weinheim 1984. xi, 423 pp., bound, DM 85.00.—ISBN 3-527-26142-7

Selectivity is a conditio sine qua non for efficiency in chemical synthesis. The discovery of new, more efficient regio-, chemo- and stereoselective methods is thus of particular importance. The advances in this field are so breathtaking that several selective syntheses are often available now for complex structures that were previously only difficultly accessible. The Achilles heel of many selective methods and syntheses is, however, their lack of practicability. Biological synthesis is still better than chemical for many complicated natural products of wide application such as penicillins, cephalosporins, steroids and macrolides. The challenge to chemical synthesis is increased by the development of gene technology. It is greatly to be welcomed that the papers presented by internationally acknowledged specialists at the 14th Workshop Conference Hoechst are now available in book form and have thus been made available to a wider, interested public. The following individual topics are treated:

Stereoselectivity in the Synthesis of Cyclic Ethers *(P. A. Bartlett)*; Some Uses of Silicon-Nitrogen Bonds in Organic Synthesis *(R. J. P. Corriu* and *J. J. E. Moreau)*; Designed Complexes—Science and Applications *(D. J. Cram* and *J. M. Cram)*; Asymmetric Synthesis of Carbonyl Compounds and Primary Amines *(D. Enders)*; Stereoselection by Allylboronates. The Highs and the Lows *(R. W. Hoffmann)*; Palytoxin *(Y. Kishi)*; Tris(dialkylamino)sulfonium Enolates and Phenoxide *(R. Noyori)*; Regio-, Diastereo- and Enantioselective Carbon-Carbon Bond Formation—Recent Studies and Applications in Organic Synthesis *(W. Oppolzer)*; Selectivity and Reactivity in Oligosaccharide Synthesis *(H. Paulsen)*; Organotin Reagents for Selective Reactions: Synthesis and Applications of α-Heterosubstituted Organotins *(M. Pereye, B. Elissondo* und *J.-P. Quintard)*; Chiral Building Blocks in Natural Product Synthesis *(G. Quinkert)*; Regioselectivity in Metal-Promoted Carbon-Carbon Coupling Reactions *(M. F. Semmelhack)*; Strategies for Controlling the Stereochemical Course of Yeast Reductions *(C. J. Sih, B. Zhou, A. S. Gopalan, W.-R. Shieh* and *F. Van Middlesworth)*; Conformational Control of Chemical Reactions *(W. C. Still)*; Radical-Mediated Cyclisation Processes *(G. Stork)*; Diastereoselectivity and Asymmetric Induction in the Diels-Alder Reaction with Inverse Electron Demand *(L. F. Tietze)*; New Palladium-Catalyzed Reactions of Allylic Compounds via π-Allylpalladium Complexes *(J. Tsuji)*; Selectivity in Excited State Chemistry *(P. A. Wender)*; Chiral Building Blocks in Alkaloid Synthesis *(E. Winterfeldt)*; Selectivity in Organic Synthesis *(H. Wynberg)*; On the Mechanism of Titanium-Tartrate Catalyzed Asymmetric Epoxidation *(K. B. Sharpless, S. S. Woodard* and *M. G. Finn)*; Selectivity in Chemical and Enzymatic Synthesis *(J. E. Baldwin)*.

The contributions, of which several have been published in the meantime in other places in this or even in an extended form, are in their majority very clearly and synoptically written. Comprehensive reference lists make it possible to become further engaged in the widely ranging topics. The book is to be recommended to all who stand somewhat at a distance from this field and wish an overview—albeit incomplete—of the present state of this most topical field of organic chemistry. The purchase of this book which offers valuable stimulation with its collection of the latest results from twenty-two research groups would also pay the preparative organic chemist working in this field. However, the price seems rather high for an extract-like "snapshot" of a rapidly developing field.

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Immuno Enzyme Techniques in Cytochemistry. By *W. D. Kuhlmann*. Verlag Chemie, Weinheim 1984. xiii, 162 pp., bound, DM 128.00.—ISBN 3-527-26078-1

Advances in fundamental biological and medical research are based to a large extent on the introduction of new methods. Nowadays, no laboratory working in cell biology can manage without gene manipulation and/or immunological techniques. Scientists are always being confronted anew with the problem of choosing and/or

meaningfully adapting the right methods for their particular purposes from the wealth of possible choice. Therefore practical handbooks fulfill an important purpose and every new publication is eagerly awaited. The work in question—written in English—is divided into eight chapters: 1) Basic Methods and Aspects in Immunological Reagent Preparation, 2) Preparation of Immunohistological Reagents, 3) Histological Immuno Enzyme Techniques, 4) General Preparation of Biological Specimens, 5) Immunoperoxidase Histology in the Light Microscope, 6) Immunohistological Assays for Electron Microscopy, 7) Immunohistological Specificity, 8) Practical Aspects.

The book claims to provide a review of the concepts and practical aspects of immunohistological methods, in particular those of immuno enzyme techniques, it promises a detailed description of the preparation and purification of the necessary reagents, wishes to warn the reader about making false interpretations and to be a trustworthy manual for all who have to become conversant with immunohistological methods.

Does it fulfill what it promises? The answer, unfortunately, is a very definite no. The reader who attempts to work through the instructions is confronted with insuperable problems. Who knows offhand what protein A is used for (p. 28, 44, 45, the explanation follows on p. 62, only p. 45 is mentioned in the index), or what an epitope is (p. 32, an antigen determinant), what type of ape is hiding behind the name *Cercopithecus aethiops* (p. 122, long-tailed monkey) and how one obtains its kidney cells, because they are required for one of the experiments.

The presentations are sometimes too trivial and sometimes too specialized for the scientist with years of laboratory experience. Unfortunately there is no general review of the immuno enzyme techniques, but merely a glimpse of the work being carried out in the author's laboratory. No details are given of how the results he has obtained may be applied to other systems; the results were sometimes obtained under extremely lavish conditions. Many of the details are imprecise; for example, it is not clear from the text nor from the legends to Figures 1—10 and 1—15 what protein is yielded by the kinetics or separation illustrated. Yet this information is essential, for these results only hold for a particular protein; they cannot be applied to others. In addition, data are given about the acrylamide concentrations to be used in producing gels (p. 26), but no mention is made of the fact that gels with these concentrations are only suitable for proteins of a particular size range. Nowadays, apparatus for polyacrylamide gel electrophoresis (often home-made) is part of the standard equipment but what laboratory has the chamber made of vitreous silica sheet? Normal glass or plate glass are usual. Vitreous silica is much too expensive. The suggested dimensions ($18 \times 9 \times 0.3$ cm^3, p. 26) are intended for special cases. As shown by the results in Figure 1—19 these proved to be quite unsuitable for the separation presented since the voltage drop over 18 cm is much too high to achieve an optimal separation of the material to be separated. A "slot-former" is a chamber-shaped piece of plastic which looks quite different than is shown in Figure 1—18.

It remains unclear as to why the section "... lectin binding technique" (p. 50/51) has been inserted. It is to be expected that the reader will know that concanavalin A (a lectin) binds glucosyl and/or mannosyl residues and that as a result these must be exposed on the surface of peroxidase molecules. The mention of GOT staining (p. 65) is just as incomprehensible. There is a lack of information about the particular advantages of the methods and their field of application. On the other hand, pure gastrin (p. 85) is used in the performance of an investigation without it being explained how this is obtained. The choice of reagents is not "a matter of personal preference" (p. 62), but depends quite definitely on the aim and the questions posed. Remarks such as "Then, alternative procedures must be elaborated" (p. 98) or "Antibody concentrations and incubation times were chosen by trial and were within the limits of immunohistological assays" (p. 120) are of very little value and serve to frustrate the reader.

Every chapter ends with a comprehensive list of references. There are no critical comments concerning the methods reported in the literature. Neither are there any persuasive arguments for the superiority of immuno enzyme techniques over other immunological methods, e.g. the indirect immune fluorescence with FITC as marker. This process is employed throughout the world and has led to spectacular results in recent years. Why was this not honored by even one single mention in the list of references?

The resolution of the figures is frequently disappointing. Figure 5-4 is incomprehensible. There are no points of reference or orientation. It is not possible to make out what is supposed to have been tagged. In many other figures (5-1, 5-2, 5-7 etc.) comparable tissue sections (partial figures) are reproduced at different magnifications—which is also confusing. What a pity—an opportunity has been wasted. Here it has only been possible to highlight a few of the aggravating deficiencies. One thing remains to be said: the price cannot in any way be justified.

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New Books

The following books have been received by the editor. All the publications listed are available through W & P Buchversand für Wissenschaft und Praxis, Boschstrasse 12, D-6940 Weinheim (Federal Republic of Germany). Tel. (06201) 606-0, Telex 465516 vchwh d, Telefax (06201) 602328.

Smectic Liquid Crystals. Textures and Structures. By *G. W. Gray* and *J. W. Goodby*. Leonard Hill, Glasgow—London 1984. xxvi, 162 pp., bound, £ 46.00.—ISBN 0-249-44168-3

Ellis Horwood Series in Analytical Chemistry. Organic Trace Analysis. By *K. Beyermann*. Ellis Horwood, Chichester 1984. 365 pp., bound, £ 35.00.—ISBN 0-85312-638-0

Einführung in die Physikalische Chemie. By *H. Labhart*. **Teil V: Molekülspektroskopie.** 2nd revised edition by *E. Haselbach*. Springer-Verlag, Berlin 1984. xi, 156 pp., stitched, DM 24.80.—ISBN 3-540-12983-9

Strategies and Tactics in Organic Synthesis. Edited by *T. Lindberg*. Academic Press, New York 1984. xiv, 370 pp., bound, $ 57.00.—ISBN 0-12-450280-6

Modern Inorganic Chemistry. Series Editor: *J. P. Fackler, Jr.* **Carbon-Functional Organosilicon Compounds.** By *V. Chvalovsky* and *J. M. Bellama.* Plenum Press, New York 1984. xiii, 301 pp., bound, $ 45.00.—ISBN 0-306-41671-9

Topics in Current Chemistry. Series Editor: *F. L. Boschke.* **Vol. 123: Structural Chemistry.** Springer-Verlag, Berlin 1984. vii, 186 pp., bound, DM 88.00.—ISBN 3-540-13099-3

Wiley Series in General Heterocyclic Chemistry. Series Editor: *E. C. Taylor* and *A. Weissberger.* **Physical Methods in Heterocyclic Chemistry.** Edited by *R. R. Gupta.* John Wiley, Chichester 1984. xi, 682 pp., bound, £ 153.00.—ISBN 0-471-09855-8

Food Analysis. Principles and Techniques. Vol. 1: Physical Characterization. Edited by *D. W. Gruenwedel* and *J. R. Whitaker.* Marcel Dekker, Basel 1984. 352 pp., bound, SFr. 166.00.—ISBN 0-8247-7181-8

Industrial Electrochemistry. By *D. Pletcher.* Chapman and Hall, London 1984. xii, 325 pp., paperback, £ 14.95.—ISBN 0-412-26530-3

Specialist Periodical Reports. Spectroscopic Properties of Inorganic and Organometallic Compounds. Vol. 16. Edited by *E. A. V. Ebsworth.* The Royal Society of Chemistry, London 1984. 363 pp., bound, £ 78.00 (price reduction for members of the Royal Society of Chemistry).—ISBN 0-85186-143-1

The Chemistry of Heterocyclic Compounds. Series Editor: *A. Weissberger* and *E. C. Taylor.* **Azepines. Part I and Part II.** Edited by *A. Rosowsky.* John Wiley, Chichester 1984. Part I: xvi, 822 pp., bound, £ 222.75.—ISBN 0-471-01878-3; Part II: xix, 889 pp., bound, £ 222.75.—ISBN 0-471-89592-x

Theilheimer's Synthetic Methods of Organic Chemistry. Vol. 38: Yearbook 1984. Edited by *A. F. Finch.* S. Karger, Basel 1984. xxiii, 620 pp., bound, SFr. 578.00.—ISBN 3-8055-3817-0

Chemistry of Peptides and Proteins. Vol. 2. Proceedings of the Fourth USSR-FRG Symposium, Tübingen, FRG, June 8—12, 1982. Edited by *W. Voelter, E. Bayer, Y. A. Ovchinnikov,* and *E. Wünsch.* Walter de Gruyter, Berlin 1984. xii, 497 pp., bound, DM 185.00.—ISBN 3-11-009580-7

Ion Exchange Technology. Edited by *D. Naden* and *M. Streat.* Ellis Horwood Publishers, Chichester 1984. 742 pp., bound, £ 45.00.—ISBN 0-85312-770-0

Rheinisch-Westfälische Akademie der Wissenschaften. Vorträge N 328: *P. Starlinger:* Transposition: Ein neuer Mechanismus zur Evolution; *K. Rajewsky:* Antikörperdiversität und Netzwerkregulation im Immunsystem. Westdeutscher Verlag, Wiesbaden 1984. 52 pp., paperback, DM 15.00.—ISBN 3-531-08328-7; ISSN 0066-5754

The Institution of Chemical Engineers. Symposium Series No. 89: Fluid Mixing II. A Symposium Organized by the Yorkshire Branch and the Fluid Mixing Processes Subject Group of the Institution of Chemical Engineers, Bradford University, April 3—5, 1984. Pergamon Press, Oxford 1984. 207 pp., bound, £ 18.70.—ISBN 0-08-031416-3

NATO ASI Series. Series C: Mathematical and Physical Sciences. Vol. 124: Magnetic Resonance. Introduction, Advanced Topics and Applications to Fossil Energy. Edited by *L. Petrakis* and *J. P. Fraissard.* D. Reidel Publishing Company, Dordrecht 1984. xi, 807 pp., bound, HFl. 255.00.—ISBN 90-277-1752-4

Allenes in Organic Synthesis. By *H. F. Schuster* and *G. M. Coppola.* John Wiley, Chichester 1984. xiii, 358 pp., bound, £ 54.95.—ISBN 0-471-87284-9

Proceedings of the Xth IUPAC Symposium on Photochemistry. CCC-Interlaken, Switzerland, July 22—27, 1984. Symposium Editor: *A. M. Braun.* Presses Polytechniques Romandes, Lausanne 1984. xl, 619 pp., paperback, SFr. 75.00.—ISBN 2-88074-064-9

Werkstoff Glas. By *K. Kühne.* Akademie-Verlag, Berlin 1984. 287 pp., paperback, DM 35.00.—Order No. 763-187-0 (6742)

Institution of Chemical Engineers Symposium Series No. 87: EFCE Event No. 299. ISCRE 8: The Eighth International Symposium on Chemical Reaction Engineering, University of Edinburgh, 10—13 September 1984. Edited by *G. S. G. Beveridge* and *P. N. Rowe.* Pergamon Press, Oxford 1984. xiv, 826 pp., bound, £ 55.00.—ISBN 0-08-030283-1

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Enzymes as Catalysts in Synthetic Organic Chemistry

New Synthetic Methods (53)

By George M. Whitesides* and Chi-Huey Wong

Enzymes have great potential as catalysts for use in synthetic organic chemistry. Applications of enzymes in synthesis have so far been limited to a relatively small number of large-scale hydrolytic processes used in industry, and to a large number of small-scale syntheses of materials used in analytical procedures and in research. Changes in the technology for production of enzymes (in part attributable to improved methods from classical microbiology, and in part to the promise of genetic engineering) and for their stabilization and manipulation now make these catalysts practical for wider use in large-scale synthetic organic chemistry. This paper reviews the status of the rapidly developing field of enzyme-catalyzed organic synthesis, and outlines both present opportunities and probable future developments in this field.

1. Introduction

Synthetic organic chemistry now faces important challenges derived from, and concerning, biology. The stunning recent advances in molecular and cellular biology—in genetics, immunology, endocrinology, neurobiology, and receptor and membrane biochemistry—have outlined broadly the course of many processes important in life. Understanding these processes in full molecular detail and using this understanding to produce chemically well-defined compounds useful in medicine, agriculture, and biology requires the preparation of classes of substances that have traditionally not been the major foci of activity in organic synthesis. Proteins, polypeptides, sugars, oligosaccharides, polysaccharides, nucleic acids, and combinations, analogues, and derivatives of these species are all centrally important in molecular biology. Their syntheses have received a relatively small fraction of the creative effort of modern synthetic organic chemistry. For chemistry to participate fully in molecular biology, it must be able to make these classes of compounds with the same high degree of skill with which it now makes hydrocarbons, heterocycles, and related classes of compounds. For molecular biology to contribute most effectively to society, its discoveries must be reduced to molecular detail and manipulated in ways that produce useful substances. Improved techniques from synthetic organic chemistry for the synthesis of biologically relevant compounds—especially those useful in modern molecular biology and biotechnology—would be of broad benefit.

The community of synthetic organic chemists has moved relatively slowly to explore many of the important synthetic problems posed by molecular biology for four reasons:

1) Many of the substances important in biology have physical properties which are unfamiliar and inconvenient. These compounds are often soluble in water, charged, nonvolatile, and high molecular weight. They may be unstable, impractical to obtain in quantity, and difficult to purify. Spectroscopy may be of limited utility in defining their structures.

2) Certain of the important generic problems encountered in the synthesis of these substances—e.g., the formation of amide, phosphodiester, and glycosidic linkages in the repetitive processes required to make macromolecules, or the manipulation of carbohydrates—have been considered in some senses to be "chemically uninteresting."

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3) Classical synthetic organic technology does *not* provide the best approach to certain of these problems—e.g., fermentation, tissue culture, and recombinant DNA technology are more useful than chemical techniques for the production of proteins, and fermentation is presently the only practical route to polysaccharides—and for many others the relative value of classical chemical and biologically derived synthetic methods remains undefined.

4) These problems have not been fashionable within the synthetic community.

Thus, for organic synthesis to function most effectively in the preparation of biologically relevant substances, modifications are required in the experimental techniques it uses, in the types of scientific problems it addresses, and in the scientific community it serves. These modifications to the scope and style of synthesis are substantial. Nonetheless, the central challenge—the synthesis of pure, well-defined molecular entities—is one at which synthetic chemists have (at least in the past) always been preeminent.

This article reviews one of the areas of synthesis which lies at the border between organic chemistry and biochemistry: the use of enzymes as catalysts in organic synthesis.[1-12] This area is the one which is the most "chemical" or "molecular" of the biologically derived synthetic technologies. Chemists comfortably use platinum as a catalyst; they will eventually use lipase with no more hesitation. Enzymology provides a class of catalysts genuinely useful in the synthesis of biologically relevant substances, and requires a less drastic change in experimental approach than does, for example, fermentation using obligate anaerobes or mammalian cell culture. Enzymology is also, in some sense, the most fundamental of the synthetic techniques derived from biology: the less familiar (to chemists) synthetic technologies based on living cells also, of course, ultimately depend on enzymes. We emphasize that enzymatic synthesis (whether biologically based or abiological) is not necessarily the most useful synthetic technique for the solution of an arbitrarily chosen biologically derived synthetic problem,[9, 10] and one function of this article is to try to define the areas of synthesis in which enzymatic methods are those of choice.

2. Areas of Current Application

Enzymes are catalysts which have already demonstrated high utility and potential in certain areas of current importance in organic and pharmaceutical chemistry.

2.1. Preparation of Chiral Synthons

The first area in which enzymes have found important, broad application is in the preparation of chiral synthons, commonly by kinetic resolution. The practical importance of this area to the pharmaceutical industry is based in part on the desire for efficient syntheses and in part on regulatory constraints: regulatory pressures increasingly favor the production of enantiomerically pure substances, rather than racemates. Chiral synthesis using optically active transition-metal catalysts is also, of course, an area of current intense activity,[13-17] and the competition between biological and transition-metal-based methods is one of real strategic interest. To date, from a practical point of view, biologically based routes to chiral substances have proved more broadly useful than catalytic methods using transition metals.

2.2. Specialty and Fine Chemicals

Enzymes have established utility in the manipulation of sugars, nucleic acids, amino acids, and lipids, and in fact the major applications of enzymology in process chemistry all lie within these areas.[18] The quantities of materials produced using enzymatic catalysis establish that, in appropriate circumstances, enzymes can be practical catalysts for large-scale processes:[9] for example, high-fructose corn syrup is produced on a scale of $> 10^5$ t per year in the USA, and aspartic acid, malic acid, and guanosine 5′-phosphate (GMP), which is used as a flavoring, are all produced in substantial quantity by enzymatic methods.

A wide variety of substances used for research in biochemistry, metabolism, and pharmacology have been best produced using enzymatic methods.

2.3. "Biological" Pharmaceuticals

One of the areas of greatest activity in modern pharmaceutical research is concerned with complex, biologically derived substances—especially proteins, polypeptides, and related materials obtained by, or stimulated by, the techniques of molecular genetics.[7, 9] Enzymology is now playing an increasingly important role in modification of materials derived from fermentation synthesis: for example, peptidases are used to cleave selectively (and, perhaps, to form selectively) peptide links, and other enzymes to attach oligosaccharide moieties to proteins or to modify those of glycoproteins. The recent commercialization of a process for conversion of porcine to human insulin by Novo Industrie provides the first large-scale example of this type of application.

2.4. Biotechnology[9, 10]

Many of the range of applications of biology subsumed in the word "biotechnology" require chemical manipulation of complex, biologically derived or biologically related substances. Clinical analysis, biologically derived sensors, and the preparation of flavor and odor compounds, for example, involve compounds which may require enzymatic synthesis or modification.

We note explicitly that the area of enzymatic catalysis in organic synthesis is, as are most areas of practical catalysis, fundamentally a process chemistry. That is, its principal objective is the efficient and economical (both in terms of money and time) synthesis of specific compounds (Fig. 1). In this sense it differs from a substantial amount of the work in organic synthesis presently carried out in universities, in which the compound that is the specific objective of the synthesis is less important than is the value of the individual steps (or the overall synthetic strategy) in demon-

strating new and often broadly generalizable chemical principles.

Synthesis

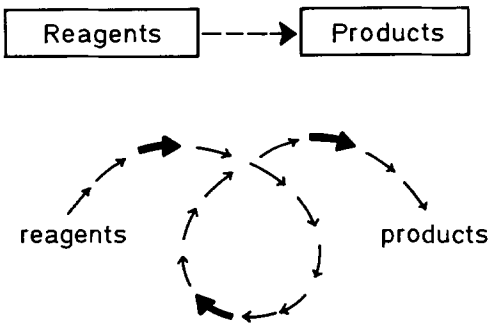


Fig. 1. Two approaches to synthesis. One (upper) is concerned with the development of practical, efficient routes to specific products. The second (lower) uses synthesis primarily to illustrate principles of reactivity and synthetic strategy. Enzyme-catalyzed synthesis (together with much of catalysis) is concerned primarily (although not exclusively) with the former objective.

3. Characteristics of Enzymes as Catalysts

Enzymes have three distinguishing characteristics as catalysts:

1) They accelerate the rates of reactions.

2) They are selective: the rate of reaction of a particular substance may be accelerated dramatically, while that of a structurally closely related substance is not.

3) They may be subject to regulation: that is, catalytic activity may be strongly influenced by the concentrations of substrates, products, or other species present in solution.

The selectivity of enzymes is the basis for much of their utility in organic synthesis. Enzymes offer the opportunity to carry out highly selective transformations—a feature of great value in working with chiral and polyfunctional molecules. The feature of regulation is critically important to the functions of enzymes in metabolic systems, but is most commonly an inconvenience in applications in organic synthesis. The most important manifestation of regulation for applications of enzymes in organic synthesis is product inhibition: that is, a decrease in the catalytic activity of an enzyme when the concentration of a product of the reaction catalyzed by that enzyme reaches a certain value.[19,20] Overcoming product inhibition may require removing the product as it is formed[20] (often an inconvenience), accepting low concentrations of product in the final reaction mixture (thereby complicating workup), or using large quantities of enzymes (with attendant increases in cost). No close analogy to regulation exists in transition-metal-based catalysis, although poisoning by product or starting material represents a loose analogy.

Enzymes have certain other characteristics which are important in considering their applications in organic synthesis:

1) Their availability, cost, and lifetime in use vary widely. A typical enzyme will contain one active site per 20000–50000 molecular weight. This high-molecular-weight equivalent per active site may be balanced by a high catalytic turnover number (moles of product produced per mole of enzyme per unit time), but is not always. The economics of enzyme use depend upon a number of factors: the cost of the enzyme, its specific activity, and its operating lifetime. Table 1 summarizes costs of research quantities of representative, commercially available enzymes useful in syn-

Table 1. Specific activities and costs of some commercially available enzymes of use in organic synthesis [a].

Enzyme [b]	E.C. Number	Specific Activity [U/mg protein]	Cost [US $/ 1000 U] [c]
Horse Liver ADH	1.1.1.1	2	50
Yeast ADH	1.1.1.1	400	0.2
ADH (*T. brockii*)	1.1.1.2	15	53
Glycerol DH (*Cellulomonas sp.*)	1.1.1.6	50	56
L-Lactic DH	1.1.1.27	1400	0.5
D-Lactic DH	1.1.1.27	300	26
Malic DH	1.1.1.37	3000	1.3
6-Phosphogluconate DH	1.1.1.44	50	280
Glucose DH (*B. cereus*)	1.1.1.47	250	160
Glucose-6-phosphate DH	1.1.1.49	400	15
Glucose Oxidase	1.1.3.4	200	0.4
Galactose Oxidase	1.1.3.9	300	20
Formate DH	1.2.1.2	3	667
Aldehyde DH	1.2.1.5	25	140
Glutamic DH	1.4.1.3	40	2.5
Leucine DH	1.4.1.9	80	1750
L-Amino Acid Oxidase	1.4.3.2	1	500
D-Amino Acid Oxidase	1.4.3.3	1	50
Catalase	1.11.1.6	20000	0.00005
Horseradish Peroxidase	1.11.1.7	330	1.8
Tyrosinase	1.14.18.1	4000	0.1
Galactosyl Transferase	2.4.1.22	5	5000
Hexokinase	2.7.1.1	300	2.7
Phosphoribulokinase	2.7.1.19	4	50
NAD Kinase	2.7.1.23	20	85
Glycerokinase	2.7.1.30	150	33
Pyruvate Kinase	2.7.1.40	500	0.6
Acetate Kinase	2.7.2.1	600	50
Polynucleotide Phosphorylase	2.7.7.8	35	428
Pig Liver Esterase	3.1.1.1	100	10
Pig Pancreatic Lipase	3.1.1.3	50000	0.00002
Phospholipase A_2	3.1.1.4	1500	5.3
Cholesterol Esterase (Bovine Pancreas)	3.1.1.13	3	200
Pancreatin [d]			
α-Amylase (*B. lichiniformis*)	3.2.1.1	500	0.01
Amylo-1,6-glucosidase	3.2.1.3	70	0.004
NADase	3.2.2.5	3	667
Chymotrypsin	3.4.21.1	50	0.1
Trypsin	3.4.21.4	10000	0.0009
Papain	3.4.22.2	40	1.5
Carboxypeptidase A	3.4.17.1	50	8
Protease [e]			
Acylase (*Aspergillus sp.*)	3.5.1.14	150	0.006
Penicillinase	3.5.2.6	2000	4
Aldolase (Rabbit Muscle)	4.1.2.13	20	5
Sialic Acid Aldolase	4.1.3.3	1	5000
Tryptophanase	4.1.99.1	1	200
δ-Aminolevulinate Dehydrase	4.2.1.24	2	7500
Phenylalanine Ammonia Lyase	4.3.1.5	3	6670
UDP-Galactose 4-Epimerase	5.1.3.2	15	1330
Glucose Isomerase	5.3.1.5	30	0.005
Phosphoglucoisomerase	5.3.1.9	800	3

[a] Prices vary widely with source and quantity. [b] Abbreviations: ADH, Alcohol Dehydrogenase; DH, Dehydrogenase. [c] 1000 U of enzymatic activity will generate approximately 1 mol of product per day under favorable conditions. [d] Pancreatin is a crude, inexpensive (US$ 20/kg) mixture of enzymes which often provides the least expensive source of activities for lipases, cholesterol esterase, and certain proteases and glycosidases. [e] A variety of relatively crude proprietary proteases (Pronase, Thermolysin, Subtilisin Carlsberg, Subtilisin BPN, Newlase, Papaya, and others) are available at low cost (US$ 0.1—1/1000 U).

thesis, together with the specific activities of these enzymes. For reference, one International Unit (IU) of catalytic activity is defined as that amount which generates 1 μmol of product per mg of enzyme per min; 700 U of enzymatic activity produces ca. 1 mol of product per day. The last column of Table 1 thus indicates roughly the cost of a quantity of enzyme sufficient to generate a mole of product per day when operating under ideal—that is, V_{max}—conditions. (In fact, few synthetic reactions are run under ideal conditions, and the quantities of enzyme required to achieve this level of synthetic productivity may be greater than the theoretical by factors of between 2 and 10^2.)

2) Enzymes may require cofactors for activity. The economics of consumption or regeneration of the cofactor may be as important as that of the enzyme itself.

3) Most enzymes are water-soluble, and are most active in aqueous solution at pH 7–8 and room temperature. The importance of water solubility in limiting the applicability of enzymes in organic synthesis has probably been overestimated by organic chemists. While most enzymes are not active with truly water-insoluble substrates, it is often possible to carry out enzyme-catalyzed reactions in heterogeneous reaction mixtures in which only a small amount of the organic substrate is present in the aqueous solution containing the enzyme.[21–24] In certain cases enzymes will tolerate modest concentrations of organic cosolvents such as ethylene glycol, glycerol, dimethyl sulfoxide (DMSO), and dimethylformamide (DMF).[25–27]

4) Several enzymes can often be used in combination to carry out processes involving sequential or parallel enzyme-catalyzed transformations. This characteristic of enzymes stems from the common environment in which they function in vivo. The development of corresponding multicatalyst systems for non-enzymatic catalysts is less common.

5) Enzymes may be degraded under relatively mild conditions. Chemists are accustomed to storing metallic catalysts for long periods of time without loss in activity. Enzymes may denature on storage by a number of mechanisms:[28–33] for example, destruction by small amounts of proteases present as contaminants in the enzymatic preparation, temperature- or medium-induced changes in conformation, microbial contamination, autoxidation. All of these characteristics render the handling of enzymes, both on storage and in use, a relatively more delicate process than the handling of many other types of catalysts.

4. Enzymatic Kinetics and Mechanisms: Relevance to Synthesis

The subject of the mechanism of action of enzymes is, of course, a major field in its own right. Knowledge of characteristic kinetic constants for enzymatic reactions (especially Michaelis-Menten and inhibition constants and pH dependencies)[19,20] is very useful although not required for synthetic application. In fact, one of the major advantages of enzymatic catalysis (relative to, for example, homogeneous and heterogeneous catalysis by metals) is that a relatively small investment of time in obtaining kinetic constants for an enzyme-catalyzed reaction yields a very large return in terms of ability to control rationally the activity of that enzyme in synthetic applications. Figure 2 and Equations (a) and (b) outline essential terms. For the simplest case in which a substrate S is converted into a product P by an enzyme E in a process following Michaelis-Menten kinetics [Eq. (a)], without inhibition by products or other species, the rate of reaction is given by the familiar Equation (b).

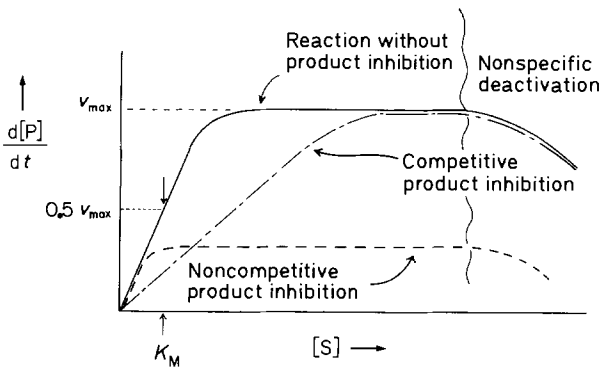


Fig. 2. Schematic representation of the relation between the reaction rate d[P]/dt and the substrate concentration [S] for a simple reaction following Michaelis-Menten kinetics (——) in the absence of inhibition by product. Curves for competitive (– – –) and noncompetitive (– – –) inhibition by product illustrate the influence of an arbitrary fixed concentration of product on the relation between d[P]/dt and [S], relative to that observed in the absence of inhibition. The slope of the curve at low [S] for an enzyme subject to competitive inhibition, and the height of the plateau for that subject to noncompetitive inhibition are determined by the concentration of the product and the inhibition constants. At high concentrations of substrate, enzymatic reactivities commonly decrease due to nonspecific deactivation.

$$S + E \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} S \cdot E \xrightarrow{k_2} P + E \qquad (a)$$

$$\frac{d[P]}{dt} = \frac{k_2[E]}{1 + \frac{K_m}{[S]}} = \frac{V_{max}}{1 + \frac{K_m}{[S]}} \qquad (b)$$

From the vantage of synthetic application, for a given quantity of enzyme, the rate of reaction increases as [S] is increased until all of the available enzyme active sites are occupied. Further increase in [S] does *not* increase the rate of reaction. In fact, if the substrate concentration is increased sufficiently, most enzymes are eventually deactivated (as the character of the solvent becomes markedly different from that of water). Maximum efficiency of use of the enzyme (usually the most expensive component of the reaction mixture) is achieved in the region of substrate concentrations in which the concentration of enzyme limits the rate (V_{max} conditions). If substrate concentrations are too low, a certain fraction of enzyme active sites are vacant at equilibrium; if substrate concentrations are too high, the enzyme is deactivated. The Michaelis constant K_m is thus invaluable in judging the *minimum* concentration of substrate which must be maintained in solution to achieve efficient use of enzyme; V_{max} is useful in indicating the most rapid rate of production of product which can be achieved for a given quantity of enzyme under ideal circumstances. Both K_m and V_{max} are measured under assay conditions.

In practice, values of K_m are often roughly the same under assay conditions and conditions used in synthesis, although higher apparent values of K_m may be observed in synthesis using immobilized enzymes if mass transport limitations are important; V_{max} under assay conditions is often much larger than the maximum rate of operation observed for the enzyme under synthetic conditions, because inhibition of enzymatic activity is common.

The discrepancy between the catalytic activity of an enzyme obtainable under ideal (assay or V_{max}) conditions and the lower value often observed under synthetic conditions is a major source of frustration to inexperienced users of enzymatic catalysis for synthetic applications. This discrepancy may have several origins: nonspecific deactivation of the enzyme by high or inappropriate concentrations of substrates, products, buffers, or ions; loss of activity on immobilization due to chemical modification or mass transport limitations; or reversible kinetic inhibition by product. The importance of product inhibition is only now beginning to be appreciated. Specific examples are given later, and a complete kinetic discussion is unnecessarily complex for synthetic applications.[20] It is, however, important to recognize that there are several important classes of inhibition (Fig. 2). The first—competitive inhibition—reflects competitive binding of substrate and product at the enzyme active site. This type of inhibition influences only K_m; its effects can, in principle, be overcome by increasing the concentration of substrate. The second—noncompetitive inhibition—leaves K_m unchanged and decreases V_{max}. This type of inhibition *cannot* be overcome by increasing substrate concentration: the only generally effective strategy is to decrease the concentration of product (e.g., by removing it continuously during reaction or by limiting the total quantity of substrate processed).[21] Yet other types of inhibition—mixed inhibition and uncompetitive inhibition—influence V_{max} and K_m simultaneously.

The important data to extract from kinetic analysis of an enzyme in order to optimize its use in synthesis are two: first, the values of K_m and V_{max} are critical in choosing values of the concentrations of substrate and enzyme; second, the product inhibition must be recognized, if present, and approximate values of K_i determined in order to choose the correct strategy—increasing substrate concentration and/or decreasing product concentration—to limit its unfavorable influence on rates of reaction.

5. Solved Problems; Current Activities; Future Problems and Opportunities

Because application of enzymes as catalysts in organic synthesis is a relatively new field, a substantial number of technical problems require solution before these applications become routine. Table 2 summarizes the status of several generic problems in this area. Those problems classified as "solved" do not necessarily have *optimal* solutions at present. The solutions now available are, however, sufficient that these problems no longer limit progress in the field. For example, many methods are now available for immobilization of enzymes.[34–39] The best strategy for immobilization of any particular enzyme is not necessarily clear, without substantial trial and error. Particularly for process applications involving long-term stability and good performance in fixed-bed reactors, improved immobilization technology would be very useful. Nonetheless, for laboratory and pilot-plant scale, existing technology is probably such that more difficult problems will be found elsewhere.

Several of the topics listed in Table 2 are discussed more fully below, but a few of the items listed in the table deserve brief comment here:

— The general thrust of *current* research in this area of applied enzymology is to establish the real practicality of

Table 2. Status of certain generic problems in enzymatic catalysis.

Solved	Current Research	Immediate Future	More Distant Fuuture
Immobilization	Development of new laboratory-scale uses of enzymes, especially simple enzymes (eaterases, amidases, isomerases)	Uses of recombinant DNA for large-scale production of enzymes	Development of new types of enzymatic activities using genetic engineering
Cofactor Regeneration AMP or ADP→ATP NAD(P)H ⇌ NAD(P)		Site-specific mutagenesis for changes in properties (K_m, K_i, selectivity, stability)	
Deactivation Thiol Autoxidation Protease Action	Use with unnatural substrates; definition of the generality of synthetic applicability of readily available enzymes	Exploration of enzymes from thermophilic and halophilic organisms for synthetic utility	
	Use with organic cosolvents; one- and two-phase systems	Evaluation of complex multienzyme systems in synthesis; comparison with whole-cell systems; "artificial metabolism"	
	Overcoming product inhibition	Applications in synthesis of fine and specialty chemicals	
	Cofactor regeneration Acetyl CoA; PAPS [a]	Chemical modification of enzymatic activities: "semisynthetic enzymes"	
	Scale-up in pharmaceutical synthesis		

[a] PAPS: 3′-phosphoadenosine-5′-phosphosulfate.

enzymes as catalysts in organic synthesis. How broadly applicable are they? Can they be used with substrates very different from their natural substrates? To what extent can their activity be changed by adding organic cosolvents? How should they be used: immobilized, in membrane reactors, or in free solution? In general, in what circumstances do they provide methods superior to existing or easily developed classical techniques for the solution of problems in organic synthesis?

— The *immediate future* will see the application of the techniques of site-specific mutagenesis and recombinant DNA technology to the large-scale production of uncommon enzymes (if warranted by the development of important processes requiring large quantities of these enzymes), the discovery of new enzymatic activities from new sources, and modest modification of enzymatic properties (for example, changes in Michaelis-Menten constants, substrate selectivities, or thermal stabilities). The first useful examples of site-specific mutagenesis are now appearing (for example, generation of T4 lysozyme containing an engineered disulfide bond to improve stability[40a] and of tyrosyl-tRNA synthetase altered to lower K_m values[40b]). The immediate future will also see the exploration of complex multienzyme systems for synthesis. In principle, the complexity of these systems may approach that of major metabolic paths (and, since these systems may not exist in nature, the phrase "artificial metabolism" seems appropriate for them). A major question in this area concerns the degree of complexity required before cell-free enzymology becomes inferior to whole-cell synthesis. The chemical modification of existing enzymes and proteins to change activity, stability, or selectivity—that is, the generation of "semisynthetic enzymes"—also holds promise.[41]

— The *distant future* holds out the potential of using highly developed structure-reactivity reactions for protein chemistry to "design" new enzymes to catalyze new reactions, and of using molecular genetics to produce these new enzymes. The prospect of being able to design and produce new catalysts is an alluring one. Its realization is, however, very far away, and even the basic principles on which the design of a new protein catalyst might be built are still being explored at the level of basic research.

With these generalities in hand concerning the use of enzymes as catalysts in organic synthesis, we turn to a discussion of specific classes of enzymes, and illustrations of their use in synthesis. In this discussion, we will consider specific enzymes, rather than generalities concerning classes of enzymes. The discussion will proceed in terms of the present ease of use of these enzymes, although not necessarily in order of the ultimate usefulness of the enzymes.

6. Specific Applications

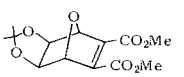
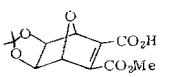
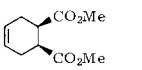
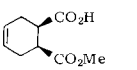
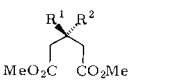
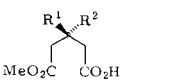
6.1. Enzymes Not Requiring Cofactors

Certain of these enzymes are among the most readily available, least expensive, and most stable. They have seen the most widespread use by synthetic organic chemists, and probably comprise the group which will first become a standard part of the synthetic organic repertoire (especially for the preparation of chiral synthons).

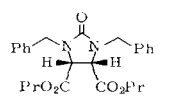
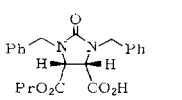
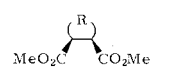
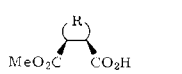
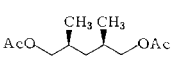
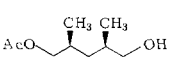
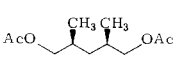
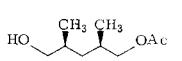
6.1.1. Esterases: Pig Liver Esterase and Lipases

A large number of examples exist illustrating the use of these classes of enzymes for kinetic resolutions.[42-68] The hydrolysis of *meso*-diesters has proved a particularly attractive strategy for obtaining chiral synthons, and both examples and theoretical analysis of this strategy are well-developed.[42-53] Table 3 gives representative examples.

Table 3. Enantioselective hydrolysis of *meso* substrates catalyzed by pig liver esterase and hog pancreatic lipase (last example).

Substrate	Product	*ee* [%]	Ref.
		77	[43]
		96	[51, 52]
		100	[42, 47, 49]

	a	b	c	d	e	f	g	h	i	j	k
R^1	OH	OH	CH_3	H	H	H	H	H	H	H	$PhCH_2OCONE$
R^2	CH_3	H	CH_2Ph	NH_2	CH_3	C_2H_5	C_3H_7	$CHMe_2$	⬡	CH_2Ph	H

		87	[46]
		90	[50]
		95	[53]
		90	[53]

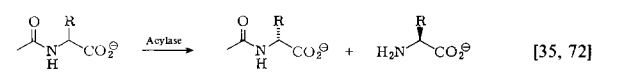
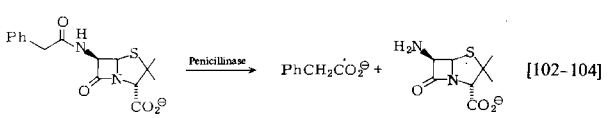
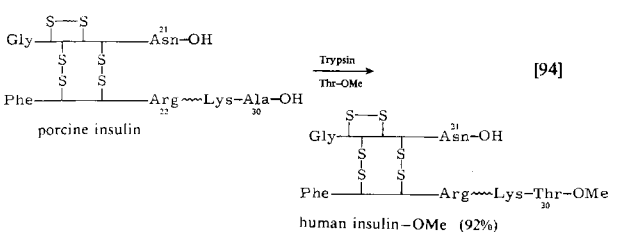
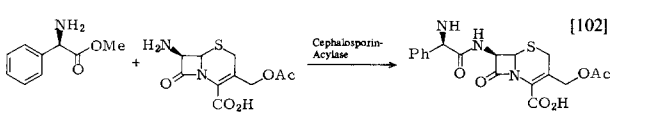
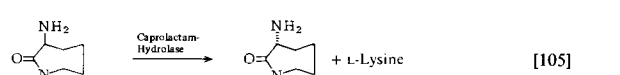
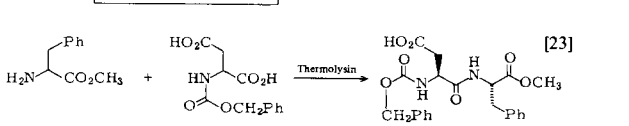
Several recent studies with these enzymes deserve further comment, since they point to certain generally useful features and problems. The lipases are rapidly developing into an extremely useful class of enzymes, especially for chiral synthesis. They have the characteristics of low cost, high stability, and high tolerance for variation in substrate structure.[53-57] They have the additional attractive feature that they do not require water-soluble substrates: They operate best at water-organic interfaces, and recent work suggests that they retain a high degree of activity in strongly dehydrating and organic systems.[60,69,70] When operating with *meso* substrates, they can generate chiral products in high yield. The utility of lipases as catalysts for the preparation of chiral substances has been demonstrated in a number of types of systems. In addition to kinetic resolution by hydrolysis, transesterification is a useful procedure.[60,61]

A recent study has compared the utility of lipase-catalyzed hydrolysis as a route to enantiomerically enriched epoxy alcohols[21] with transition-metal-catalyzed epoxidation.[17] The enzymatic hydrolysis suffers from the disadvantage that it is a kinetic resolution: that is, it relies on the selective hydrolysis of one enantiomer in the presence of the second to achieve separation, and thus, in principle, yields a maximum of 50% of product based on racemic starting material. Even given this disadvantage, however, it is in certain instances a more practical route to large quantities of an optically active epoxy alcohol than the transition-metal-catalyzed system. The enzymatic and transition-metal catalysts now available show very different substrate selectivities, and are thus, in a broad sense, complementary rather than competitive.

6.1.2. Amidases

A second broadly applicable class of hydrolytic enzymes is the amidases. The most important applications for these enzymes to date have been in kinetic resolutions of amino acids[35,72-80] (typically by hydrolysis of *N*-acylamino acids)[35,72] and in formation of amide bonds[12,81-83] in polypeptides and proteins (Table 4).[11,84-101]

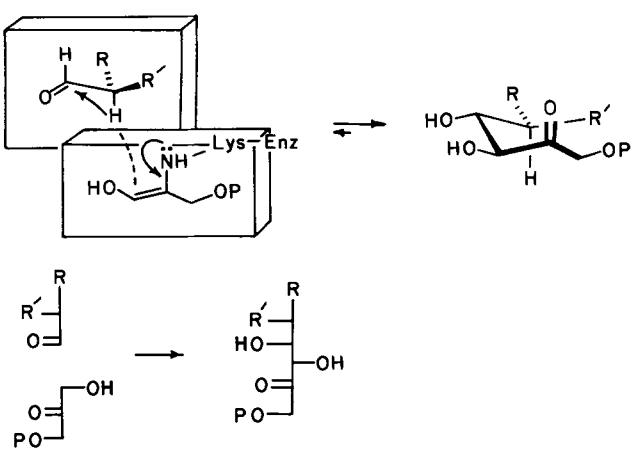
Table 4. Illustrations of uses of amidases.

Reaction	Ref.
	[35, 72]
	[83, 101]
	[102-104]
	[94]
	[102]
	[105]
	[23]

A substantial body of work has been devoted to the development of methods for formation of amide bonds between unprotected amino acids and amino acid esters using amidases. The several successful demonstrations of this type of enzyme-catalyzed dehydration establish that this type of process will be important in specific circumstances.[83] It is also clear, however, that the development of the specific reaction conditions required to effect a given dehydration demand patience and skill, and will be worthwhile only in instances in which substantial quantities of the product are desired. The most spectacular example of this technology to date is certainly the semisynthesis of human insulin from porcine insulin by Novo.[94] Future applications will rest in routine kinetic resolutions of amines, in the preparation of di- or oligopeptides,[23] in reactions incorporating organic media or reversed micelles,[101] and in the post-translational modification of proteins[106,107] obtained either by isolation from natural sources or by recombinant DNA methodology.

6.1.3. Aldolases

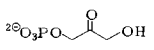
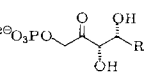
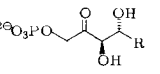
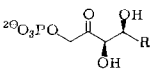
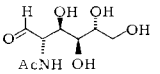
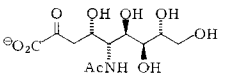
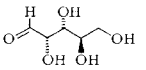
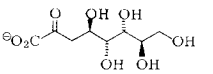
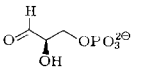
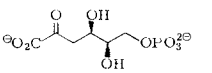
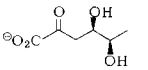
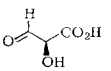
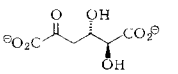
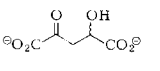
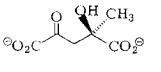
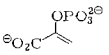
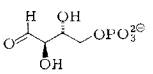
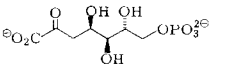
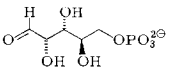
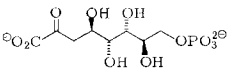
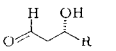
Rabbit muscle aldolase is a readily available enzyme that catalyzes the condensation of dihydroxyacetone phosphate (and a few close analogues) with aldehydes (Scheme 1).[108] This enzyme accepts a number of aldehydes as substrates, and has proved useful in the preparation of a number of rare, unnatural, and isotopically labeled sugars.[109,110] The preparation of 6-deoxyfructose-1-phosphate (a precursor to the flavoring agent Furaneol) provides one example.[109]



Scheme 1. Stereochemistry of carbon-carbon bond formation catalyzed by rabbit muscle aldolase. R is widely variable. R′ must be H or OH. Dihydroxyacetone phosphate is only slightly variable. $P = PO_3^{2\ominus}$.

Although rabbit muscle aldolase is the only enzyme in this class which has been explored for synthetic application, a large number of relatively readily available enzymes display the ability to catalyze aldol and reverse aldol reactions (Table 5).[111-121] Given the current interest in synthetic organic chemistry in directed aldol reactions,[122-126] and in the synthesis of carbohydrates,[127-130] we expect that the aldolases will be one class of enzymes which will experience substantial development as synthetic catalysts over the next years.

Table 5. Enzymes that catalyze aldol reactions.

Donor	Acceptor	Enzyme [a]	Product	Ref.
		FDP-Aldolase		[108–111]
		Fuc-1-P-Aldolase		[112]
		Rha-1-P-Aldolase		[113]
		Sialinsäure-Aldolase		[114]
		KDO-Aldolase		[115]
		KDPG-Aldolase		[116]
		KDF-Aldolase		[116]
		KDG-Aldolase		[116]
		KHG-Aldolase		[117]
		MHKG-Aldolase		[116]
		KDHA-Aldolase		[118]
		KDO-8-P-Synthase		[119]
		Desoxyribose-Aldolase		[120, 121]

[a] Abbreviations: FDP, D-fructose-1,6-diphosphate; Fuc-1-P, L-fuculose-1-phosphate; Rha-1-P, L-rhamnulose-1-phosphate; KDO, 3-deoxy-D-mannooctulosonate; KDPG, 2-keto-3-deoxy-6-phosphogluconate; KDF, 2-keto-3-deoxy-D-fuconate; KDG, 2-keto-3-deoxy-D-glucarate; KHG, 2-keto-4-hydroxyglutarate; MHKG, 4-methyl-4-hydroxy-2-ketoglutarate; KDHA, 2-keto-3-deoxyheptonate.

6.1.4. Isomerases and Lyases

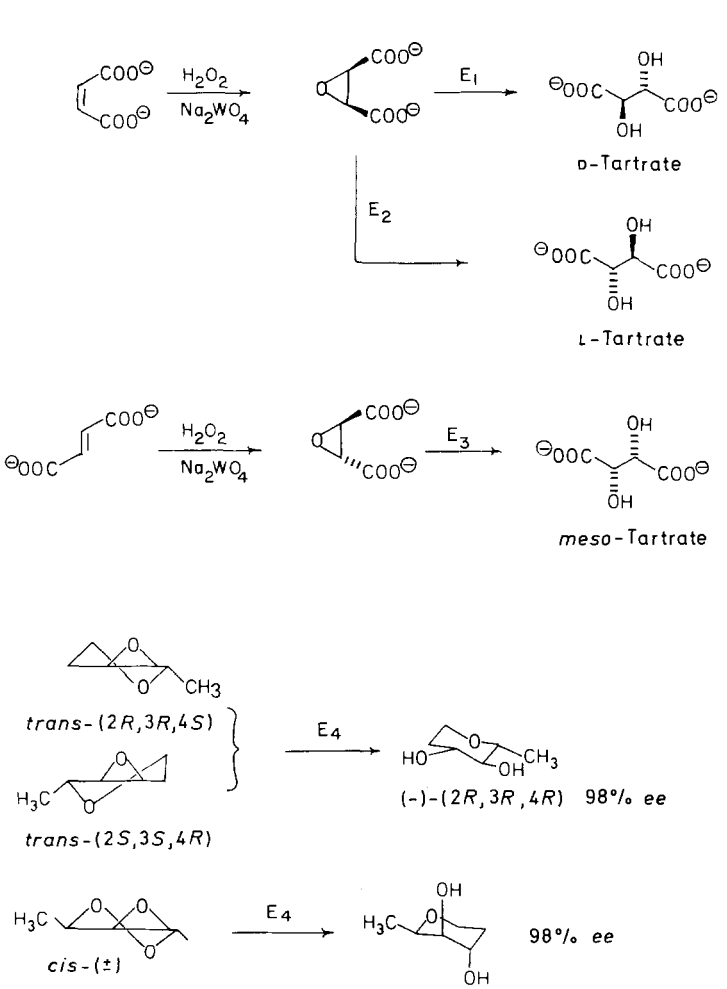
Several important commercial applications of enzymes rest on these types of enzymes. For example, glycosidases are used in large quantity in conversion of cornstarch to glucose,[131–134] and glucose isomerase catalyzes the equilibration of glucose and fructose.[135–141] Aspartic acid is prepared by addition of ammonia to fumaric acid in a reaction catalyzed by aspartase,[142] and malic acid by hydration of fumaric acid catalyzed by fumarase.[143] These transformations, by themselves, are not of major interest to synthetic chemists. The enzymes responsible for them are, however, readily available, and the range of substrates that they will accept has not been explored in detail.

6.1.5. Other Enzymes

Cyanohydrolases from several sources catalyze the enantioselective condensation of HCN with aldehydes.[144] *S*-Adenosylhomocysteine hydrolase catalyzes the synthesis of *S*-adenosylhomocysteine (or analogues) from homocysteine and adenosine (or analogues).[145–149] NADase catalyzes exchange of the nicotinamide residue of NAD with nicotinamide analogues. This enzymatic process provides a useful route to analogues of NAD.[150–152] Different phospholipases are available for selective hydrolysis of phospholipids. Phospholipases A_1 and A_2, for example, catalyze the hydrolysis of the ester groups at *sn*-1 and *sn*-2 positions of the glycerol moiety, respectively.[153–155] Phos-

pholipase D catalyzes transphosphatidylation using phosphatidylcholine and other amino alcohols as substrates.[153-155] These three enzymes have been used to prepare different types of phospholipids.[156] Glycosidases (for example, β-galactosidases) are useful in preparing glycosides and oligosaccharides.[157,158] 1-Deoxy-1-fluorosucrose—a compound which is stable to hydrolysis by invertase and which is recognized by sucrose carrier protein—has been prepared from UDP-glucose and 1-deoxy-1-fluoro-D-fructose in a reaction catalyzed by sucrose synthetase.[159]

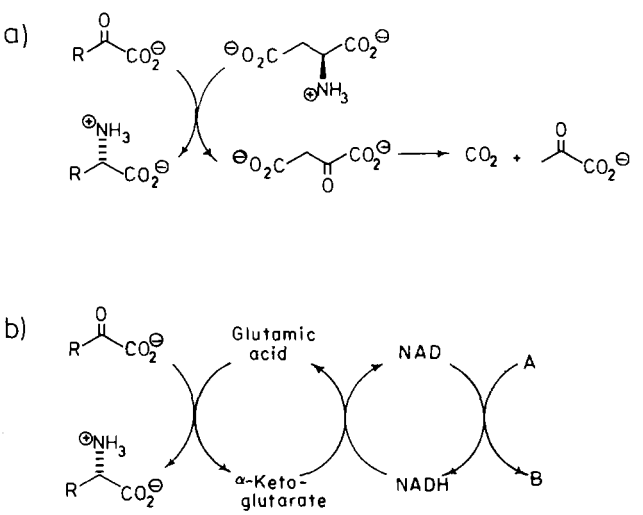
Enzymes catalyzing addition of ammonia or hydrolytic removal of amino groups also have potential application. L-Phenylalanine has been synthesized by addition of isotopically labeled ammonia to cinnamic acid catalyzed by phenylalanine ammonia lyase.[4] Large-scale production of L-citruline from L-arginine provides a representative example of hydrolytic deamination.[35] Regiospecific epoxide opening catalyzed by epoxide hydrases may have potential in the preparation of polyhydroxy compounds.[160] Scheme 2 illustrates the use of this class of enzymes in the synthesis of D-,[161] L-,[162] and *meso*-tartaric acid,[163] and hydroxypyran derivatives.[164,165] Another potentially useful group of hydrolytic enzymes is the nitrile hydratases.[166] One such enzyme catalyzes the hydrolysis of acrylonitrile to acrylamide.[167]



Scheme 2. Reactions involving epoxide hydrolases. Abbreviations: E_1, D-tartrate epoxidase; E_2, L-tartrate epoxidase; E_3, *meso*-tartrate epoxidase; E_4, epoxide hydrolase from rabbit liver microsomes.

6.2. Enzymes Not Requiring Added Cofactors, Especially Enzymes Containing Flavins, Pyridoxal Phosphate, Porphyrins, and Coordinated Metals

In these cases, cofactors are either covalently attached to or tightly non-covalently bound to the enzymes. They are regenerated automatically during the catalytic cycle. The pyridoxal phosphate-dependent transaminases catalyze the synthesis of amino acids via transfer of the amino group from an amino acid to an α-keto acid. In most cases L-glutamate is the amine donor and is converted into α-ketoglutarate. A useful strategy for the synthesis of α-amino acids is based on transaminase-catalyzed amine transfer between an α-keto acid and L-glutamate and coupled in situ regeneration of the glutamate by reductive amination of α-ketoglutarate in a reaction catalyzed by glutamic dehydrogenase. Another group of transamination reactions using L-aspartic acid as an amine donor has the possible advantage for synthetic application that the keto acid produced (oxaloacetic acid) decarboxylates spontaneously in situ to pyruvate; this decarboxylation drives the transamination reactions[168] (Scheme 3). These methods are particularly useful for the preparation of compounds containing isotopes of short half-life, such as ^{11}C (20 min) or ^{13}N (10 min), in high purity.[169,170]



Scheme 3. Procedures for enzyme-catalyzed transamination involving an α-keto acid and a) aspartic acid or b) glutamic acid as the amine donor. Compound A is a hydride donor (for examples, see Table 7) used for in situ regeneration of NADH from NAD.

The pyridoxal phosphate-dependent enzymes tyrosinase and tryptophanase catalyze the synthesis of L-tyrosine and L-tryptophan, respectively, by condensation of three small molecules: phenol (indole for tryptophanase), pyruvate, and ammonia. By replacing the aromatic components with other phenolic analogues, new amino acids can be prepared. L-DOPA, for example, can be prepared by replacing phenol with catechol. A similar approach has been used to prepare tryptophan analogues.[171,172] An efficient synthesis of porphobilinogen from δ-aminolevulinate using catalysis by the pyridoxal phosphate-containing enzyme δ-aminolevulinate dehydratase has been demonstrated.[173,174] The flavoenzyme glucose oxidase is widely

used in the food industry as an antioxidant.[175] Under anaerobic conditions, glucose oxidase also catalyzes the transfer of electrons from glucose to acceptors such as benzoquinone.[176] In addition to determination of the optical purity of amino acids,[177] L- and D-amino acid oxidases have been used to produce α-keto acids.[35]

The $Cu^{2\oplus}$-containing enzyme galactose oxidase catalyzes the oxidation of D-galactose to D-galactaldehyde; this enzyme also catalyzes the stereospecific oxidation of glycerol and 3-halo-1,2-propanediols to L-glyceraldehyde and L-3-haloglyceraldehydes.[178] Investigations of the substrate specificity of this enzyme using a number of polyols has permitted the development of a model of the enzyme active site which rationalizes the stereospecific transformation of polyhydroxy compounds to aldehydes.[179] Several unusual L-sugars have been prepared using this method.[179] Another potentially useful $Cu^{2\oplus}$-containing enzyme, dopamine β-monooxygenase, catalyzes the stereospecific hydroxylation of the *pro-R* benzylic hydrogen of dopamine to give norepinephrine. It also catalyzes the stereoselective oxidation of heteroatoms such as S and Se, and of certain olefins.[180]

The $Fe^{2\oplus}$-containing peroxidases are able to catalyze the addition of the elements of HOX to olefin substrates starting with H_2O_2 and $X^{\ominus}$;[181-184] they also catalyze oxidation of primary alcohols and heteroatoms.[185-187] Mixtures of organic dihalides are generated by reaction between olefins, H_2O_2, and a mixture of inorganic halides; the products include compounds containing C–F bonds.[188] Horseradish peroxidase also catalyzes the selective hydroxylation of aromatic compounds at 0°C in the presence of dihydroxyfumarate, and several pharmaceuticals including L-DOPA have been prepared using this enzyme on a millimolar scale.[189] Peroxidase appears to generate highly reactive and unselective species such as singlet oxygen and hydroxy radicals during its catalytic reactions.[190,191] Whether these enzyme-based hydroxylation processes are competitive with those using fermentation[192] or organometallic catalysis[14] remains to be demonstrated. In recent, interesting work horseradish peroxidase has been modified with 2-chloro-4,6-bis[ω-methoxypoly(oxyethylene)]-*s*-triazine.[193] The modified enzyme is soluble and still active in benzene. This technique allows manipulation of apparently homogeneous solutions of the enzyme in an organic solvent. The same immobilization procedure has been used to prepare hydrophobic lipase for use in synthesis in organic media.[62]

Lipoxygenase has been used to prepare a hydroperoxy derivative for use in the synthesis of prostaglandins.[194,195] The $Fe^{2\oplus}$-containing enzyme isopenicillin cyclase has been isolated and used to prepare several analogues of isopenicillin N.[196-199] Such enzymatic reactions may be useful in generating new β-lactam antibiotics.

Another class of iron and copper monooxidases that incorporate molecular oxygen into organic substances also has been explored with interesting results, but so far without real practical utility. These enzymes convert saturated hydrocarbons to alcohols, olefins to epoxides, and heteroatoms such as N and S to oxides. They also cleave aromatic rings and steroid derivatives and dealkylate *N*- or *O*-alkyl groups.[180] Of the presently known oxygen-incorporating enzymes, bacterial methane monooxygenase[200-202] (catalyzing the hydroxylation of saturated hydrocarbons), ω-hydroxylase (catalyzing the selective epoxidation of olefins),[203-206] hepatic hydroxylase (catalyzing the oxidation of heteroatoms for preparation of drug metabolites),[207,208] and steroid hydroxylases[209,210] are in principle attractive for synthetic development. Practical use of these enzymes is limited by severe technical problems: the instability and low specific activity of the enzymes; the requirement for multiple interacting enzymes to couple NAD(P)H oxidation to reduction of O_2; the inefficient coupling of NAD(P)H oxidation to oxygen activation (with production of hydrogen peroxide and superoxide as the undesirable competing side reactions); the requirement for NAD(P)H regeneration. Certain of these problems will not be easily solved, and although these monooxygenases are potentially attractive catalysts, procedures based on fermentation and other whole-cell processes[211] are presently more practical. The problems associated with these systems are discussed in more detail below. Other oxidative enzymes—particularly cyclohexanone monooxygenase[212] (which catalyzes enzymatic Baeyer-Villager oxidation) and lipoxygenase[213]—have seen some applications in synthesis, and deserve development.

6.3. Enzymes Requiring Added Cofactors

6.3.1. Enzymes Requiring Nucleoside Triphosphates, Especially ATP

A substantial fraction of the enzymes involved in complex biosynthesis (as opposed to biodegradation) require as cofactor a nucleoside triphosphate (especially ATP) or a nicotinamide cofactor (NAD(P)H). These enzymes have not been widely used in practical-scale organic synthesis, in large part because of the cost of the cofactors when used as stoichiometric reagents. ATP costs approximately US $ 800/mol. It is, however, a relatively stable substance: in solution, the most important degradation reaction is usually the hydrolysis of the ribose triphosphate group to a di- or monophosphate (probably by traces of ATPases present in solution).[214] Thus, an efficient strategy for regeneration of ATP from ADP and AMP renders enzymatic systems requiring these cofactors practical for use. The problem of ATP regeneration is now effectively solved.[215-221] The general strategy is to use a readily obtained phosphate donor, and to regenerate ATP from ADP or AMP in situ enzymatically.[222-224] Table 6 summarizes the most

Table 6. Procedures for ATP regeneration [a].

Procedure	$\Delta G'^{\circ}_{hyd}$ [kcal/mol]	Ref.
$CH_3COPO_3^{2\ominus}$ + ADP $\xrightarrow{AcK}$ ATP + $CH_3CO^{\ominus}$	−10.1	[218]
$=\!\!<^{OPO_3^{2\ominus}}_{CO_2^{\ominus}}$ + ADP $\xrightarrow{PK}$ ATP + $CH_3CCO_2^{\ominus}$	−12.8	[220]
$CH_3OCOPO_3^{2\ominus}$ + ADP $\xrightarrow{AcK}$ ATP + CH_3OH + CO_2	−12.4	[221]

[a] Abbreviations: AcK, acetate kinase; PK, pyruvate kinase.

useful procedures now available for ATP regeneration. Procedures based on different phosphate donors (e.g., carbamoyl phosphate), fermentation, and other techniques are not presently practical.[225]

The most generally useful of the procedures using high-energy phosphate donors is based on acetyl phosphate. This material is readily obtained,[218,221] and two acetate kinases are commercially available. Although most of the published work has involved *E. coli* acetate kinase, the *Bacillus stearothermophilus* enzyme may be superior: the *E. coli* enzyme contains an SH group close to the active site, and is sensitive to autoxidation; the *B. stearothermophilus* enzyme is thiol-free.[219] Acetyl phosphate has two disadvantages: it is only a moderately strong phosphorylating agent (as judged by its free energy of hydrolysis, $\Delta G^{\circ\prime}$ at pH 7, see Table 6) and it is relatively hydrolytically unstable in aqueous solution. The hydrolytic instability both destroys acetyl phosphate and produces phosphate ion in solution; this phosphate complexes with and sometimes precipitates the $Mg^{2\oplus}$ required for kinase activity, and may render slow reactions difficult to control.

Regeneration systems based on phosphoenol pyruvate (PEP) are more stable: PEP is resistant to hydrolysis, and is also a very strong phosphorylating agent. Its synthesis is, however, more complex than that for acetyl phosphate.[220] A newly developed reagent, methoxycarbonyl phosphate, is as easily prepared as acetyl phosphate and roughly as strong a phosphorylating agent as PEP; it has, however, the disadvantage of even more severe hydrolytic instability than acetyl phosphate.[221] A number of other systems for regeneration of ATP have also been suggested,[35,225] but do not seem to be practical.

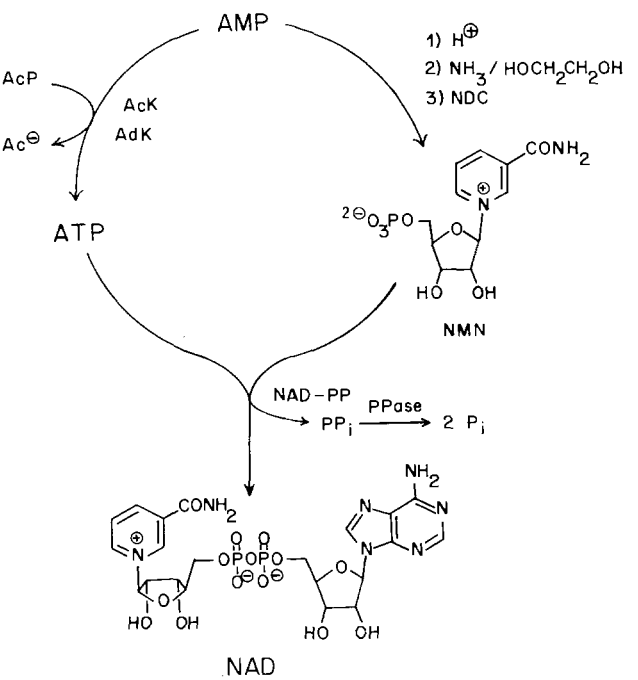
For certain large-scale applications, even given a good regeneration system for in situ reconversion of AD(M)P to ATP, the initial cost of the ATP may be significant. AMP can be purchased inexpensively in kilogram quantities and converted to ATP either in situ or in a separate step.[226] Alternatively, an efficient preparation of crude ATP from RNA has been developed.[226-228] These syntheses should render the cost of the adenosine mononucleotide moieties required for this type of synthesis unimportant on a process scale.

The other nucleoside triphosphates (GTP, UTP, CTP) and the deoxynucleoside triphosphates (dATP, dGTP, dUTP, TTP) are less important in most plausible organic synthetic applications than is ATP. Fortunately, acetate kinase and pyruvate kinase will accept all of these species as cofactors,[218,229] and thus the acetyl phosphate (methoxycarbonyl phosphate)/acetate kinase and PEP/pyruvate kinase systems will regenerate all of these nucleoside and deoxynucleoside triphosphates from the corresponding diphosphates.

Most of the simple applications of ATP regeneration systems have been to the preparation of sugar phosphates using kinases. Glucose-6-phosphate is a useful reagent for reduced nicotinamide cofactor regeneration;[230] dihydroxyacetone phosphate is a reagent for use in aldol reactions catalyzed by rabbit muscle aldolase;[108,109] *sn*-glycerol-3-phosphate[233] has the correct absolute configuration to serve as the basis for the synthesis of phospholipids; arginine phosphate[221,231] and creatine phosphate[224] illustrate the synthesis of materials which themselves have high phosphate-donor potentials, and are therefore thermodynamically difficult to prepare. These kinases are also useful in the preparation of modified nucleoside triphosphates (e.g., ATP-γ-S[232] and ATP-α-S[233]).

Of these simple kinase-based systems, the most broadly applicable in synthesis is, at present, that using glycerol kinase. This enzyme accepts a number of three- and four-carbon substrates, and yields enantiomerically enriched products.[234] It can be used in kinetic resolutions.

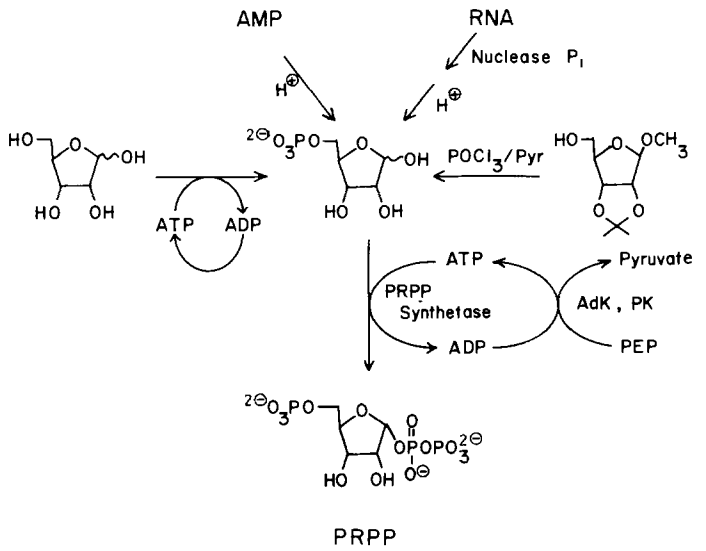
More complicated processes requiring regeneration of ATP are illustrated by syntheses of NAD(P) and phosphoribosyl pyrophosphate (PRPP). The synthesis of NAD(P) (Scheme 4)[235,236] illustrates a practical procedure which successfully combines classical organic and enzymatic synthetic methods. The reaction sequence avoids the use of protecting groups, chromatographic separations, and complicated purifications. This preparation still does not compete with isolation as a source of NAD,[237-239] but it does provide sufficient chemical flexibility to permit synthesis of a number of isotopically and structurally modified analogues of NAD(P).



Scheme 4. Synthesis of NAD from AMP. Abbreviations: AcP, acetyl phosphate; AcK, acetate kinase; AdK, adenylate kinase; NAD-PP, NAD pyrophosphorylase; PPase, pyrophosphorylase; PP_i, pyrophosphate; NMN, nicotinamide mononucleotide; NDC, *N*-(2,4-dinitrophenyl)-3-carbamoylpyridinium chloride.

The synthesis of 5-phospho-D-ribosyl-1-pyrophosphate (PRPP)—a key intermediate in the biosynthesis of nucleotides—is another example which involves the use of an ATP regeneration system in a large-scale preparation of a substance difficult to synthesize using classical techniques.[240] This procedure should open new routes to nucleotides and other analogues.

One feature of the syntheses summarized in Schemes 4 and 5 deserves special comment: the use of enzymatic selectivity to circumvent the normal requirement for purifi-



Scheme 5. Synthesis of 5-phospho-D-ribosyl-1-pyrophosphate (PRPP). Abbreviations: Pyr, pyridine; PK, pyruvate kinase; PEP, phosphoenolpyruvate.

cation of intermediates. In classical multistep synthesis, it is important to purify intermediates, because impurities present in them will react in subsequent steps and, ultimately, generate mixtures of products which can be purified only with difficulty. In enzyme-catalyzed synthesis, requirements for purification of an intermediate may be less strict, because the enzyme will only accept its substrate. Processing of a crude reaction mixture through an enzyme-catalyzed step thus constitutes a form of purification. In Scheme 4, for example, the conversion of AMP to NAD was carried through with essentially no purification of intermediates at any point; the final crude NAD was accepted as a substrate by enzymes. Since purification of these types of molecules is often a major nuisance, the ability to use crude reaction mixtures directly in enzymatic synthesis may be a major practical advantage of an enzyme-based strategy.

6.3.2. *Enzymes Requiring Reduced Nicotinamide Cofactors (NADH or NADPH)*

The problem of cofactor regeneration involving the nicotinamide cofactors is more complex than that for the nucleoside triphosphates: the nicotinamide cofactors are more expensive than ATP (the least expensive is NAD: ca. US$ 1000/mol), and are, more importantly, intrinsically unstable in solution. The reduced nicotinamide cofactors are destroyed by several processes, the most important of which is a Lewis acid-catalyzed protonation on the dihydronicotinamide ring, followed by addition of water to the resulting iminium salt and further irreversible degradation.[230, 241] Thus, even given the existence of a good regeneration system, it is still important to keep the rate of the enzymatic reaction high, since the ratio of productive turnover of the nicotinamide cofactor by enzyme-catalyzed reaction to nonproductive hydrolytic destruction depends upon this rate. A very large amount of work has been devoted to developing and testing various types of systems for NAD(P)H reduction;[36, 230, 242–255] examples are summarized in Table 7. Of these, three now seem useful for synthetic applications.

Table 7. Systems for in situ regeneration of NAD(P)H from NAD(P) [a].

Regeneration Reaction	Ref.
$HCOO^{\ominus} + NAD \xrightarrow{FDH} CO_2 + NADH$	[36, 244]
G-6-P + NAD(P) $\xrightarrow{\text{G-6-PDH}}$ 6-PG + NAD(P)H	[230]
Glucose + NAD(P) $\xrightarrow{GDH}$ Gluconate + NAD(P)H	[255]
$H_2 + NAD(P) \xrightarrow[MV, LipDH]{H_2ase} H^{\oplus} + NAD(P)H$	[247]
$C_2H_5OH + NAD(P) \xrightarrow{ADH/AldDH} CH_3CO_2^{\ominus} + NAD(P)H$	[251]
$CH_3OH + NAD \xrightarrow{ADH/AldDH/FDH} CO_2 + NADH$	[251]
$H_2 + NAD \xrightarrow[MV]{Proteus\ mirabilis} H^{\oplus} + NADH$	[252]

[a] Abbreviations: FDH, formate dehydrogenase; G-6-P, glucose-6-phosphate; G-6-PDH, glucose-6-phosphate dehydrogenase (*L. mesenteroides*); 6-PG, 6-phosphogluconate; GDH, glucose dehydrogenase (*B. cereus*); H_2ase, hydrogenase; MV, methyl viologen; LipDH, lipoamide dehydrogenase; ADH, alcohol dehydrogenase; AldDH, aldehyde dehydrogenase.

Formate/Formate Dehydrogenase has two advantages as a regeneration scheme: formate is a strong reducing agent, and the product of reaction, CO_2, causes no complications in workup. Formate dehydrogenase (from yeast), although commercially available, is still relatively expensive; a good preparation has been reported by *Kula* et al.[36]

Glucose/Glucose Dehydrogenase is also an attractive system.[255] The enzyme (from *B. cereus*) is commercially available, thermally stable, and applicable to both NAD and NADP. The major disadvantages of the system are the expense of the enzyme and the requirement to separate product from glucose and gluconic acid.

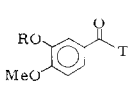
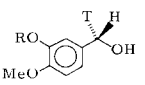
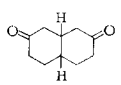
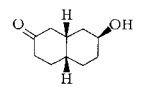
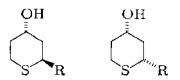
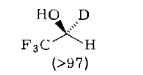
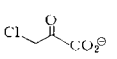
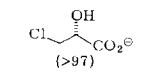
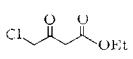
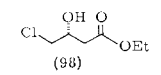
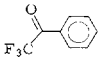
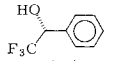
Glucose-6-phosphate/Glucose-6-phosphate Dehydrogenase has the advantage that the enzyme is very inexpensive and stable, and that the enzyme system accepts both NAD and NADP as substrates.[230] The glucose-6-phosphate must, however, be prepared (by hexokinase-catalyzed phosphorylation of glucose with in situ ATP regeneration) and the product must be separated from the 6-phosphogluconic acid produced as product.

A scheme starting with methanol and using a coupled enzyme system of methanol dehydrogenase, formaldehyde dehydrogenase, and formate dehydrogenase probably represents the most economical system available from the vantage of the ultimate hydride donor.[251] The system is not convenient to use for small-scale work, because it requires three enzymes. For large-scale work, however, it might well be worth the effort to develop a single microbial source for the three enzymes which could be used in a whole-cell package. The remaining systems for reduced nicotinamide cofactor regeneration are presently primarily of academic interest, although electrochemical procedures continue to attract attention.[252] In practice, schemes that use inexpensive reducing agents (H_2, electrons) emphasize the wrong feature: the expense in the reaction lies in the enzyme and the cofactor, not in the ultimate reducing

agent. These systems should not be discounted: with appropriate development, they may ultimately prove useful. They are not, however, the systems which are presently the most useful in organic synthesis.

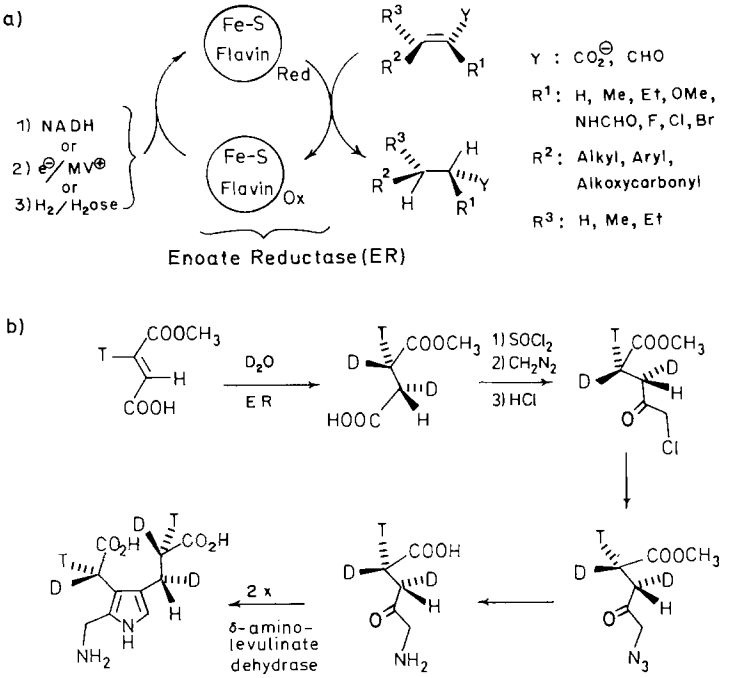
Synthetic application of the enzymes requiring reduced nicotinamide cofactors has so far been restricted to research applications. The most highly developed process is that described by *Kula* et al. for the production of amino acids.[136] Other applications have involved asymmetric reductions of carbonyl compounds, and production of isotopically labeled species (Table 8).[256–259] (A system based on deuterated formate and formate dehydrogenase provides the best system presently available for the introduction of deuterium through a nicotinamide-cofactor-catalyzed process.)[259] It is, however, important to emphasize that the problem of cofactor regeneration is only one of several that must be solved in utilization of the NAD(P)H-requiring oxidoreductases. At least as important are the problems of enzyme cost, enzyme stability, and product inhibition. This last problem is particularly difficult to solve in a general way, and is important because it places constraints on the ultimate concentrations of products attainable and on the rates of reaction.[260]

Table 8. Alcohol dehydrogenase-catalyzed reductions of carbonyl compounds using NAD(P)H as the hydride donor.

Substrate	Enzyme [a] (cofactor)	Product (*ee* [%])	Ref.
	HLADH (NADH)	 (100)	[256]
	HLADH (NADH)	 (100)	[261]
	HLADH (NADH)	 (100) (100)	[261]
	HLADH (NADH)	 (>97)	[259]
	L-LDH (NADH)	 (>97)	[262]
	HLADH (NADH)	 (98)	[255]
	TADH (NADPH)	 (91)	[255]

[a] Abbreviations: HLADH, horse liver alcohol dehydrogenase; L-LDH, L-lactic dehydrogenase; TADH, alcohol dehydrogenase from *Thermoanaerobium brockii*.

Another reducing enzyme that shows promising synthetic utility is the enoate reductase from the anaerobe *Clostridium kluyvery*.[252,263] The enzyme reduces different α,β-unsaturated carboxylate anions stereospecifically to the saturated carboxylate anions using NADH as a cofactor (Scheme 6a). A preliminary study regarding the reaction mechanism indicated that the reducing equivalent was transferred from NADH through the enzyme-associated iron-sulfur-flavin cluster to the substrate, and proton exchange between the reduced cluster and water was observed. The iron-sulfur cluster can be reduced with reduced methyl viologen produced electrochemically, and large-scale organic synthesis using a reactor suitable for electro-enzymatic reductions has been demonstrated.[264] Regeneration of NADH using H_2 and an anaerobic microorganism that contains hydrogenase has been developed and the regeneration system has been coupled with the *Clostridium* reduction of enoates.[252,265] The enoate reductase has also been used to prepare isotopically labeled chiral δ-aminolevulinic acid (Scheme 6b).[4] Similar asymmetric reduction of the CC double bond of α,β-unsaturated carbonyl compounds catalyzed by fermenting yeast has also been reported, but the enzyme responsible has not been isolated.[266] The reaction proceeds with formal *trans* addition of hydrogen across the double bond, with a *pro-R* hydrogen being introduced at the position α to the electrophilic substituent. It is unlikely that the yeast enzyme contains an oxygen sensitive iron-sulfur cluster because fermenting yeast is aerobic.



Scheme 6. Asymmetric reduction of carbon-carbon double bonds catalyzed by enoate reductase (ER). a) General reaction scheme; b) synthesis of isotopically labeled, chiral δ-aminolevulinic acid.

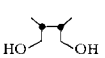
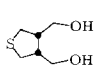
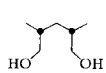
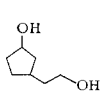
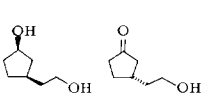
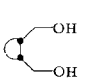
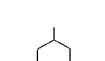
6.3.3. *Enzymes Requiring Oxidized Nicotinamide Cofactors (NAD or NADP)*

The problem of regeneration of *oxidized* nicotinamide cofactors is still not completely solved. The same constraints apply in this system as to those involving the reduced nicotinamide cofactors, but, in addition, the problem of product inhibition (especially kinetically mixed and uncompetitive inhibition[20]) is often severe.[260,267] The oxidized nicotinamide cofactors are also hydrolytically un-

stable in solution, and are subject to destruction in several types of enzyme-catalyzed processes. The most widely used procedure for in situ regeneration of NAD from NADH is that developed by *Jones* et al.[268] This system is based on the (non-enzyme-catalyzed) reoxidation of NADH by oxidized flavin; the reduced flavin is in turn oxidized by molecular oxygen. The disadvantage of this system is that large quantities of flavin are required to achieve useful rates, and that the separation of product from flavin is inconvenient. A number of other systems have been proposed for this regeneration.[2,242,243,269,270] Probably the most general involves oxidation of NADH to NAD coupled with enzyme-catalyzed reduction of α-ketoglutarate and ammonia to glutamic acid.[267,269] This system has the advantage that it avoids the exposure of the enzymatic system to dioxygen, with the concomitant risk of oxidation of enzymes or substrates. It has the disadvantage that glutamic acid must be separated from the product at the conclusion of the reaction. An enzyme-catalyzed system based on diaphorase and methylene blue is also useful for reoxidation of NADH to NAD when dioxygen (the ultimate oxidizing agent) can be tolerated by the system.[243,267,270,271] The flavin mononucleotide (FMN) reductase (E.C. 1.6.8.1) from photobacterium species catalyzes the reaction of NAD(P)H with dioxygen and FMN;[271] this enzyme has satisfactory specific activity (ca. 100 U/mg) and markedly improves the efficiency of the regeneration system developed by *Jones* et al.

The most important body of work devoted to synthetic applications of enzymes requiring oxidized nicotinamide cofactors has been that of *Jones* and coworkers, and of other groups,[272-277] concerning applications of horse liver alcohol dehydrogenase. Examples of these transformations are given in Table 9. These reactions, although highly practical on the scale of several grams, have not been carried to large-scale work. Several problems have hindered this stage of development. First, until recently, the available regeneration systems have not been truly practical for large-scale work. Second, horse liver alcohol dehydrogenase is particularly subject to product inhibition. Many of the most successful examples of *Jones* et al. are based on the oxidation of *meso*-diols to optically active lactones. These systems seem to be relatively free of product inhibition. Attempts to achieve kinetic resolutions of simple alcohols by oxidation of one enantiomer have, in general, been relatively unsuccessful on large scale. The active site of alcohol dehydrogenase appears to be hydrophobic, and to bind the product ketone more strongly than the reactant alcohol.[274,278,279] This specific system has been analyzed in some detail. There appears to be no general strategy to deal with product inhibition, other than to remove the product as it is formed by extraction or by some other technique.[21,30] When extraction is feasible (using, for example, a two-phase water-organic system to remove the ketone selectively as it is produced), the problem can be circumvented. In other circumstances, it is more troublesome.

Table 9. HLADH-Catalyzed oxidation of diols using NAD as a cofactor.

Substrate	Product	*ee* [%]	Ref.
		100	[272]
		100	[272]
		100	[272]
		100	[274]
		100	[275]
		96	[276]

6.3.4. *Enzymes Requiring S-Adenosyl Methionine, Acetyl-CoA, PAPS, or Other Cofactors*

S-Adenosylmethionine (SAM) is an important one-carbon donor in many enzyme-catalyzed reactions.[280-282] A study of the enzymatic synthesis of SAM from ATP and methionine catalyzed by SAM synthetase from yeast concluded that the practicality of the reaction hinged upon the availability of SAM synthetase.[282] The preparation of substantial quantities of homogeneous SAM synthetase from a genetically engineered strain of *E. coli* has been described.[283] This enzyme is, however, seriously inhibited by product. The inhibition constant (K_i) of SAM vs. ATP (a competitive inhibitor) or methionine (a noncompetitive inhibitor) is ca. 0.01 mM.[282] The corresponding K_i values for the enzyme from yeast are ca. 6 mM.[284] If the *E. coli* enzyme could be modified using site-specific mutagenesis and recombinant DNA technology to increase the K_i values significantly, this procedure for the preparation of SAM could form the basis for a practical method for preparation of quantities of SAM for *stoichiometric* use in enzyme-catalyzed synthesis. No strategy for in situ regeneration of SAM is now evident. In a transmethylation using SAM as methyl donor, the product of SAM is *S*-adenosylhomocysteine (SAH). At present, there is no enzyme known which catalyzes the selective methylation of SAH to SAM. Although chemical procedures are available for the synthesis of SAM from SAH,[285] they produce racemic products and enzymes only accept the (−)-isomer.[280,286] In an alternative route to (±)-SAM, which does not require ATP as a starting material, L-homocysteine and adenosine are converted into SAH chemically[287] or enzymatically,[145-149] and SAH is methylated chemically. If resolution of SAM could be accomplished conveniently, this procedure might be valuable.

Little work has been devoted so far to synthetic applications of reactions requiring acetyl-CoA and its analogues as cofactors. Although CoASH is a broadly important cofactor in biochemistry, from a strategic viewpoint it is unclear that reactions involving it will be as important in enzyme-catalyzed synthesis as are reactions involving other

cofactors. Acetyl-CoA is central in reactions leading to fatty acids, polyketides, and derived species.[288] It is precisely these classes of compounds which classical organic synthesis is most successful in preparing. Whether enzymatic procedures offer advantages relative to chemical or fermentation routes to these compounds remains to be established.

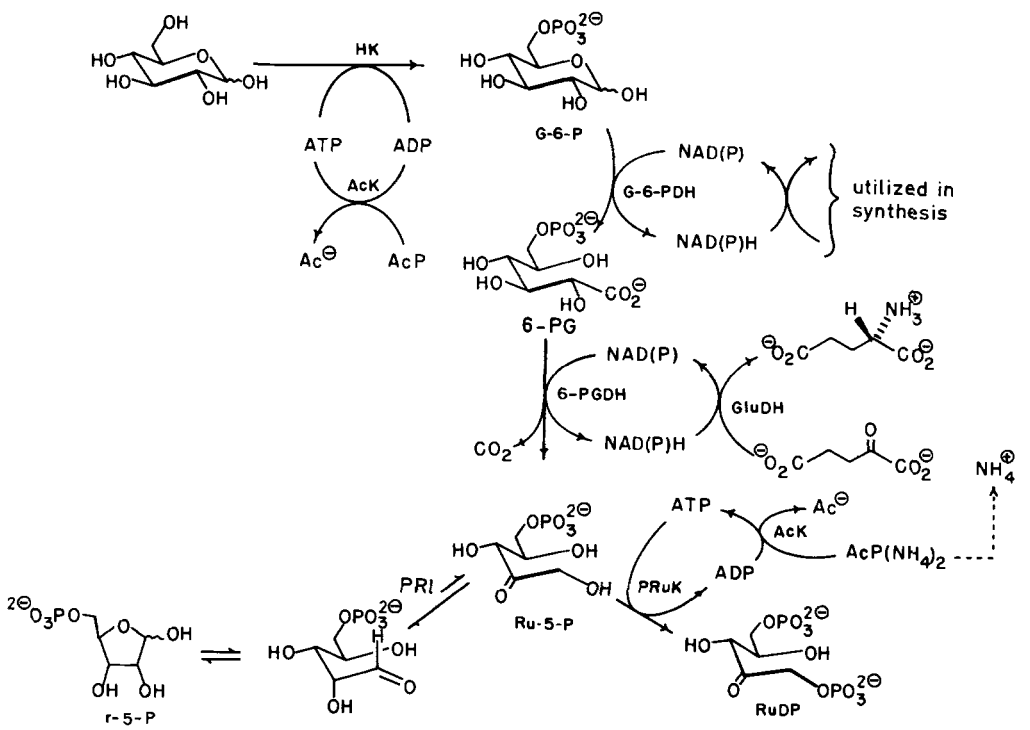
3′-Phosphoadenosine-5′-phosphosulfate (PAPS) is a sulfate donor, universally used in biochemistry for sulfation of polysaccharides and for activation of sulfate. It is regenerated in vivo by a complex set of reactions involving the enzymes ATP-sulfurylase and adenylsulfate kinase.[289,290] Although sulfation of polysaccharides is an interesting and potentially important target reaction for enzyme-catalyzed synthesis (for example, in the modification of heparin[291] or the synthesis of chondroitin sulfate[292]), no straightforward method now exists to achieve either the synthesis or regeneration of PAPS.

7. Syntheses Involving Multienzyme Systems

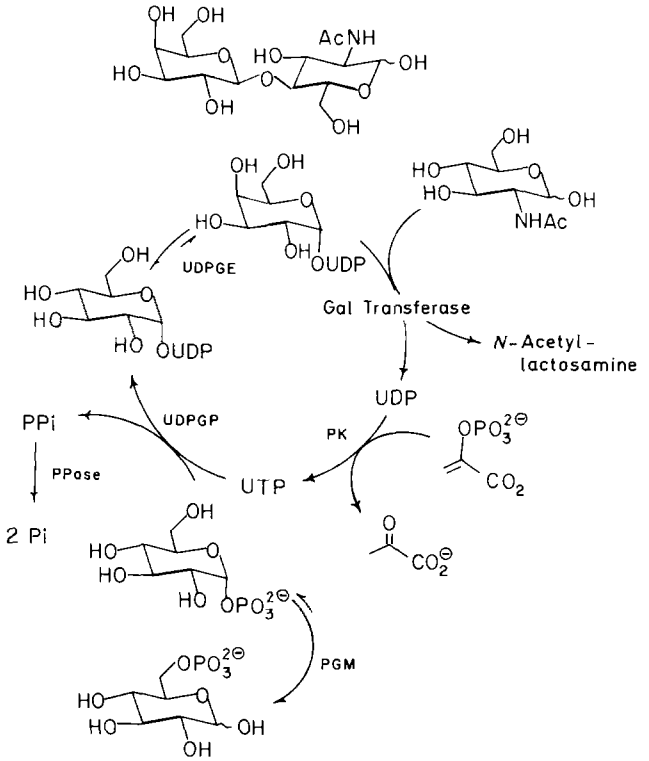
A potentially important characteristic of enzymes as catalysts in organic synthesis is that, because most enzymes operate with reasonable efficiency at values of pH between 6.5 and 8.5 and at temperatures around room temperature, it is often possible to assemble complex systems containing multiple enzymes cooperating in sequence or in parallel to achieve multi-step processing of substrates. The synthesis of ribulose-1,5-diphosphate (RuDP), an important substrate in plant biochemistry (Scheme 7),[217] provides an example of a synthesis for which enzymatic catalysis provides the best solution. This synthesis, despite its apparent complexity, is actually quite straightforward, and several hundered grams of RuDP has been prepared in the course of the several reactions devoted to developing it. The point of technical interest in this synthesis is the final conversion of 6-phosphogluconate to RuDP. The kinase that converts ribulose-5-phosphate to RuDP is oxygen sensitive. Thus, the in situ regeneration of NAD from NADH required in conversion of 6-phosphogluconate to ribulose-5-phosphate cannot be carried out using an oxygen-based regeneration system. This regeneration is, however, conveniently carried out anaerobically using the α-ketoglutarate/glutamate dehydrogenase system. This part of the synthesis requires the cooperative action of four enzymes: 6-phosphogluconate dehydrogenase and 5-phosphoribulokinase for the principal conversions, and glutamate dehydrogenase and acetate kinase for in situ regeneration of cofactors.

The conversion of glucose-6-phosphate and *N*-acetylglucosamine to lactosamine provides a more complex example.[293] Lactosamine is a core disaccharide, common in glycoproteins. This synthesis (Scheme 8) illustrates the cooperative interaction of six enzymes, and establishes the utility (howbeit on a small scale) of the Leloir pathway enzymes for oligosaccharide synthesis. This type of procedure has subsequently been extended to trisaccharides.[294]

The conversion of glucose to ethanol provides a final example of a coupled multienzyme system (Scheme 9; in this scheme, several enzymes required to regulate the concen-



Scheme 7. Enzymatic syntheses of RuDP. Abbreviations: G-6-P, glucose-6-phosphate; 6-PG, 6-phosphogluconate; Ru-5-P, ribulose-5-phosphate; AcP, acetyl phosphate; Ac, acetate; 6-PGDH, 6-phosphogluconate dehydrogenase; GluDH, glutamic acid dehydrogenase; PRuK, 5-phosphoribulokinase; PRI, phosphoriboisomerase; AcK, acetate kinase; HK, hexokinase; r-5-P, ribose-5-phosphate.



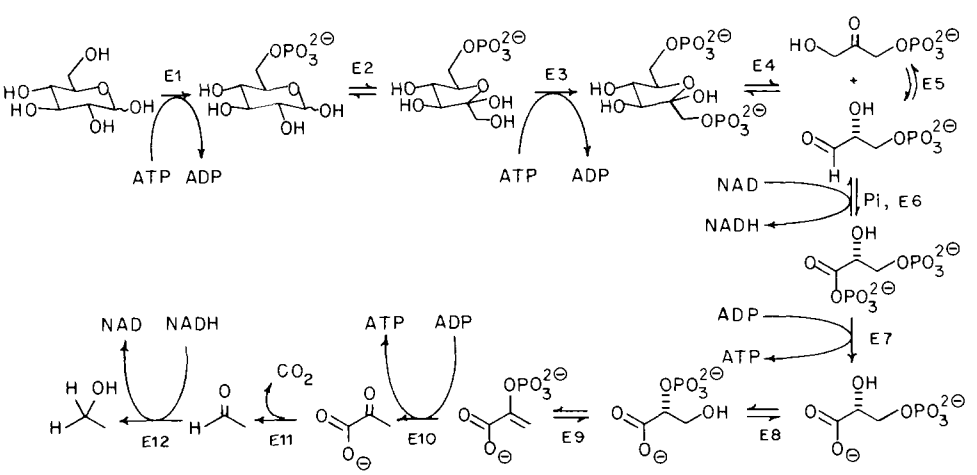
Scheme 8. Synthesis of *N*-acetyllactosamine. Abbreviations: Gal transferase, galactosyl transferase; PK, pyruvate kinase; PGM, phosphoglucomutase; UDPGP, UDP-glucose pyrophosphorylase; UDPGE, UDP-glucose epimerase; PPase, inorganic pyrophosphatase.

tration of ATP are omitted for simplicity). This system was not developed for synthetic purposes—there are simpler ways of obtaining ethanol—but rather to study the mechanism of ethanol toxicity in yeast and to examine the kinetic characteristics of a regulated multienzyme system.[295] Nonetheless, it establishes that it is practical to construct processes requiring sequential operation of many cooperating enzymes.

8. More Difficult Enzymatic Systems: Oxygenases and Systems for Syntheses of Macromolecules

The practicality of using monooxygenase systems has been the subject of speculation in applied enzymology for some years. Certain enzyme systems, operating in vivo, catalyze hydroxylation, epoxidation, and related oxidation reactions with selectivities that cannot be matched using classical synthetic technology. These in-vivo systems are widely important in the oxidative functionalization of steroids and other hydrocarbons (using fungal systems), and interesting isolated examples having emerged from other areas of fermentation chemistry.[211,296–299] An important recent example is the conversion of benzene to *cis*-3,5-cyclohexadiene-1,2-diol by fermentation.[300] Many of these transformations are accomplished by cytochrome P450 or non-heme iron-sulfur enzymes.[301,302] The cytochrome P-450's have been widely studied mechanistically, because of their importance in steroid metabolism and carcinogen production; the non-heme iron-sulfur proteins are less well understood.

From a practical point of view, microbial systems based on non-heme iron-sulfur and copper-sulfur enzymes are the most interesting.[200–202,303] Although these systems have been extensively examined, current indications suggest that they will not be useful for enzymatic transformations in vitro in the immediate future. They suffer from several disadvantages. First, in vitro, operating lifetimes of the enzymes are short. Many of the cytochrome P450 enzymes are membrane-bound or membrane-associated, and it is conceivable (although not yet practical) that appropriate use of surfactants or model membranes might provide valuable stabilization. The in-vivo lifetimes of the simpler microbial monooxygenases have not been carefully examined, but they also seem to be short. Perhaps more importantly, these enzymes require accessory enzyme systems as a source of reducing equivalents, ultimately used to convert dioxygen to a more reactive species at the



Scheme 9. Enzymatic pathway from glucose to ethanol. Enzymes: E1, hexokinase; E2, phosphoglucomutase; E3, phosphofructokinase; E4, aldolase; E5, triosephosphate isomerase; E6, 3-phosphoglycerate dehydrogenase; E7, 3-phosphoglycerate kinase; E8, phosphoglycerate mutase; E9, enolase; E10, pyruvate kinase; E11, pyruvate decarboxylase; E12, alcohol dehydrogenase.

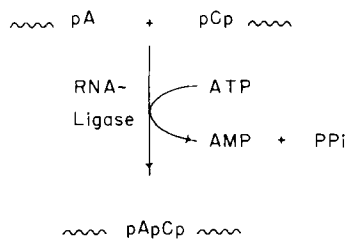
hydrogen peroxide oxidation level. These accessory enzymes typically require NADH or NADPH as the ultimate reducing agent. Thus, the final system contains a number of sensitive enzymatic components. Further, the efficiency of the coupling of oxidation of NADH to reduction of dioxygen has, so far, been poor in vitro: the majority of NAD(P)H is "wasted" in production of hydrogen peroxide or superoxide, both themselves species capable of reacting with and inactivating enzymes. It may be that the problems associated with these potentially valuable monooxygenases will ultimately be solved, but for the immediate future, these systems do not represent practical methods for oxidative functionalization of hydrocarbons.

A second class of enzymes that is attracting interest is that responsible for the synthesis of polysaccharides, oligosaccharides, and proteins.[304-306] Each of these systems represents a different set of problems. Cell-surface oligosaccharides are of substantial interest as, inter alia, disease-associated antigens and histocompatibility markers, and as reagents of possible interest in drug delivery.[304,307] In most systems, they are assembled by enzymes utilizing the Leloir pathway and localized in the Golgi apparatus.[308] These membrane-bound enzymes are usually obtainable only in small quantities. It is unresolved whether it will be more practical to base synthetic schemes on isolated enzymes or to rely on isolation from natural sources or screening for high-producing mutants for fermentation synthesis. The enzymatic systems involved in synthesis of many polysaccharides (especially those of microbial origin) are, in principle, more straightforward. Since polysaccharides cannot presently be prepared by any classical chemical technique, and because these substances have properties valuable in modification of the rheological properties of aqueous solutions and in pharmacological applications,[304-306] enzyme systems that synthesize polysaccharides may prove valuable. Again, however, no practical example yet demonstrates the utility of such systems.

Cell-free protein synthesis might provide a technique complementary to DNA methodology for certain applications.[309,310] At present, however, the complexity of the systems of enzymes required to accomplish this type of process is such that it is impractical on scales larger than micrograms.

The central scientific discoveries that have focused interest on biologically based syntheses are those leading to recombinant DNA (rDNA) technology. This technique depends on a number of enzymes that make it possible to implant desired genes into a foreign organism to produce desired proteins.[311,312] Of the enzymes used in rDNA technology, DNA ligase and restriction endonucleases are two of the most important. DNA molecules can be cleaved specifically with specific restriction endonucleases and joined with another restriction-enzyme-modified DNA fragment in a reaction catalyzed by DNA ligase. These chemical transformations cannot be accomplished by classical synthetic techniques, and the enzymatic methods might be useful in practical-scale nucleic acid chemistry. The enzymes used in rDNA research are, however, expensive. Technical problems concerning stabilization and large-scale production of enzymes need to be solved if this type of enzymology is ever to be used for preparative chemical synthesis (large-scale work is unnecessary for use in genetic engineering, because microbial growth provides large amplification). We note also that since the condensation reactions involved in forming phosphodiester links require either NAD (in reactions catalyzed by NAD ligase from bacteria, and generating AMP and NMN) or ATP (catalyzed by T_4 DNA ligase from phage-infected bacteria or from eukaryotes, and generating AMP and pyrophosphate),[310] cofactor regeneration may be required for large-scale production.

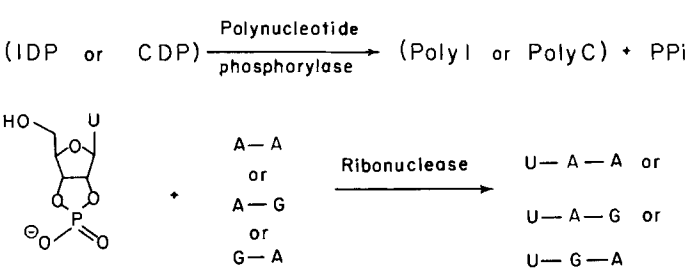
Another ligase that has been used increasingly is RNA ligase.[311,313-315] The enzyme T_4 RNA ligase catalyzes the synthesis of single-stranded oligonucleotides of different lengths from a 3′-terminal hydroxyl acceptor and a 5′-terminal phosphate donor oligoribonucleotide through the formation of a 3′→5′ phosphodiester bond, with hydrolysis of ATP to AMP and pyrophosphate. The 5′-terminal phosphate donor can be nucleotides as small as monomer units and the 3′-terminal hydroxyl acceptor can be a dimer, trimer, or oligomer.[311] The enzyme also accepts single-stranded DNA as a substrate (Scheme 10). This enzyme



Scheme 10. A representative scheme for the RNA-ligase-catalyzed formation of a 3′→5′ phosphodiester bond between oligonucleotides containing terminal A and pC.

has been used to couple short, chemically synthesized oligonucleotides to longer oligomers.[313] It also has been used for modification of nucleic acids by introducing radioactive probes and by replacing nucleotide residues.[311-316] Since applied biology based on rRNA technology may be important for the future, and since chemical methods for the synthesis of RNA are not as well developed as those for DNA, RNA ligase could play an important role in this area.

Two other examples of polynucleotide synthesis deserving mention are the polynucleotide phosphorylase-catalyzed synthesis of polyI:C[317] (an inducer of interferon) and the ribonuclease-catalyzed synthesis of trinucleotide codons[318] (Scheme 11). These two enzymes have a broad



Scheme 11. Synthesis of polynucleotides catalyzed by polynucleotide phosphorylase, and of trinucleotides catalyzed by riconuclease.

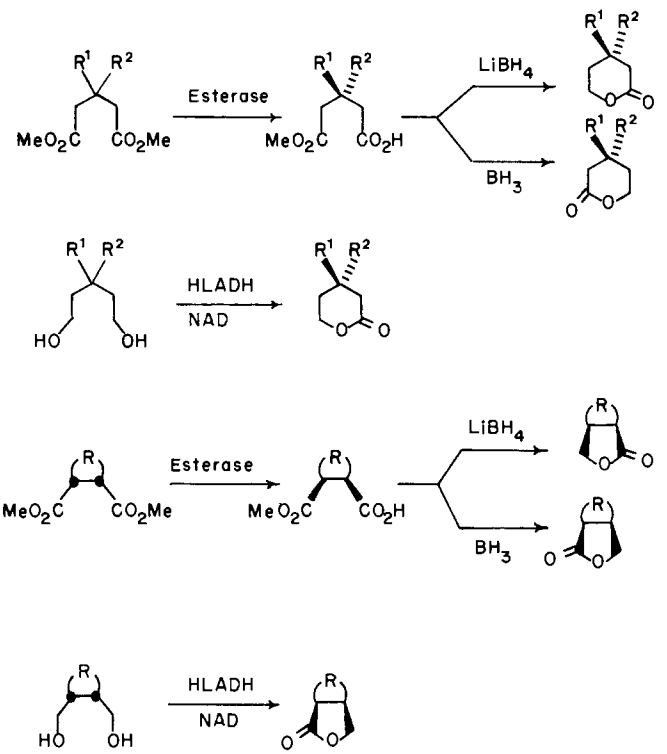
range of specificity; they can thus be useful for the synthesis of other polynucleotides.

9. Summary and Outlook

Enzymes are catalysts that are useful in a variety of synthetic problems: synthesis of chiral fragments; transformations of sugars, nucleotides, and related species; synthesis of compounds important in metabolism and analogues of these metabolites (amino acids, sugar phosphates, etc.); transformations of peptides and proteins; transformations of compounds present in foods and other transformations in which classical chemical methodology is constrained by regulation. What are the technical problems that must be solved to consolidate and extend these uses? What are the barriers that a synthetic organic chemist must overcome in order to use enzyme-catalyzed synthesis?

The two major barriers to the use of enzymes are probably educational. The first is that of learning the basic techniques of enzymology and biochemistry, especially the specialized techniques of analysis and isolation of enzymes. Neither is difficult, but both require skills that are not familiar to most classically trained synthetic chemists. Standard biochemistry textbooks are helpful in learning these techniques; *Bergmeyer*'s series provides an indispensible reference for enzymatic assays.[319] A short apprenticeship in a biochemistry laboratory is exceedingly helpful. A second, more serious problem (at least in considering the feasibility of including enzymology in a proposed synthetic sequence) is finding out whether an enzyme is known (or, better yet, commercially available) that can plausibly carry out the transformation of interest. This problem is a difficult one to solve. There is presently no reference that describes enzymology from the vantage of a synthetic chemist, that outlines the types of synthetically useful transformations which might be expected from a given class of enzymes, or that details the enzymes capable of conducting a particular type of transformation. Most enzymes have not, in fact, been examined for their utility in synthesis, and the nomenclature of enzymology is not helpful in establishing activity for new transformations. This article lists several of the enzymatic systems that have been explored in sufficient detail to be helpful in organic synthesis; the series *Methods in Enzymology* and *Bergmeyer*'s series give sample procedures involving enzymes (usually on an analytical scale) that are helpful in suggesting new applications. In the absence of specific solutions from these sources, the synthetic chemist can only consult his biochemical colleagues, and test enzymes known to operate on substrates analogous to those of interest in the proposed process.

If an enzyme can be found that effects the desired transformation, what determines the practicality of a process based on this enzyme? Clearly, technical features—the availability of the enzyme, its specificity, specific activity, and stability, its cofactor requirements—are of primary importance in evaluating the practicality of a specific enzyme. Of greater interest to most organic synthetic chemists is a broader question of strategy. Enzymes should be regarded simply as one more type of catalyst, and the best synthetic procedures will be those that make the most efficient and best integrated use of all of the available techniques—classical organic synthesis, homogeneous and heterogeneous catalysis by metals, catalysis by enzymes, fermentation, electrochemistry, conventional resolution, and other methods. In certain instances—for example, the use of DNA ligase and restriction endonuclease to close and open nicks in DNA—enzymes have no competition from other techniques. In production of chiral synthons for use in synthesis of pharmaceuticals, the range of options open to the synthetic chemist is much larger. The optimal strategies for using enzymes are still evolving. For example, is it more efficient to use horse liver alcohol dehydrogenase to oxidize a *meso*-diol to a lactone (taking into account the problems of cofactor regeneration and product inhibition) or to use an esterase in combination with a chemical oxidation (Scheme 12)? For resolution of a new epoxy alcohol, is it better to use asymmetric epoxidation[17] or an esterase? For production of large quantities of short oligopeptides, is catalysis by selected amidases starting from minimally protected amino acids in dehydrating media preferred, or are conventional chemical coupling procedures superior? None of these questions presently have categorical answers. The general point is, however, that the range of plausible applications of enzymes in organic synthesis is much larger than might be supposed by the range of their present use. Enough experimental background is now available that many of the generic problems involved in applying enzymes as catalysts have been solved.



Scheme 12. Alternative routes to optically active lactones.

Certain problems in synthesis will unquestionably benefit from use of enzymatic catalysis. Synthetic chemists capable of using this class of catalysts will have a clear advan-

tage in their ability to tackle the new generation of problems in synthesis appearing at the border between chemistry and biology. Those unwilling to use these and other biologically derived synthetic techniques may find themselves excluded from some of the most exciting problems in molecular science.

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The Construction of New Proteins and Enzymes—a Prospect for the Future?**

By Manfred Mutter*

Dedicated to Professor Paul J. Flory on the occasion of his 75th birthday

Only a vanishingly small proportion of the almost infinite number of possible proteins occur in nature. Can this remaining potential of structural and functional diversity be used in the construction of new proteins? Is a "second evolution" of proteins and enzymes about to occur? These questions have suddenly become of interest because the recombinant DNA technique allows the synthesis of any given amino acid sequence. Examples of enzyme models demonstrate clearly that the unusual catalytic properties of enzymes are associated with the presence of a specifically folded polypeptide chain which has a complex three-dimensional form. The critical hurdle in the path of artificial proteins is thus the design of amino acid sequences which are able to fold into *tertiary structures*.—Recent studies on the topology and the mechanism of folding have provided considerable insight into the occurrence of, and the rules governing the three-dimensional architecture of proteins. Secondary structures apparently play a key role in the folding process; helices and "β-structures" act as nucleation centers directing folding and account for the surprisingly small number of different folding topologies. The problem of secondary structure formation can be investigated directly by means of conformational studies on model peptides. Oligopeptides with tailor-made physicochemical, structural and conformational properties can already be designed. The theoretical and experimental basis for the construction of polypeptides with stable tertiary structures is therefore established. The path to macromolecules with an immense variety of novel properties lays before us.

1. Introduction

The unusual catalytic properties of enzymes are the focus of interest in diverse research activities. The capability of enzymes to accelerate reactions specifically and selectively is being increasingly exploited by chemists, as it far exceeds that of synthetic catalysts.

Of the astronomical number of possible amino-acid sequences, only an incredibly small proportion occurs in nature. Those chains which can fold to produce a globular, three-dimensional structure (tertiary structure), and can thus perform biological functions, have been selected in the evolutionary process. Proteins and enzymes are thus optimized systems for performing specific biological functions and this is reflected by a complexity of structures and functions that is still poorly understood. In the light of this background the following question arises: Can new molecules with enzyme-like structural and functional properties be created? This problem could be approached in two ways:

—by transferring enzyme-specific characteristics to more easily accessible molecules,

—by designing new proteins with unnatural amino acid sequences ("artificial proteins"[*]).

What are the possibilities and limits of the scientific and practical uses of the construction of new proteins and enzymes?

Critical analysis of the "enzyme-like" catalysts that have so far been developed shows that the complex relationships between enzyme-specific structural features and properties (such as the spatial orientation of reactive groups, specific ligand and substrate binding, creation of a local hydrophobic environment, or allosteric control) only occur with multifunctional, *macromolecular* structures.[1,2,10] On the other hand, the imitation of *individual* enzyme-typical properties by simple structures is of considerable importance for practical applications. The following questions must be answered in connection with the construction of artificial enzymes:

Is the complex, *three-dimensional* architecture of proteins a prerequisite for enzyme-analogous functions? Has nature created 'surplus' complexity—in the sense of 'molecular tinkering'?[45]

These questions will be dealt with in Section 2 of the present progress report; the problem will be illustrated using the hydrolytic activity of "enzyme models" based on polymers, particularly polypeptides.

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[**] Extended version of a lecture given on being awarded the Max Bergmann Prize, 3rd Max Bergmann Conference, October 7—9, 1982, Bolzano (Italy).

[*] "Artificial proteins" are defined here as polypeptide chains, containing an amino acid sequence non-homologous to one in nature, that are able to fold into a tertiary structure and thus possess features typical of proteins; "artificial enzymes" are artificial proteins with catalytic activity.

The idea of constructing new proteins with tailor-made functional properties has become of topical interest due to the development of the DNA recombination technique (genetic engineering).[3] In principle, it is already possible to reliably construct any given amino acid sequence. The almost unlimited number of sequence permutations provides an immense potential of structural and functional diversity for designing new proteins. The problem that has to be solved is therefore not so much the synthesis of the primary sequence but rather the understanding of how proteins acquire their spatial structures. The "tertiary structure puzzle" is thus the real obstacle hindering the construction of artificial proteins. Even though the "folding code" still has to be deciphered,[4] X-ray structural analysis has at least thrown considerable light on the rules governing the spatial construction of proteins.[4-6] In Sections 3 and 4 of this report a discussion of these fundamental considerations is followed by a discussion of a strategy for constructing new proteins based on current knowledge of the relationships between primary, secondary, and tertiary structures.

2. Must Enzymes Have a Tertiary Structure?

A look at the sometimes surprisingly clearly organized and comparatively simple structures of the active centers of enzymes[7-9] suggests that perhaps an enzyme-analogous function could be obtained by developing much more simple molecules. The formation of an active center in which, for example, functional groups interact specifically as a result of spatial fixation does not seem in principle to be limited to peptide structures (i.e. to a backbone consisting of amino acid building blocks). This likewise applies to other typical structural features of enzymes e.g. to a hydrophobic nucleus within a hydrophilic solubilizing surface (Fig. 1).[10]

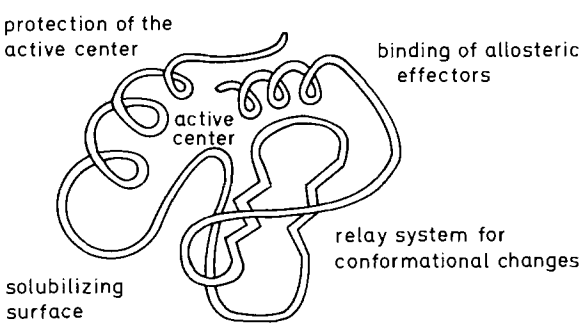
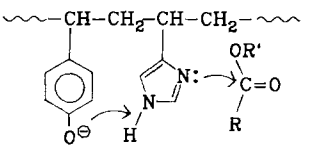


Fig. 1. General structural and functional characteristics of enzymes. The different properties of an enzyme are based on its complex three-dimensional structure which results from the characteristic folding of the polypeptide chain.

The selection of models which follow aim to imitate these features of enzymes.

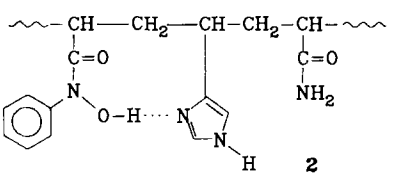
2.1. Polymeric Catalysts as Enzyme Models

The range of possibilities for the synthesis, functionalization, and derivatization of synthetic polymers gives the imagination of almost unlimited scope for imitating enzyme-specific properties. The majority of publications on polymeric catalysis are concerned with the influence of hydrophobic and cooperative effects on the catalytic activity of imidazole as a model for enzymes containing histidine.[1,2,11-13] A copolymer composed of 4-vinylimidazole and *p*-vinylphenol accelerates the reaction rate of the hydrolysis of active esters significantly compared with the monomeric starting compounds. This can be explained in terms of a cooperative mechanism.[14,15]



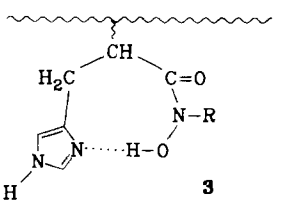
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Cooperative effects of spatially neighboring functional groups are also found in copolymers of the type **2**, in which the nucleophilicity of the hydroxamic acid group is



2

enhanced by hydrogen bond formation (in a similar manner to the serine-OH of α-chymotrypsin).[16,17] Compounds of type **2** react according to a typical two-step mechanism in which the deacylation step is accelerated by the neighboring imidazole group and is two orders of magnitude higher than with the monomers. The catalytic activity can be increased further if the functional groups participating in cooperative interactions are covalently fixed in the basic building block **3**.[13,18,19]



3

However, the catalytic activity of these systems is sometimes appreciably reduced by polymer effects which are caused by conformational and sterically controlled interactions within the tangled polymer.[1]

Polymeric catalysts with a random-coil structure have randomly orientated functional groups due to the high flexibility of the chain.[20,83] Moreover, the structure is generally heterogeneous so that experimentally determined rate constants are often difficult to interpret. This applies particularly to "enzyme models" which are based on statistical functionalization or polymer-analogous derivatization of cross-linked or branched polymers (e.g. polyethyleneimine).[21-24] Due to the complex interactions between the catalyst, substrate and solvent, systematic investigation of the individual parameters of critical importance for catalysis is

only possible in models with a well-defined structural organization. This requirement is satisfied in "single center" models[2, 25, 26, 28] (Fig. 2).

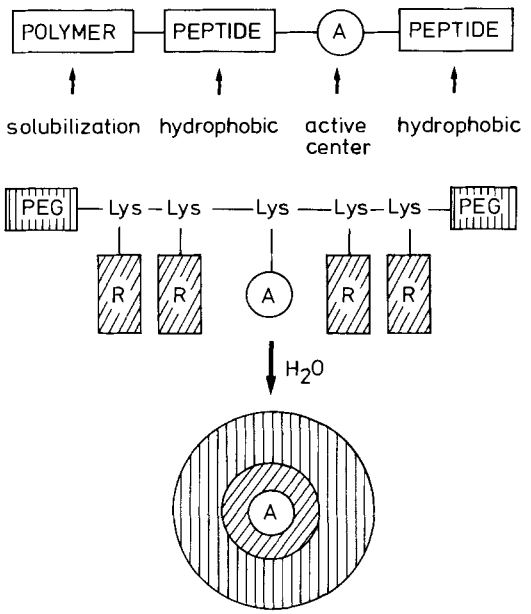


Fig. 2. Single-center model for the study of enzyme-like catalysis. The peptide (e.g. oligolysine) with a hydrophobic side chain R (e.g. a mesogenic N^{ε}-amino protecting group) is synthesized stepwise on soluble polymers (e.g. PEG, polyethyleneglycol) so that the active center A (e.g. NH_2, imidazole, histidine hydroxamic acid) can be incorporated selectively. In contrast to polyfunctional models, the macromolecule only possesses *one* active center in a well-defined environment. In an aqueous medium aggregation of the side chains results in the formation of micelle-like structures in which A is located in the hydrophobic core and the solubilized PEG chain imitates the enzyme surface [25, 26, 28].

The differential functional and structural characteristics of an enzyme are copied here using a block copolymer. The polymer block aids solubilization and also allows stepwise synthesis of the peptide block[27, 81, 89] whose functional and physicochemical properties can be modified in a specific way.[26, 28, 161] In the system shown in Figure 2 for example, the hydrolytic activity with *p*-nitrophenyl laurate can be increased by a factor of up to 10^4 by micelle-like inclusion of the active center in a hydrophobic environment.[26] The selective synthesis of oligopeptide chains in the *side-chain* of polyfunctional supports represents a variation of this principle[29, 169, 170] (Fig. 3).

An important step in the direction of enzyme-like catalysis is the spatial fixation of functional groups by stiffening

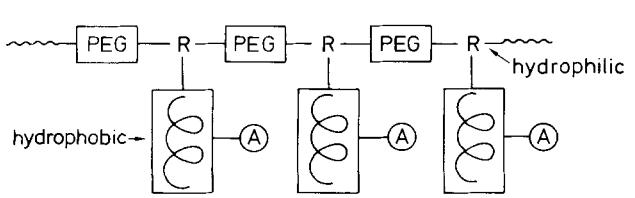


Fig. 3. Polymeric catalysts as enzyme models: Oligopeptides which tend to form secondary structures are built up in the side chains of sequential polyether blocks (PEG). In an aqueous environment the amphiphilic character of the macromolecule results in the formation of cluster-like structures in which the active centers A are located in the hydrophobic peptide layer [29].

the flexible backbone. Polypeptide chains are suitable candidates for this as they can form hydrogen bonds. Polymerization of amino acids of the active center of α-chymotrypsin produces, however, polypeptides with a random-coil structure and consequently very low catalytic activities.[30–32]

Chain flexibility can be reduced by cyclization of the peptide.[53–149] However, hydrolysis experiments using cyclic model peptides of type **4**, in which cooperative inter-

cyclo(-Gly-L-His-L-Ser-Gly-L-His-L-Ser-) **4**

actions between the side chains of Ser and His can be expected, demonstrate that the rate of hydrolysis of *p*-nitrophenyl acetate is only slightly affected.[33–35] The synthesis of peptide sequences with secondary structure opens up completely new possibilities for modelling enzyme activities; catalytically active groups can be immobilized and specifically positioned with respect to each other by selectively incorporating trifunctional amino acids in α-helix- or β-structure-forming host peptides[36–38] (Fig. 4).

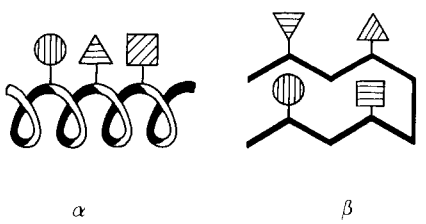
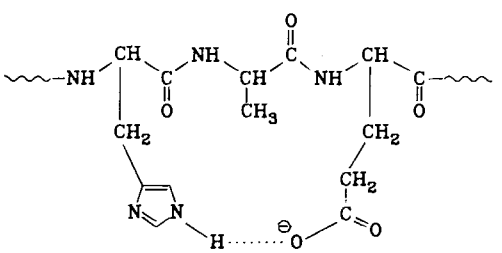


Fig. 4. Secondary-structure-forming peptides as enzyme models: Specifically incorporated functional groups can be positioned with respect to each other due to the formation of α-helix and β-structures or β-hairpins; these groups thus exhibit enzyme-like cooperative effects.

Formation of a partial α-helix structure in the sequence **5** produces a cooperative effect between the His and Glu side chains.[37]

Poly(L-His-L-Ala-L-Glu) **5**



Similarly, stabilization of the helix structure is observed for the sequence **6** (which serves as a model for the active

H-(L-Met)$_6$-L-Glu-(L-Met)$_2$-L-His-(L-Met)$_3$-L-Ser-(L-Met)$_6$-OH **6**

center of α-chymotrypsin) as a result of the formation of a hydrogen bonding system between the Ser, His and Glu side chains.[39]

The sequence **7**, designed on the basis of CPK model studies, is a novel variation.[40] The functional groups are

Ac-His-Phe-Gly-Cys-D-Phe-Ser-Gly-Glu-Cys-NH_2 **7**

orientated and fixed by incorporating a β-turn and by S–S bridge formation. The hydrophobic pocket required for substrate binding is provided by the strong interactions of the Phe side chains. The low catalytic activity of this model indicates that formation of a hydrogen bonding system is a necessary but not sole condition for α-chymotrypsin-like hydrolytic activities.[41] This finding seems to be confirmed by recent studies.[42,43]

2.2. What can "Synthetic Enzymes" Learn from Natural Enzymes?

The examples selected from the large number of enzyme models show that synthetic catalysts are indeed "capable of learning"; enzyme-specific properties such as reaction acceleration as a result of cooperativity or modification of the microenvironment of active groups, saturation kinetics, substrate affinity and specificity, can, within certain limits, be conferred on functional polymers and polypeptides. However, the effects are found to be several *orders of magnitude* smaller than those of natural enzymes. It is therefore debatable whether terms such as "enzyme-like polymers" or "synthetic enzymes" ("synzymes") are justified.[1] Any improvements of synthetic catalysts are, however, of practical importance for applications in organic synthesis: although this has not yet been successfully achieved,[1,2,44] studies on the significance of hydrophobic and cooperative effects have yielded results that point the way for further investigations. On the other hand, the examples given demonstrate that the simplified model concepts for enzymatic catalysis are far removed from reality. *Morawetz*'s remark[167] that synthetic macromolecular catalysts have produced "no new information whatsoever for the enzyme chemist" is a logical consequence and still largely applies today. The mechanism of the catalytic function is often less easy to understand in model systems than in the enzyme itself; this is particularly true of polymeric catalysts (both homogeneous and heterogeneous) whose active groups are arranged statistically.[1,2,11,12]

Enzymatic catalysis involves the complex interplay of individual effects[48–52] and is thus dependent on a macromolecular structure whose backbone and reactive groups exhibit a definite spatial architecture. The ability to fold specifically to form a rigid backbone conformation with crystal-like packing[9] would, however, appear to be a privilege of polypeptide chains.[10,20] Consequently the *first step* on the way to artificial proteins and enzymes must be the development of amino acid sequences that can fold into tertiary structures. The infinite diversity of potential primary sequence variations reflects both the complexity and the degree of difficulty of this undertaking. The question "How do proteins acquire their tertiary structure?" must therefore be dealt with first.

3. The Puzzle of "Tertiary Structure"

The questions as to "why" and "how" proteins fold still remain unanswered despite the enormous amount of information on their folding mechanism, topology and structure-activity relationships.[4,5,46,47,163] *Jaenicke* has recently published a clearly presented article on the problem of protein folding.[5] Only those aspects of this subject that are of importance for the present problem will therefore be discussed here.

3.1. Why Does a Polypeptide Fold into a Tertiary Structure?

It has been possible to answer this question from the point of view of the energy balance of a single polypeptide chain in a defined medium ever since *Anfinsen*'s fundamental renaturation-denaturation studies on ribonuclease.[54,55,64] The energy balance of the entire system for the thermodynamically controlled equilibrium between the unfolded (denatured) and folded (native) conformations

$$\Delta G = \Delta H - T\Delta S_{SOL} - T\Delta S_{CH}$$

proves to be a relatively small difference between large values. The chain entropy ΔS_{CH} that predominates in the denatured state must be compensated in the native conformation by the sum of the intramolecular interaction energies ΔH (hydrogen bonds, Van der Waals forces, and Coulomb forces) and the (positive) solvation entropy ΔS_{SOL} ("hydrophobic interaction"). A stable tertiary structure is thus an optimized system in which the driving forces for folding are the minimization of hydrophobic areas of contact with the hydrophilic solvent and the optimization of intramolecular interactions.[55–57] The formation of a stable tertiary structure in solution is a specific property of polypeptides, which possess structure-stabilizing components formed by intramolecular hydrogen bonding in addition to the highly restricted conformational space of the individual amino acid building blocks[168] (reduction of ΔS_{CH}). Synthetic polymers, with their much more flexible chains, cannot emulate this. The ability of a polypeptide chain to form a stable tertiary structure is, however, more of an exception than a rule. Presumably, only very few of the large number of possible peptide chains (a peptide chain with n amino acids can have 20^n different sequences) can produce a stable tertiary structure (estimated number of proteins found in nature $\sim 10^9 - 10^{10}$). It is thus clear that the statistical synthesis of primary sequences yields polypeptides with random coil conformations.

3.2. How Does a Polypeptide Fold into Its Tertiary Structure?

All the information that a polypeptide requires to fold into its unique, native conformation is stored in its primary sequence. It can now be assumed that the native conformation represents a thermodynamically favorable conformation with a minimum free energy.[9,55,58–60] This is the only way of explaining why the polypeptide chains belonging to one species fold to select a single, native conformation from a multitude of starting conformations (a peptide chain containing 150 amino acids has $\sim 10^{45}$ potential conformations!). Whether this conformation represents the *overall* minimum of the multidimensional hypersurface of the conformational space is still a matter of debate.[4,5,46,50]

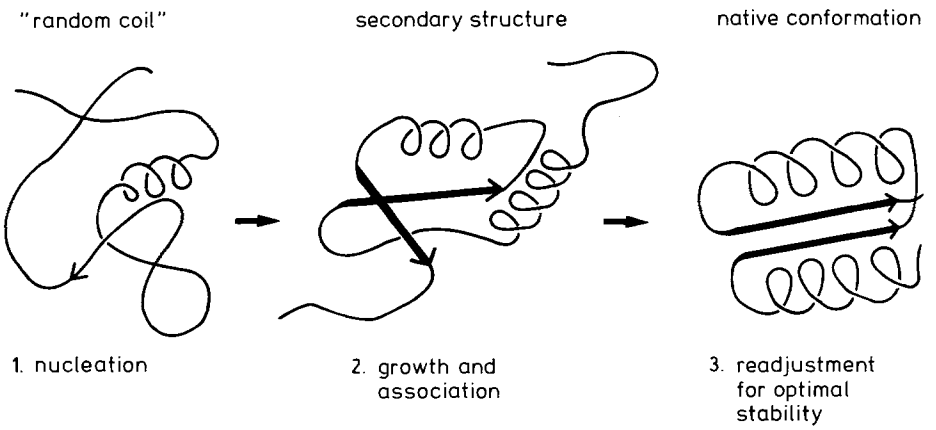


Fig. 6. Hypothetical mechanism of the folding of a linear polypeptide chain into its native conformation [4, 6, 46]. In a first nucleation step the unfolded, disordered polypeptide chain (random coil) forms regions with secondary structure (especially α-helices, β-hairpins, β-sheets) as a result of short-range interactions; these regions, which are stabilized by medium-range interactions, control folding into the tertiary structure by means of aggregation. The native conformation is then formed as a result of long-range interactions, whereby the protein assumes a crystal-like density due to optimal intramolecular readjustment of the side chains.

Experiments with the aim of predicting the native conformation from the primary sequence by means of empirical conformational energy calculations have so far failed due to the "multi-minima problem".[55,60-64] A multitude of local minima occurs in the minimization of the conformational energy of even medium-sized peptides[60-63], so that it is almost impossible to find the overall or lowest-energy minimum without other starting assumptions (e.g. the starting conformation for energy minimization in the vicinity of the overall minimum[60-62]) (Fig. 5).

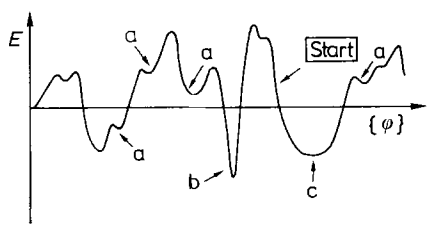


Fig. 5. Multidimensional hypersurface of the conformational energy: During minimization of the conformational energy E (sum of the Van der Waals, Coulomb, and rotation potential terms [20]), a large number of local minima (a) is found. This so-called "multi-minima problem" means that the conformation of the biologically active protein cannot be calculated solely from the amino acid sequence without preliminary experimental information about its structure (which would, for example, result in a *starting* conformation close to the overall minimum (c)). Whether the native molecule occurs in a local (a), absolute (b), or overall (c, with inclusion of the chain entropy) minimum is still a matter of controversy [5, 46].

Current concepts of the folding mechanism presume that the molecule does not try out all the possible folding pathways (and thus all the potential conformations—a peptide chain of 150 amino acids residues would require $\sim 10^{26}$ years to do this) but that a kinetically controlled, multistep folding process is adopted[4,6,46,65-68] (Fig. 6).

Fluctuating nucleation centers are formed in the first step of a single-chain, single-domain protein as a result of short-range interactions; these centers consist mainly of α-helices, β-structures, and β-bends (folding sites).[6,69-71] It is assumed that these nucleation centers are not stationary but rather distribute themselves along the peptide chain in rapid equilibrium with the disordered (random coil) conformation in accordance with their initiation enthalpies. In the second stage, secondary structure blocks associate under the influence of medium- and long-range interactions. Finally, specific readjustments are made to the side chains within the molecular chain in a slow process which involves optimization of all the intramolecular interactions; the areas of secondary structure formed originally may disappear.[183] The last folding step consists of the association of domains or subunits. The intermediary formation of *secondary structures* thus occupies a key position in the folding process.

3.3. The 'Anatomy' of the Tertiary Structure

X-ray structural analyses of a rapidly growing number of proteins have led to the surprising result that the number of different topologies is very small. After extensive study of the recurring features of protein structures, the proteins so far investigated can be divided into a small number of groups that exhibit similar patterns of tertiary structure.[6,9,69,72-74] Structural order principles within the hierarchical organization of proteins provide the basis for this type of protein classification (Fig. 7).

Folding units with characteristic organization of the secondary structure blocks (supersecondary structures)[75,76] appear to be *the* building element of proteins. The central importance of secondary structure blocks in the formation of tertiary structures is ultimately due to the folding mechanism itself. During the folding process only sufficiently stable intermediate structures are relevant for the kinetics of protein folding. Energetic consideration of the initiation and growth of potential intermediate structural units (α-helices, β-hairpins, β-bends, hydrophobic clusters) shows that α-helices and β-hairpins are especially suitable as nucleation centers for folding.[7] It can be deduced from these considerations that

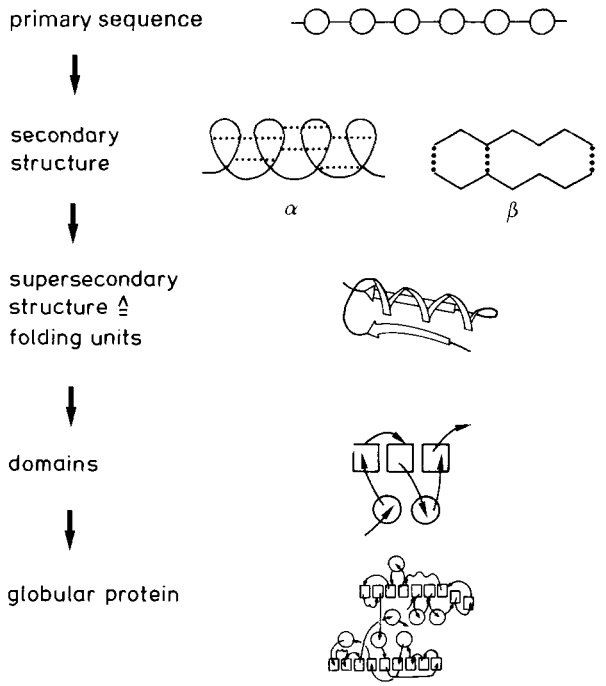


Fig. 7. Hierarchy of protein topology [69, 72]: Secondary structures such as α-helices and β-sheets associate to form characteristic supersecondary structures (e.g. βαβ folding units) via loops, these structures can be considered as the smallest building elements of domains. The globular structure is a result of intramolecular interactions between independently foldable domains.

1) the nucleation centers formed in the first stage of folding determine the topology and thus the structural type of the protein;
2) frequently occurring folding units that are independent of the primary sequence and the function of the protein are energetically preferred types of structure (Fig. 8).

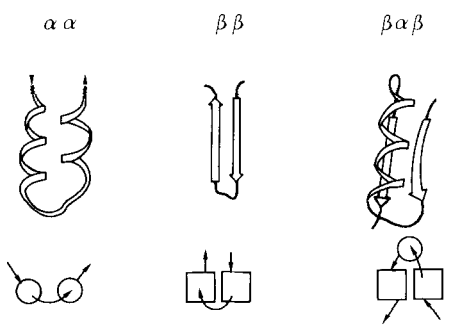


Fig. 8. Folding units (supersecondary structures) as the smallest building elements of a tertiary structure [6, 75, 76]; αα: two helical segments are connected by a loop; ββ: antiparallel pleated sheet that is linked to a β-hairpin via a β-turn or loop; βαβ: a helix lies above, and antiparallel to a β-sheet. The special stability of this folding unit is due to the amphiphilic character of the secondary structure blocks which produces a hydrophobic cluster inside the molecule and a hydrophilic surface.

In view of these aspects, it is not surprising that in many cases the tertiary structures of proteins are largely unaffected by exchange of amino acids.[77,78] On the other hand, systematic alteration of the primary sequence within the active center by means of point mutations provides insight into the structure-activity relationship of enzymes and permits the selective modification of specific properties ("protein engineering"[79]). Degeneration of the folding code is of critical importance for the construction of artificial proteins; a given tertiary structure is not bound to a specific primary sequence. The modification or complete exchange of the primary sequence with retention of the tertiary structure thus provides guidelines for the construction of artificial proteins.

4. The Secondary Structure as the Key to the Construction of New Proteins

A review of the current knowledge of the tertiary structures of proteins shows that the "folding code" is still far from being deciphered.[5] At the moment the multi-minima problem and the complexity of the folding mechanism seem to obstruct insurmountably the prediction of tertiary structures (3°) from primary sequences (1°) without prior assumptions:

$$1° \not\longrightarrow 3°$$

The deciphering of the folding code is not, however, a prerequisite for the construction of new proteins. The critical question here is: Can a coding primary sequence be found (from many potential sequences) for a given tertiary structure?

$$3° \xrightarrow{?} 1°$$

4.1. Protein Topology as a Starting Basis

Analysis of protein topologies and the postulated folding mechanism indicates the central importance of *secondary structure* in the formation of the tertiary structures of proteins.[69,72] Comparison of common topologies in proteins with different functions gives surprisingly good agreement of the spatial constructions of folding units.[80,164-166] Although the 'βαβ' type folding units shown in Figure 9 do not correspond with one another as regards their function and primary sequences, their geometrical projections[80] (length and arrangement of the helix and β-sheet blocks) are almost identical.

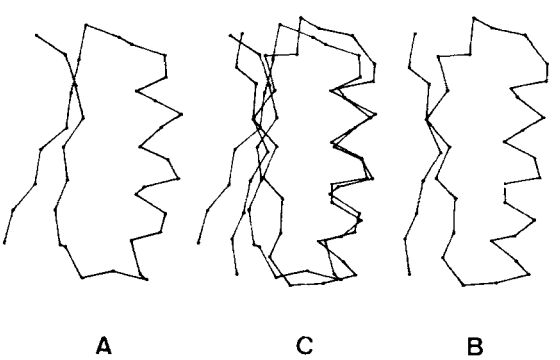


Fig. 9. Comparison of the spatial architecture of βαβ folding units [80]: Despite their different amino acid sequences the two peptide segments (A = 5-lactate dehydrogenase, sequence D47-D84; B = l-arabinose binding protein, sequence L3-P41) possess a characteristic folding unit of the βαβ type with an almost identical spatial structure as is shown by superposition of the two peptides (C).

The formation of the same spatial structures despite different coding of the peptide chains indicates that independently foldable regions within the protein are involved. Accordingly, these "supersecondary" structures represent the smallest polypeptide chains that are capable of folding and are possibly a measure of the "critical size" required for a tertiary structure. However, long-range interactions are still usually needed to stabilize the entire structure; this is due to the lability of the secondary structure blocks which form the tertiary structure.

Conformational studies on partial sequences have revealed that isolated segments do not usually have the same conformations as those found in the complete protein. A transition from a secondary structure to a random-coil conformation is often observed. The development of peptide segments with *stable secondary structures* thus represents a decisive hurdle on the way to constructing a tertiary structure with minimal size and maximal stability:

$$3^\circ \xrightarrow{\text{topology}} 2^\circ \xrightarrow{?} 1^\circ$$

4.2. Primary Sequence and Secondary Structure

Systematic conformational studies on model peptides are especially informative for the determination of the relationship between primary sequence and secondary structure. During the past few years investigations on monodisperse homo- and co-oligopeptides have in particular provided considerable insight into the formation, stability and sequence-dependence of secondary structures.[81, 82, 84, 85, 89, 90–95, 106]

4.2.1. Critical Chain Lengths of α-Helices and β-Structures

Circular dichroism measurements[82, 84, 86, 87] show that in the stepwise synthesis of helix-forming homooligopeptides there is a continuous transition from the disordered (random-coil) conformation to the α-helix structure. The critical chain length for inducing a helical structure is seven amino-acid residues in helix-promoting solvents such as trifluoroethanol and complete formation of a helical structure in solution is observed with fifteen amino-acid residues (Fig. 10).

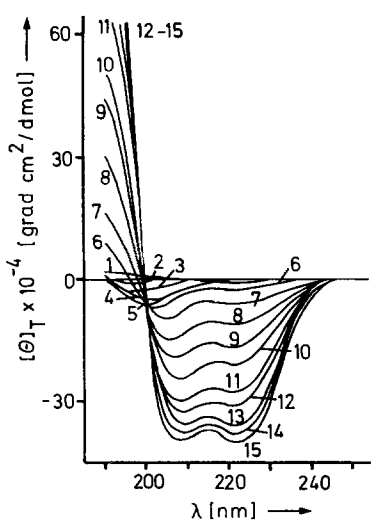


Fig. 10. Critical chain length c_n for α-helix formation: On extending the chain length, the homooligopeptide Boc-(Met)$_n$-PEG in trifluoroethanol gradually changes from a disordered conformation (n = 6) to an α-helical structure which is completely established when there are approximately 15 amino acid residues (characteristic Cotton effects in the CD spectrum at λ = 207 nm and 222 nm) [87].

β-Structures are generally formed with shorter chain lengths (n ≈ 6), the random-coil→β-conformation transition being sometimes very sharp (Fig. 11).[88, 96, 125] These

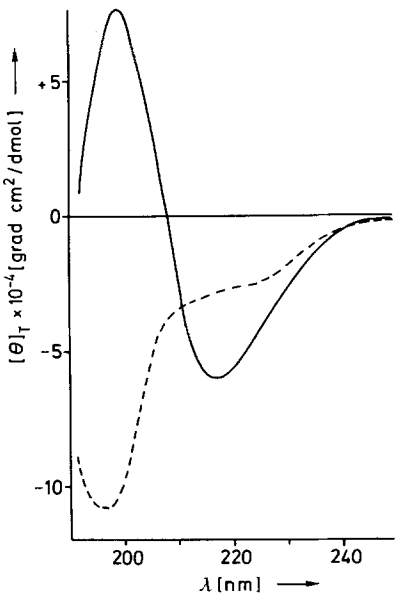


Fig. 11. Critical chain length c_n for the formation of β-structures: CD spectrum of (Ser-Leu)$_4$-Gly-PEG (—) in H_2O and Leu-(Ser-Leu)$_3$-Gly-PEG (---). The amphiphilic peptide with eight amino acid residues exhibits a sharp conformational transition from the disordered conformation to the β-structure (negative Cotton effect at λ = 218 nm). The C-terminal PEG chain solubilizes the otherwise poorly soluble peptide [125].

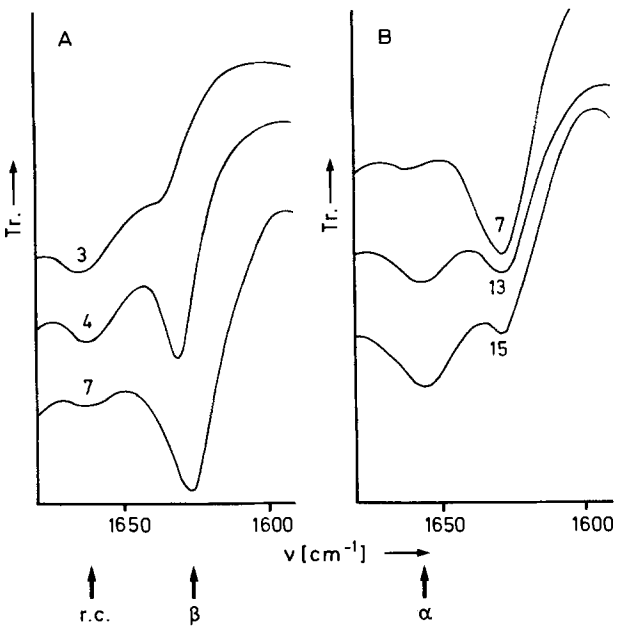


Fig. 12. IR spectrum of [Lys(Z)]$_n$-PEG in the solid state [96]. The oligopeptide shows a conformational transition from the random coil (r.c.)→β-structure→α-helix which can be clearly seen using the amide I absorption band. The band at ν = 1656 cm^{-1} (n = 3, 4), which is typical of the r.c. conformation decreases on chain extension in favor of the band at ν = 1635 cm^{-1} (n = 7, β-structure) (A); the transition to the α-helix is characterized by the reappearance of an absorption band at ν = 1655 cm^{-1} (n = 13–15) (B). (Tr = transmission.)

experimental findings reflect the different free energies for the initiation and growth of α-helices and β-structures.[64, 71] This also accounts for the random coil→β-structure→α-helix conformational transition that is frequently observed in the stepwise chain extension of homooligopeptides[81, 86, 87, 96] (Fig. 12).

The critical chain lengths for the formation of α-helices and β-structures are significantly smaller for *homo*oligopeptides than for *sequential* peptides. Interestingly, these critical chain lengths required for obtaining stable secondary structures correspond to the lengths of secondary structure blocks often observed in proteins despite the absence of long-range interactions which contribute to stabilization in the protein.[6, 69] *Homooligopeptides* are therefore potential candidates for stable nucleation centers in the construction of proteins.

4.2.2. *The Stability of Secondary Structures*

The stability of secondary structures is determined by a combination of short-range (side chain with its own backbone) and medium-range (neighborhood-dependent) interactions within the peptide chain. It is now accepted that short-range interactions determine the initiation of α-helices, β-structures, and β-hairpins.[60, 97, 98] Studies on host-guest peptides (Fig. 13) have shown, however, that the stability of β-structures is significantly affected by neighborhood interactions.[81, 99–101] The incorporation of guest amino acids in a β-structure-forming host homooligopeptide leads to destabilization of the secondary structure regardless of the specific conformational properties of the guest amino acid.[36, 81, 102] Accordingly, the stability of secondary structures is determined by the internal symmetry of the peptide side chains and is greatest in *homooligopeptides*. Incorporation of merely one guest amino acid with a voluminous side group (e.g. L-Val) into the center of a host peptide (e.g. oligo-L-Ala) can result in complete destruction of the secondary structure.[36, 102, 103] This information can only be obtained experimentally and is of fundamental importance for the design of sequences with functional properties, which form secondary structures.

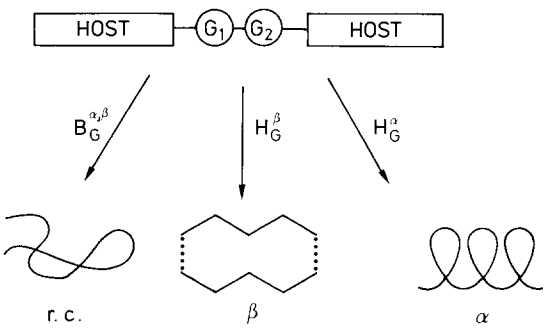


Fig. 13. Host-guest model for the study of the conformational preferences of amino-acids and peptides [36, 102]. The incorporation of guest amino-acids (G) influences the tendency of the host peptide to form secondary structures (e.g. oligo-Ala, -Val, -Met) in a characteristic fashion. The introduction of secondary-structure-breaking amino-acids (B = hydrogen-bond breaker [105]) produces the random coil (r.c.) conformation. In contrast, the incorporation of α-helix- or β-structure-forming amino acids (H = hydrogen-bond former [105]) stabilizes the secondary structure of the host-guest peptide. These model peptides can be used to determine the conformational parameters of individual amino acids (and their derivatives with protected side-chains) under different experimental conditions as well as to establish the role of short- and medium-range interactions in the formation of secondary structures.

4.2.3. *The Prediction of Secondary Structures*

Prediction of secondary structures for given primary sequences with the aid of statistically determined conformational parameters and empirical rules ("prediction codes") is already one of the standard methods used to investigate the conformation-dependent properties of peptides and proteins.[104–116] The empirical prediction schemes originally developed by *Chou* and *Fasman*[104, 105] were clearly presented and thus useable by the protein chemist in his daily work; they have, however, been continually modified due to the rapidly expanding amount of data available (from X-ray structural analyses of proteins). The improvements made to the accuracy of prediction hardly seem, however, to justify the increased complexity of the various prediction algorithms.[81, 109, 114] The statistical-mechanical method of *Scheraga* and *Tanaka* serves as a symptomatic example of this;[107] this method was the first to include neighborhood-dependent interactions in the computer-assisted calculations. The α-helix regions and—with greater uncertainty—the β-sheets and the β-bends can be located in proteins but the position of the ends of periodic secondary structures still presents considerable difficulties. Significant improvement of empirical prediction algorithms is not to be expected due to the inherent limitations of the method (e.g. long-range interactions are not considered quantitatively).[81, 109] Prediction of the secondary structures of *short-chain* peptides with a *given primary sequence* with the aid of these statistical algorithms is even more difficult on account of the effects exerted by solvents and by terminal groups on the preferred conformation in solution. The experimental information obtained from studying model peptides yields considerably more reliable insight into the relationship between the primary sequence and the secondary structure.[36, 81] Empirical prediction methods are consequently only of limited value for the present problem.

4.3. Peptides with Secondary Structure as "Building Elements"

The availability of tailor-made oligopeptide blocks with stable secondary structures for use as building elements (having specified chain lengths and physical properties) is a strategic prerequisite for the construction of artificial proteins. Systematic studies on model peptides have revealed that homooligopeptides of medium chain length tend to form secondary structures. The preferred type of conformation is determined by the side chains. Although the hydrophobic aliphatic amino acids produce stable β-structures in the order Ala < Leu < Val < Ile even with chain lengths of n = 6–8, the values of n for helix formation are considerably higher, particularly in aqueous systems. A 'trick' can be used to regulate the length of the helix block: incorporation of a strong helix-inducing amino acid such

as aminoisobutyric acid (Aib) reduces the critical chain length for helix formation as desired depending on the incorporated Aib.[117-121] Even pentapeptides containing Aib can form a helical structure.[122]

The amphiphilicity of secondary-structure-forming peptide blocks plays a critical role as the driving force for the folding of a linear polypeptide chain into a tertiary structure. Alternating hydrophobic and hydrophilic amino acid residues in the primary sequence produce layer structures[123-125] which are characterized by the formation of hydrophobic clusters (with release of solvation entropy ΔS_{SOL} (Fig. 14). Interestingly, the critical chain lengths for

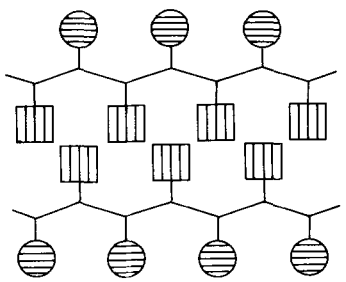


Fig. 14. Formation of a hydrophobic cluster due to the production of layer structures in amphiphilic peptides [123, 125]. The repetitive structure results, if β-sheets are formed (cf. Fig. 11), in a conformation in which the hydrophobic (▥) and hydrophilic (⊜) side chains are orientated on different sides of the peptide backbone.

the formation of amphiphilic β-structures lie in the same order of magnitude as those for homooligopeptides.[125] The sequence $(Ser\text{-}Leu)_n$ forms, for example, a complete β-structure in water even when n = 4 (Fig. 11).

Amphiphilic helices can be produced in a similar fashion by repetitive incorporation of hydrophilic amino acids (Glu, Gln, Lys) in basic hydrophobic structures.[126,127] A continuous transition to a helical structure, similar to that observed in homooligopeptides, is also found for the sequence $(Ala\text{-}Aib\text{-}Glu\text{-}Glu)_m$[127] (Fig. 15).

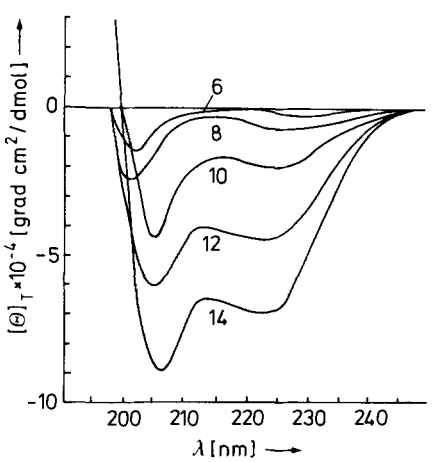


Fig. 15. Critical chain length c_n of amphiphilic helical structures: CD spectrum of $(Ala\text{-}Aib\text{-}Glu\text{-}Glu)_m$-PEG in H_2O [127]. The transition from a disordered conformation (random coil) to a helical structure occurs when there are approximately 10 amino acid residues. The amphiphilic helix in which the hydrophilic (Glu) and hydrophobic (Ala, Aib) amino acid residues are situated on different sides of the helix cylinder is completely established when the chain length is n ≈ 14.

The production of hydrophobic interactions along the helical axis generally seems to be a critical driving force for helix formation. A method (helical wheel) for predicting α-helices is thus based on the concept of determining amphiphilic structures along the peptide chain.[108,115]

β-Turns (β-bends) play an outstanding role as nucleation centers; they are produced as a result of short-range interactions. This dominance of short-range interactions is reflected in the differing coding tendencies of the individual amino acids to form β-turns. Empirically[128,129] and experimentally[130-132] determined parameters can be used to predict β-turns. The examples selected show that secondary-structure-forming peptide blocks with tailor-made structural, conformational and physico-chemical properties can, in principle, already be designed and synthesized.

4.4. From Secondary to Tertiary Structure

Analysis of the topology, folding mechanism and the relationship between the primary and secondary structures forms the basis of a general strategy for constructing polypeptide chains that can fold into tertiary structures (Fig. 16). The starting point for the design of a tertiary structure is provided by tailor-made oligopeptides with a secondary structure, which act as stable nucleation centers and determine the topology of the chain backbone. The laws governing the folding topology of natural proteins serve as "building plans" for the three-dimensional architecture whereby frequently observed folding units should be regarded as the smallest domains of an artificial protein (Figs. 7, 8). The primary sequence is designed bearing in mind

—the maximum stability of the secondary structure blocks (homooligopeptides) and
—the optimum intramolecular interaction energy of the folded polypeptide (amphiphilic sequences).

It is an advantage to have hydrophilic amino acids in the loops, as these are less important for the overall stability.

Functional amino acids or active centers must be inserted into the backbone of the host peptide without reducing the stability of the tertiary structure. Experimental results[36] show that the following priorities should be chosen: loops > α-helix > β-sheets. Suitable modifications of the primary sequence can be made in order to stabilize the tertiary structure (e.g. by S—S bonds, Coulombic contacts, complex formation). These changes can be planned most efficiently by molecular modeling in conjunction with conformational energy calculations.

The concept described here for the construction of foldable polypeptide chains is closely related to the current understanding of the protein folding mechanism. The tertiary structure results from the association of rigid secondary structure blocks in a kind of intramolecular aggregation. This strategy thus differs fundamentally from the concept of changing given *primary sequences* of proteins by replacing amino-acids while retaining the secondary or tertiary structure;[79,150] such modeling of peptides and proteins with the aim of altering their physicochemical or func-

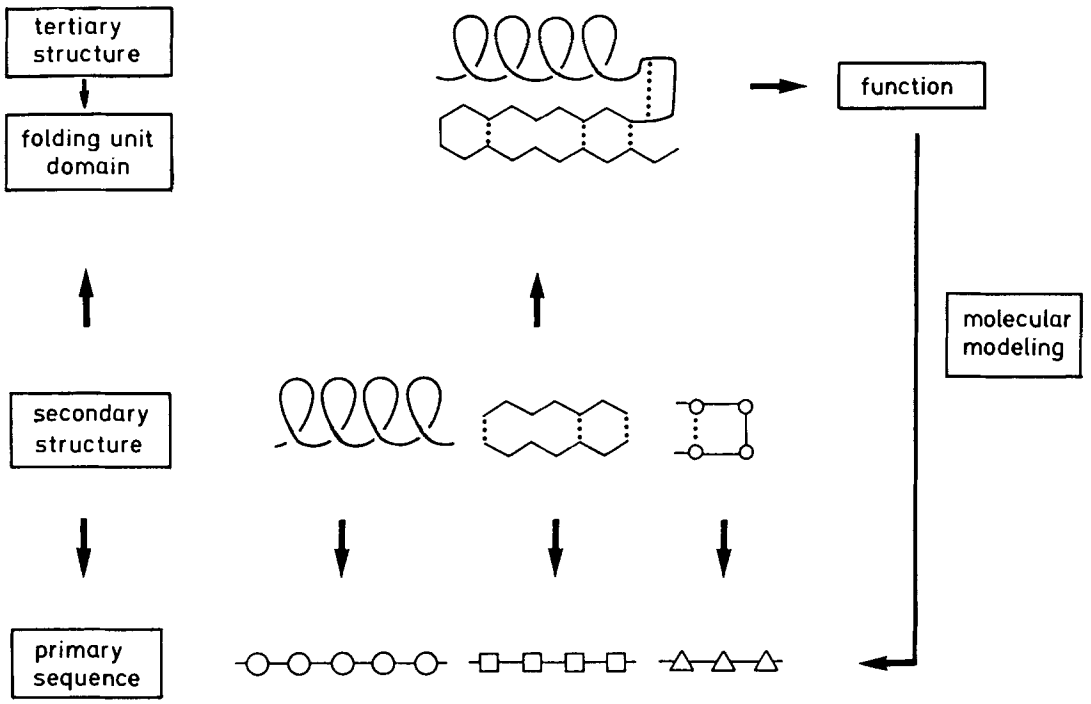


Fig. 16. General strategy for the construction of polypeptides with tertiary structure: Secondary structure blocks (stable nucleation centers) associate to form characteristic folding units and domains. The primary sequence is chosen such that the secondary structure (helix, β-sheet, β-turn; e.g. homo- or co-oligopeptide) of the peptide segments are most stable and ensure that optimum intramolecular interactions of their side chains are formed during the folding process. The overall stability of the three-dimensional structure must be maintained, if functional groups or active centers are selectively incorporated into the primary sequence; the necessary changes of sequence can be planned by "molecular modeling" [80].

tional properties can, however, be regarded as a special test for the general strategy used to construct artificial proteins that is described here.

4.5. Energy Balance of Model Proteins

The folding mechanism of model proteins (e.g. βαβ unit) can be considered as a two-step process (Fig. 17): I) Formation of the secondary structure; II) folding into the tertiary structure.

Unlike natural proteins (which have a fluctuating secondary structure), the equilibrium in the first folding step of model proteins lies almost completely on the side of the thermodynamically *stable* secondary structure. As a result of the stiffening of the peptide chain (restriction of conformational space), this rapid nucleation step provides the critical energy contribution for the formation of a tertiary structure and directs the subsequent folding process. The driving forces for folding into a tertiary structure (2nd step) are hydrophobic interactions resulting from the amphiphilic nature of the secondary structure blocks. In the case of natural proteins, the large loss of chain entropy in the folding step must be compensated by optimum intramolecular interactions and a high gain of solvation entropy (liberated solvent). However, in model proteins with a stable secondary structure a much smaller energy contribution is sufficient to overcome the much lower loss of chain entropy after the first nucleation step (ΔG = difference between small numbers). In natural proteins, where stabilization of secondary structure blocks by long range interactions is essential, "isolation" of these segments most often causes a transition to a disordered conformation. On the other hand, it can be concluded from a comparison of the energy balances that artificial proteins should have a

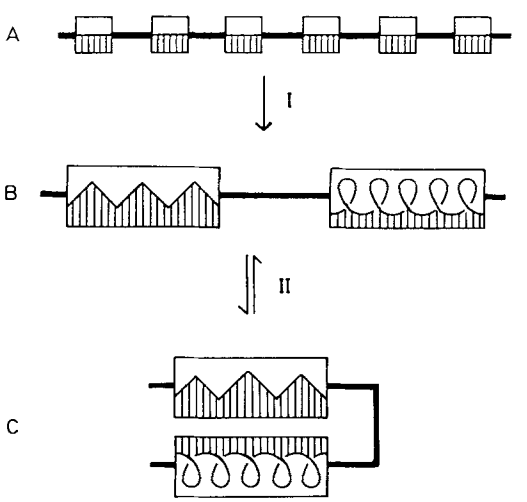


Fig. 17. Folding scheme of artificial proteins: In contrast to the folding process of natural proteins, the first nucleation step (I) leads from a disordered conformation (A) to *stable* secondary structures which act as nucleation centers (B) and thus determines the subsequent folding pattern as well as the overall topology of the molecule. The driving force for folding (II) into a stable tertiary structure (C) is the formation of hydrophobic clusters inside the polypeptide with release of solvation entropy) as a result of the amphiphilic nature of the secondary structure blocks. The molecule attempts to minimize its hydrophobic areas of contact with the solvent (H_2O).

more stable tertiary structure as a result of the higher stabilities of the secondary structure elements.

It is not yet known which is the critical chain length for the formation of a tertiary structure. Experiments on enzymatically cleaved proteins indicate a minimum length of approximately 40 amino-acid residues.[133-135] Interestingly, this number is of the same order of magnitude as is found for βαβ folding units.

4.6. Synthesis of Peptides

The chemical synthesis of longer peptide chains is still a central problem of protein chemistry despite the considerable progress that has been made in the strategy of the various synthetic methods and protecting group techniques.[136-139, 180] On a long-term basis the development of the recombinant DNA technique undoubtedly opens up entirely new possibilities for the construction of novel peptides and proteins.[3, 140] The aim of constructing peptides and proteins of any given chain length and primary sequence reliably, still unobtainable in chemical peptide synthesis, has suddenly become feasible due to this development. It is therefore evident that in the future the synthesis of *proteins* clearly belongs to the field of genetic engineering. On the other hand, the *combination* of biotechnological and chemical synthetic strategies opens up new perspectives for the modification and construction of artificial proteins. This approach has the special advantage that the entire potential of chemical peptide synthesis can be exploited for the functional and structural modification of peptide sequences (e.g. the incorporation of unnatural or of D-amino acids). Semisynthesis in which naturally and synthetically prepared segments are linked enzymatically[141-143, 155] will be of great importance in the future.

The synthesis of folding units with chain lengths of approximately 30–40 amino-acid residues seems to be the limit of chemical peptide synthesis when efficiency and reliability are considered; even this goal can only be achieved if the entire potential of the current synthetic strategies is used. Stepwise peptide synthesis on polymer supports is regaining importance due to the recent improvements made in protecting group strategy,[172, 173] anchoring techniques,[138, 139, 173-175, 181] and support properties.[138, 173, 176, 177] The development of efficient separation methods, especially preparative high pressure liquid chromatography (HPLC), has led in particular to an important breakthrough in solid-phase synthesis. Medium-sized peptides of up to 20 amino-acid residues can be purified reliably by using the HPLC technique.[172, 178] Although the synthesis of higher peptides on polymeric supports still appears to be difficult, it has often provided valuable preliminary information about the physicochemical and structural properties of the desired peptide. The combination of stepwise synthesis on a support and subsequent condensation of the segments, either in solution or on polymeric supports, could prove to be the best method for synthesizing longer chain peptides. The superstructure of an amphiphilic peptide sequence with alternating amino acid sequences is drastically destabilized by errors in the sequences:[171] this can be avoided by the coupling of dipeptides during stepwise synthesis.

The use of soluble polymeric supports[27, 138] offers special advantages for the synthesis of folding units: the preferred conformation of the solubilized peptide chain can be determined spectroscopically[89, 179, 182] in each step of the synthesis. The peptide segments with a secondary structure employed to construct folding units can be structurally *and* conformationally characterized in this way *prior to* fragment condensation.

The construction of oligopeptides which form secondary structures is a special challenge to the synthetic chemist because the conformation and the physicochemical properties of a peptide are closely related:[144-148, 162] the poor solubility of individual segments is a limiting problem; the formation of β-sheets which are associated intermolecularly causes aggregation and thus insolubility of both hydrophobic and latently amphiphilic peptide chains (Fig. 18).[26, 148] This solubility minimum can be overcome with

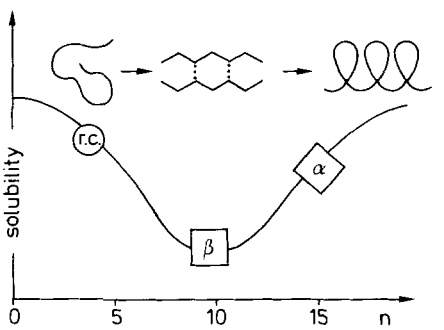


Fig. 18. Relationship between the conformations and physicochemical properties of peptides: When the chain length of a peptide (e.g. Oligo-Lys(Z), -Glu(Bzl), -Leu) is extended, a conformational transition from the disordered (r.c.) conformation to a β-structure is often observed; this is accompanied by a drastic decrease in the solubility of the peptide and accounts for the poor solubility of medium-length peptide segments. When the critical chain length for the α-helix is reached the solubility increases due to the formation of *intra*molecular hydrogen bonds. This close relationship between the preferred conformation and the properties of the peptide such as its solubility behavior, aggregation tendency or reactivity is of fundamental importance for the synthesis of higher peptides [144, 145, 162].

medium-length peptide sequences by extending the chain length since the tendency of the peptide to undergo intramolecular interactions increases (transition to a helical structure or folding).[81, 144, 145] Such conformational transformations are of considerable importance for the strategy used to construct folding units; for example, the solubility problem can be partially overcome by synthesizing the β-structure-forming peptide block on polyethyleneglycols[27, 138] and subsequently attaching the readily soluble helical segment. Enzymatic linkage of unprotected (and thus readily soluble) segments also provides another promising possibility, but this technique still requires further practical development.

In addition to the normal analytical characterization of the primary sequence (purity criteria), the identification of the tertiary structure is a special problem as biological activity tests cannot be used to check the purity and structure. Since X-ray structural analysis can only be employed in exceptional cases, a wide spectrum of spectroscopic methods (particularly CD, IR, NMR, fluorescence measurements), chemical methods (e.g. catalytic effects and complex formation), physicochemical methods (e.g. aggrega-

tion behavior, light scattering, Kerr effect), and, if possible, biochemical methods must be used to characterize the spatial structure. Another aspect deserves attention: folding into the tertiary structure only proceeds spontaneously under special conditions.[110] In addition to the design and synthesis of the primary sequence, the study of the optimum conditions for folding is therefore also important.

4.7. State of the Art in the Construction of Artificial Proteins

The relationship between the primary sequence and the secondary structure of peptides described in this report has been the focus of experimental and theoretical studies for many years; it seems that the time has now come for the investigation of a difficult, but equally fascinating, problem: the transition from the secondary to the tertiary structure. At the moment, the border area between the secondary and the tertiary structures is the center of active studies: experiments on modeling the *secondary structure* of biologically active peptides and proteins is a first important step in this connection. Substitution of helix-forming sequences in medium-sized peptides by amphiphilic model peptides with more stable secondary structures has already produced interesting results, e.g. modification of biological activity in substrate-receptor binding.[150, 151] It has been shown that the biological activity of the ribonuclease-S peptide is largely retained if a secondary structure block is replaced by a model peptide.[152] A model peptide which is capable of interaction with DNA has been developed on the basis of empirical conformational predictions.[153, 154] Studies on the modeling of the domains of natural proteins and enzymes as well as on the synthesis of folding units with novel catalytic and functional properties are in progress in the author's own laboratory. All the secondary structure blocks (α-helix 36-50, β-sheets 22-29 and 53-58) of the βαβ folding unit of the thioredoxin sequence 22-58 have, for example, been replaced by simple model sequences with retention of the active center (Cys^{32}-Gly-Pro-Cys^{35}) (Fig. 19); further small changes have no effect. Spectroscopic data indicate that the tertiary structures of the model and natural sequences (as isolated structural units and within the complete protein) are the same.[127]

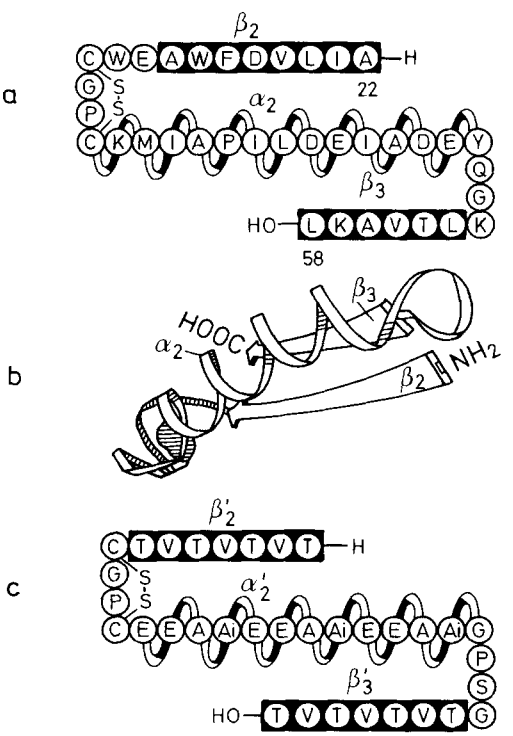


Fig. 19. Modeling of the partial sequence 22-58 of thioredoxin. The active center Cys^{32}-Gly-Pro-Cys^{35} is retained when the natural amino acid sequence (a) is replaced by an amphiphilic model helix (Glu-Glu-Ala-Aib)$_3$(α_2') and by two amphiphilic β-structure blocks containing the sequence (Thr-Val)$_3$-Thr(β_2' and β_3') (c). The spatial structure of this partial sequence corresponds to a βαβ folding unit (b) and is also retained in the model peptide despite the radical modification of the primary sequence [127].

Despite these encouraging beginnings in the construction of artificial proteins, many questions still remain unanswered. Little is known, for example, about the competition between the aggregation of polypeptide chains and their intramolecular folding. It can be shown that the amphiphilic helical and β-structure blocks used as building elements tend to aggregate in aqueous systems.[26, 148] This aggregation tendency of amphiphilic secondary structures is the driving force for intramolecular folding. Preliminary experiments on βαβ folding units appear to confirm this hypothesis.

5. Concluding Remarks

Albert Einstein's statement that "The religiousness of the research worker is founded in his delighted amazement at the harmony of natural laws which reveal such a superior reasonableness that, in comparison, all meaningful human thinking and systems represent nothing more than a feeble reflection"[156] could be used to describe the situation outlined in the present report. On the one hand we are trying to construct new proteins, "*amazed*" by the tertiary structures of proteins, and on the other hand the enzyme models that have so far been synthesized seem to be a "*feeble reflection*" of reality. In this context an attempt to construct new proteins may be regarded as a tremendous *interdisciplinary* learning process (Fig. 20) in which the curriculum is dictated by the study of the enzymes: "The molecule knows how to fold, so we may learn how it does it".[157]

The general strategy developed here employs the method of *deduction*.[158] A primary sequence is derived from the "idea of tertiary structure"[184] which has been borrowed from nature. According to *Popper*,[159] success ("verification") and failure ("falsification") in building new proteins are test criteria for our theory as to how tertiary structures are formed.

As is often the case in research, the range of potential applications and possibilities is growing more rapidly than the fundamental aims can be realized:

—tailor-made catalysts
—immunological and biochemical applications,
and last but not least
—the deciphering of the folding code

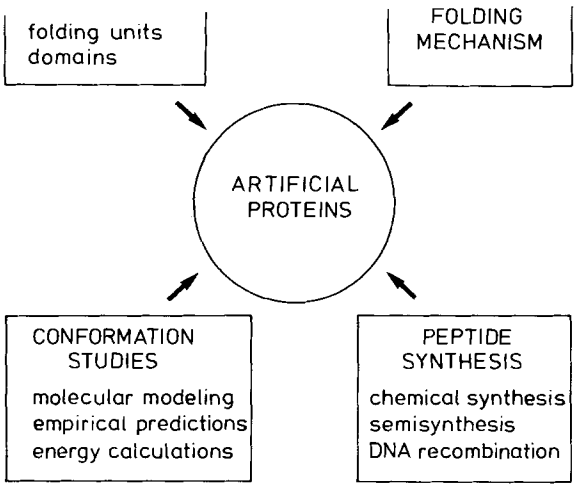


Fig. 20. The construction of artificial proteins as an interdisciplinary task. The experimental findings obtained on the *topology* (from X-ray structural analyses) and the *folding mechanism* (from denaturation-renaturation studies) of naturally occurring proteins provide the starting point for the construction of artificial proteins. Experimental *conformational studies* on model peptides supply the basis for designing peptide sequences with tailor-made conformational and physicochemical properties; theoretical studies are also useful. Finally, the possibility of *synthesizing* any given amino acid sequence is a prerequisite for the realization of the overall concept. The combination of chemical and biotechnological synthetic strategies is becoming increasingly important in this context. Access to new proteins is thus equally challenging for the conformation analyst, the biochemist, and last but not least for the peptide chemist.

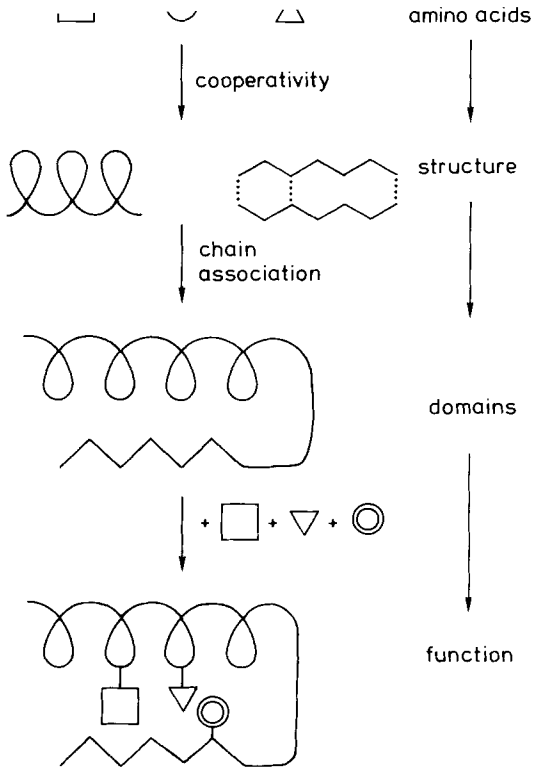


Fig. 21. Hypothetical evolution of natural proteins. According to this hypothesis, cooperative effects during the condensation of amino acids result in the preferential formation of homooligopeptides with a stable secondary structure; these peptides can then associate to form large domains (proteinoids) as a result of mutual interactions. A functional potential of increasing complexity is finally obtained by stepwise incorporation of functional amino acids within the chain backbone ("structure before function" hypothesis).

are hopes that are associated with the synthesis of artificial proteins. In view of the complexity of the problem to be solved, socratic modesty is called for—at least as far as the time scale of development is concerned. The construction of artificial proteins is thus a *prospect for the future.*

The real fascination for the peptide chemist is the inclusion of a new dimension in planning syntheses—the three-dimensional architecture of polypeptides. It may thus be possible to develop a "new quality" of synthetic macromolecules which manifests itself in enzymatic catalysis and can be recognized schematically in enzyme models.

Following this look into the future we will finally take a look at the question: How did proteins originate? On the basis of experimental data it is conceivable that the formation of homooligopeptides with secondary structure was favored by cooperative effects. Simple forms of tertiary structure ("proteinoids") were then produced due to association of these blocks as in the folding mechanism of proteins. These proteinoids were "functionalized" while retaining their three-dimensional structures by incorporation of "guest amino acids" and thus gradually acquired catalytic activity ("structure before function", Fig. 21). If the strategy for building artificial proteins and the hypothesis described here were to correspond with the natural origin of proteins, this would be a necessary consequence of the nature of the problem rather than just a coincidence.[160]

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Phase Behavior of Ternary Systems of the Type H_2O–Oil–Nonionic Amphiphile (Microemulsions)

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Liquid multicomponent systems of the type H_2O–oil–amphiphile–electrolyte are of growing interest, both in industry and in research. In applications technology, there are two problems to solve: 1. To prepare stable homogeneous solutions of H_2O and nonpolar liquids with as little amphiphile as possible which can be diluted with H_2O in all proportions without phase separation; e.g., concentrated solutions of drugs, herbicides, or insecticides. 2. To prepare stable mixtures of an aqueous, an amphiphile, and an oil phase with as little amphiphile as possible which are employed in tertiary oil recovery and in the pharmaceutical industry. Furthermore, such systems may be used for performing chemical reactions in heterogeneous liquid mixtures with continuously variable properties. In research, such systems are of interest for both experimental and theoretical studies of critical phenomena, especially near so-called tricritical points. Last but not least, their properties may stimulate further research in the field of associated solutions. In this paper we summarize the results of our studies on the phase behavior of ternary systems with nonionic amphiphiles, in particular with respect to the evolution of liquid three-phase bodies. The results suggest that the tricritical points in such systems should be regarded as kinds of pivot points from which the phase behavior evolves. If this were an approach to reality, the phase behavior would be governed in more or less good approximation by universal scaling laws, irrespective of the particular microstructure of the solutions. Finally, we discuss the effect of electrolytes on the phase behavior both in a quaternary phase tetrahedron and a pseudoternary phase prism representation. Although in practice most systems consist of mixtures of oils, amphiphiles, and electrolytes, an understanding of the phase behavior of truly ternary and quaternary systems with chemically well-defined components permits at least qualitative predictions with respect to the phase behavior of the multicomponent mixtures encountered in practice.

1. Introduction

In order to increase the mutual solubility between two partially miscible substances, a third component must be added that is equally well soluble in the two other substances.[1] In the case of H_2O and oil this is evidently an amphiphile, either nonionic or ionic, or a combination of the two. To illustrate the problem one may represent the phase diagrams of the two ternary systems

$$\underset{\mathbf{A}}{H_2O} - \underset{\mathbf{B}}{\text{oil}} - \underset{\mathbf{C}}{\text{nonionic amphiphile}} \qquad (1)$$

$$\underset{\mathbf{A}}{H_2O} - \underset{\mathbf{B}}{\text{oil}} - \underset{\mathbf{D}}{\text{ionic amphiphile}} \qquad (2)$$

at constant temperature T and pressure p in Gibbs triangles as shown schematically in Figure 1. The composition may be expressed either in mole, volume, or weight fractions. In this paper we shall use weight fractions, although, when considering molecular interactions, mole fractions are the more appropriate composition variables.

The upper triangle in Figure 1 shows the idealized phase diagram of system (1), the lower one that of system (2). Both triangles join at their common H_2O–oil side. The mutual solubility between **A** and **B** is very low. However, if one adds an appropriate amphiphile, either nonionic (**C**) or ionic (**D**), the solubility increases until the two phases eventually merge at a plait point. For reasons of clarity, the lyotropic mesophases at high concentrations of **C** and **D** have been omitted in Figure 1.

One may construct two tetrahedra by taking either the upper **A**–**B**–**C** triangle as base and placing **D** on top, or vice versa. Which of the two tetrahedra is the more conve-

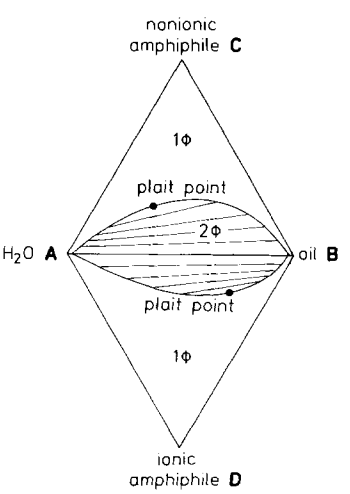


Fig. 1. Top: Phase diagram of system (1): H_2O–oil–nonionic amphiphile. Bottom: Phase diagram of system (2): H_2O–oil–ionic amphiphile (schematic). Both amphiphiles are equally well soluble in H_2O and oil. 1ϕ and 2ϕ signify one-phase and two-phase systems, respectively.

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nient depends on which of the amphiphiles is considered as major and which as minor component. In both cases the body of heterogeneous phases within the tetrahedron has the shape of an orange segment the edge of which is the **A**–**B** edge of the tetrahedron. The problem is then to find, for a given oil in a given temperature and pressure range, an amphiphile or a combination of amphiphiles the addition of which makes this segment as small as possible.

The phase diagrams of such systems depend strongly on temperature (cf. Section 5). In order to study the effect of temperature on the phase behavior of these quaternary systems, one, therefore, first has to study the temperature dependence of each of the four ternary systems. This is done by representing the sides of the tetrahedron in upright prisms with the corresponding Gibbs triangle as base and temperature as ordinate. If each of these four prisms is known, one may readily construct the tetrahedron at each temperature of interest.

The systems that have been studied previously are best divided into three classes: class (1) and (2) as above, and class (3):

$$\underset{\mathbf{A}}{H_2O} - \underset{\mathbf{B}}{\text{oil}} - \underset{\mathbf{C}}{\text{nonionic amphiphile}} - \underset{\mathbf{D}}{\text{ionic amphiphile}} \qquad (3)$$

each, if necessary, including inorganic electrolytes (**E**) as fourth or fifth component. If an inorganic salt is included as fifth component, one can attempt to represent the quinary system in a pseudoquaternary tetrahedron by combining two of the components into a pseudocomponent. Which combination is chosen as pseudocomponent, is again a question of convenience.

From the vast literature, one may take the following studies as representative examples: Systems of class (1): among others, studies by *Shinoda* et al.,[2] *Friberg* et al.,[3] *Scriven* et al.,[4] and *Kahlweit* et al.[5] Systems of class (2): among others, studies by *Eckwall*,[6] *Shinoda* et al.,[7] *Schechter* et al.,[8] and *Ninham* et al.[9] Systems of class (3): first studies by *Schulman* et al.[10] and thereafter in particular by French groups.[11]

The phase behavior of systems of class (1), including electrolytes as fourth component, can be considered as being clarified.[5] In the case of systems of class (2), *Eckwall* employed ionic surfactants which are much more readily soluble in water than in oil, whereas the other authors[7–9] chose ionic surfactants with comparable solubility in water and oil in that they employed surfactants with either double-tailed or branched carbon chains. As a consequence, the phase diagrams of their systems look more similar to that shown on the lower triangle in Figure 1.

In the case of systems of class (3), *Schulman* et al. chose—in our opinion—a rather inappropriate combination of nonionic and ionic amphiphiles, namely alcohols that are more readily soluble in oil than in water, and ionic surfactants that are much more readily soluble in water than in oil (Fig. 2).

In view of *Bancroft*'s rule, however, we presume that a combination of two amphiphiles which are both equally well soluble in water and oil is most efficient in preparing stable homogeneous solutions of water and oil. It is essential, therefore, to study the temperature dependence of the phase behavior of systems of class (2), **A**–**B**–**D**, with ionic amphiphiles with 'balanced' hydrophilic and hydrophobic groups. If the prisms of these systems are known, one may combine them with appropriate nonionic amphiphiles and study the efficiency of the quaternary systems of class (3). With this goal in mind, we shall, in this review,

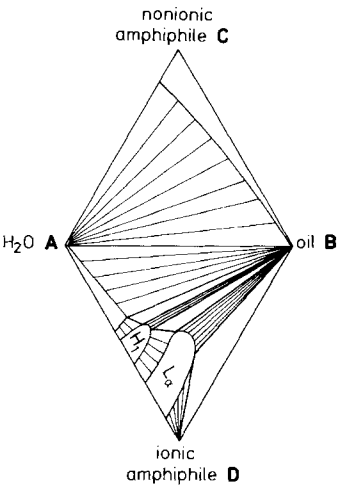


Fig. 2. Phase diagram of systems (1) and (2) [10] (schematic). The alcohol (as nonionic amphiphile) is much more readily soluble in oil than in H_2O, whereas the ionic detergent is more readily soluble in H_2O than in oil. H_1 and L_α are lyotropic mesophases (schematic, after [6]).

summarize the results of our studies of the phase behavior of systems of class (1), **A**–**B**–**C**, with an inorganic electrolyte as fourth component. In Sections 3 and 4, we shall discuss the phase diagrams of the three binary systems **A**–**B**, **B**–**C**, and **A**–**C**, while in Sections 5 and 6, we shall demonstrate the interplay of these three binary systems as it determines the phase behavior of the ternary system. Finally, in Section 7 we shall consider the effect of an added inorganic electrolyte.

2. Statement of the Problem

Multicomponent liquid systems of the class H_2O–oil–nonionic amphiphile–electrolyte are of growing interest, both in industry and in research. In practice, there are two problems to be solved that are closely related to each other:

1. To prepare a stable homogeneous solution of H_2O and oil with as little amphiphile as possible (Fig. 3). H_2O

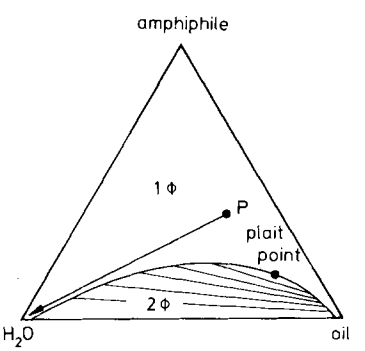


Fig. 3. An example from practice: Dilution of a homogeneous oil-rich solution of composition P with H_2O without phase separation (schematic).

and oil are almost insoluble in each other. Their 'central' miscibility gap extends into the Gibbs triangle. Since the addition of an appropriate nonionic amphiphile increases their mutual solubility, the gap shrinks with increasing concentration of the third component until the two phases, the compositions of which are connected by the 'tie lines', merge at the isothermal critical point or 'plait point'. The declination of the tie lines is determined by the distribution coefficient of the amphiphile between water and oil. The problem then, is to find, for a given oil in a given temperature and pressure range, an amphiphile which makes the central gap as small as possible, so that a homogeneous oil-rich solution (e.g. point P) can be diluted with H_2O in all proportions without phase separation.

2. A mixture having a composition within the central gap may separate into three phases instead of two phases (Fig. 4). The interfacial tension between these phases is, in general, very low. This slows down the coarsening of emulsions, a property which is not only of interest for chemical flooding in tertiary oil recovery, but also for the pharmaceutical industry and for performing chemical reactions in heterogeneous liquid mixtures.

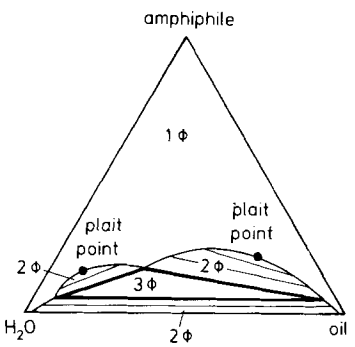


Fig. 4. An example from practice: Formation of a three-phase triangle within a central miscibility gap with low interfacial tensions between the three phases (schematic). 3 Φ: three-phase system.

The separation into three phases occurs, however, only within a certain temperature interval. Again, the problem is to find, for a given oil (mixture) and a given aqueous salt solution (the 'brine') in a given temperature and pressure range, an amphiphile which enforces the formation of such a 'three-phase triangle' as close as possible to the H_2O–oil side of the Gibbs triangle and with an area as large as possible.

Such systems are of interest for experimental and theoretical studies of critical phenomena, in particular near tricritical points. Last but not least, their properties may stimulate further research in the field of associated solutions. With respect to the properties of such mixtures, one should distinguish between their macroscopic equilibrium and dynamic properties, and their microstructure. With respect to their microstructure, the homogeneous solutions of such mixtures, in particular the amphiphile rich phase of the three-phase triangle, are frequently called 'microemulsions'. This term originates from the work of *Schulman* et al. in the fifties, who considered such mixtures as 'optically isotropic, fluid, transparent oil and water dispersions, consisting of uniform droplets of either oil or water in the appropriate continuous phase'[12] stabilized by an interfacial layer of nonionic and ionic amphiphile molecules. Since then, quite a number of other models for the microstructure have been proposed. A discussion of these models goes beyond the scope of this review, for we shall show that the macroscopic equilibrium properties can be readily understood on the basis of the theory of phase diagrams developed by the Dutch[13] and the German[14] schools at the beginning of this century without assuming any particular microstructure of the solutions.

In Sections 5 and 6 we shall discuss the phase behavior of ternary systems of class (1), while the effect of an added electrolyte will be considered in Section 7. As nonionic amphiphiles we have chosen *n*-alkylpolyglycol ethers C_iE_j (i denotes the number of carbon atoms in the hydrophobic alkyl chain and j the number of hydrophilic ethoxy groups: C_iE_j: $H(CH_2)_i(OCH_2CH_2)_jH$, $j=0$), also including short chain alcohols (C_iE_0: $H(CH_2)_iOH$). Even 'simple' systems of this class show all the qualitative features found with the more complex systems (Section 6). This holds, in particular, for the formation of the three-phase bodies within the phase prism.

The formation of the three-phase triangles has been described qualitatively by *Schreinemakers*:[13] They originate from the interplay of the miscibility gaps of the three binary systems representing the sides of the prism, provided these gaps are in the appropriate position with respect to temperature. A semiquantitative treatment, based on earlier considerations by *Meijering*,[15] has been published by *Griffiths* et al.[16] The formation of a three-phase body within the phase prism is thus not a peculiar property of systems with water and amphiphile as components, but can also be found in many other ternary systems, e.g. in metallic alloys. These systems, and such systems with water and amphiphile as components, differ insofar as hydrogen bond formation between H_2O and amphiphile molecules leads to complete miscibility between these components at ambient temperatures. With rising temperature, however, these hydrogen bonds break and the miscibility gap appears again, being, for thermodynamic reasons, a closed upper loop.[17] Since the lower gap generally lies below the melting point of the mixture, it is the upper loop which, by interacting with the lower miscibility gaps of the two other binary systems, causes the formation of the three-phase body in systems of the class **A**–**B**–**C**. Apart from this difference, the evolution of the three-phase triangles and the change of their shape with temperature corresponds to that in any other ternary system with a three-phase body.

The classification of the phase diagrams of such systems by *Winsor*[18] may be somewhat misleading, insofar as it may create the impression that his classification holds for systems with water and nonionic amphiphiles only. *Winsor* distinguished three types of phase diagrams:

I) two phases with the amphiphile dissolved mainly in the aqueous phase,
II) two phases with the amphiphile dissolved mainly in the oil phase,
III) three phases.

The type of phase diagram observed in such systems changes systematically with temperature (Section 5). At

low temperatures one finds type I, at high temperatures type II. In between, one may or may not find type III, depending on the chemical nature of the oil and the amphiphile.

3. The Three Binary Systems

An appropriate way in which to interpret the phase behavior of a ternary system is to first consider the phase diagrams of the three binary systems representing the sides of the phase prism. For thermodynamic reasons, each of these systems shows a lower miscibility gap with an upper critical point. Both the critical temperature and the critical composition depend on pressure. The effect of pressure on the phase diagrams of binary systems has recently been described in a review article by *Schneider*.[19] At the low pressures normally used in practice, the effect is rather weak.

Figure 5 shows the unfolded phase prism with schematic diagrams of the three binary phases. The phase diagram of the H_2O–oil system is the simplest of the three. The upper critical point of its (lower) miscibility gap lies well above the boiling point of the mixture, so that the very low mutual solubility between the two liquids increases only slightly between melting and boiling point.

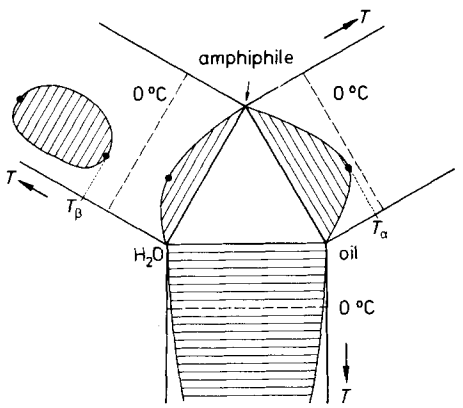


Fig. 5. Unfolded phase prism of the ternary system H_2O(**A**)–oil(**B**)–nonionic amphiphile (**C**) with the phase diagrams of the three binary systems **A**–**B**, **B**–**C**, and **A**–**C** (schematic).

The phase diagram of the binary system oil–nonionic amphiphile appears to be almost as simple. Its upper critical point lies, in general, not too far from the melting point of the mixture, with its critical composition on the oil-rich side. Its upper critical temperature, T_α, depends on the chemical nature of both the oil and the amphiphile: the more the two substances 'dislike' each other, i.e. the more hydrophobic the oil and the more hydrophilic the amphiphile, the higher T_α. As example, Figure 6 shows the miscibility gaps for C_6E_5 and some *n*-alkanes. T_α rises with increasing carbon number k of the oil by about 10° per $\Delta k = 2$.

The phase diagram of the binary system H_2O–nonionic amphiphile is the most complicated of the three, and, furthermore, fascinating. The lower miscibility gap lies, in general, below the melting point of the mixture. At ambient temperatures and low concentrations of the amphiphile, the solutions are molecular disperse. Above a critical concentration, the amphiphile molecules form association colloids (micelles). At even higher concentrations, the system shows lyotropic mesophases (liquid crystals). These

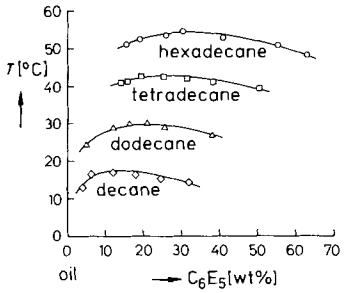


Fig. 6. Lower miscibility gap between some *n*-alkanes as oil and C_6E_5 as nonionic amphiphile. The upper critical temperature T_α rises with increasing hydrophobicity of the oil.

mesophases show up, however, only with the more amphiphilic substances. 'Simple' C_iE_j molecules, i.e. those with low i and j, form no mesophases at all. Irrespective of the existence of these mesophases most of the systems show an upper miscibility gap (at 1 bar) which is a closed loop with an upper as well as a lower critical point. Position and shape of this loop depend on the chemical nature of the amphiphile. This loop, in particular its lower critical temperature, T_β, plays an important role in the phase behavior of the ternary system (cf. Section 4).

4. The Upper Loop in the System H_2O–C_iE_j

Amphiphilic molecules can be looked upon as 'chemical dipoles' which differ from electrical dipoles in that the 'charge' of each pole can be changed independently of the other, and, furthermore, that equal charges attract each other. In the literature, their 'dipole moment' is frequently expressed in terms of a *HLB* value (*H*ydrophilic-*L*ypophilic-*B*alance; hydrophilic-hydrophobic equilibrium), which, for nonionic amphiphiles, is evaluated from

$$HLB = 20\ (M_H/M)$$

where M_H is the molar mass of the hydrophilic group, and M the total molar mass of the substance. It appears, however, that the *HLB* value is not the appropriate measure for the amphiphilicity, since two amphiphiles with quite different molar masses may have similar *HLB* values. Experience, on the other hand, shows that the efficiency of amphiphiles with respect to the increase of the mutual solubility between water and oil increases with their molar mass (Table 1).

The minimum amount of amphiphile (c_{min}) needed to emulsify the H_2O–oil mixture decreases strongly with increasing 'dipole moment' of the amphiphile, whereas the *HLB* value remains almost constant. An apparent relation exists between c_{min} and c_β, whereas T_β remains almost constant.

With respect to the upper loop of the H_2O–C_iE_j system, one can visualize it as a vertical section through a 'nose' in *c*-*T*-*p* space at constant *p*.[20] Figure 7 (left) shows the loop

Table 1. Solubilization capacity of some *n*-alkylpolyglycol ethers.

Amphiphile	*HLB*	c_{min} [a] [wt %]	T_β [°C]	c_β [b] [wt %]
C_4E_1	10.3	58.9	48.7	29.0
C_6E_3	12.7	47.4	45.4	13.5
C_8E_4	12.6	29.6	39.6	6.9
$C_{10}E_5$	12.5	19.7	40.3	3.5
$C_{12}E_6$	12.4	10.6	48.0	2.2

[a] Least concentration of the amphiphile for the homogenization of a 1 : 1 mixture (wt %) of H_2O and *n*-decane at ca. 40°C. [b] Critical concentration of amphiphile in the upper loop.

of the $H_2O-C_4E_1$ system as it shrinks with increasing pressure and disappears at about 800 bar. Figure 8 shows the corresponding 'nose' schematically.

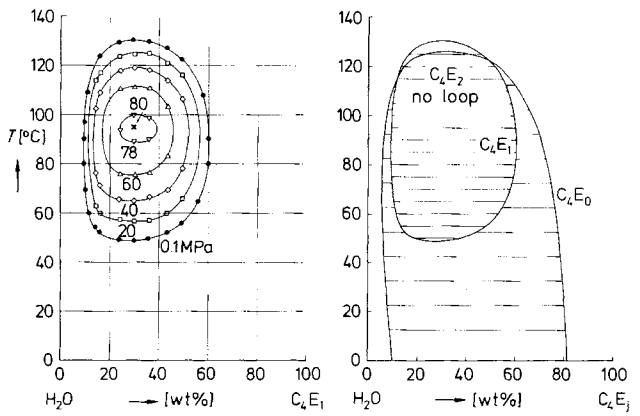


Fig. 7. Left: Shrinking of the upper loop of the system $H_2O-C_4E_1$ with increasing pressure [20]. Right: Shrinking of the upper loop of the system $H_2O-C_4E_j$ with increasing hydrophilicity (j).

The same effect can be achieved by either decreasing the hydrophobicity of the amphiphile (decreasing i at constant j) or by increasing the hydrophilicity (increasing j at constant i). A simple example of the latter is shown in Figure 7 (right): for C_4E_0 (1-butanol), the lower critical temperature T_β lies well below the melting point of the mixture at 1 bar. As one increases the hydrophilicity, by proceeding to C_4E_1, T_β rises to 48°C. As one increases the hydrophilicity further, by proceeding to C_4E_2, the loop disappears altogether. The nose has become too short to show up at 1 bar. However, the nose may still 'lurk' behind the *c*-*T* plane at 1 bar (Fig. 8), and may thus still influence the phase behavior of the ternary system.

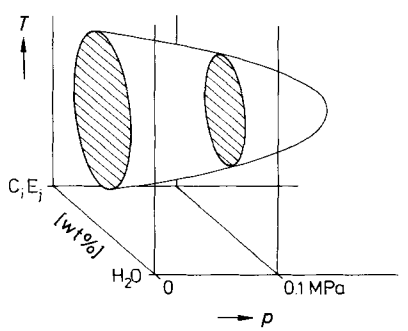


Fig. 8. Upper closed loop of the binary system $H_2O-C_iE_j$ as vertical section (constant pressure) through the 'nose' in the *c*–*T*–*p* space (schematic, after [20]).

A simple example for the effect of decreasing the hydrophobicity of the amphiphile (decreasing i at constant j) is shown in Figure 9. Here, we have chosen the system $H_2O-C_4E_1$ and then decreased the hydrophobicity of the amphiphile by replacing pure C_4E_1 by a mixture of C_3E_1 and C_4E_1 with gradually increasing ratio C_3E_1/C_4E_1. The profile of the nose (full line) has the same shape as that of the pressure nose found by *Schneider*[20] (broken line), its axis being just a little lower on the temperature scale. Both sections were measured at 30 wt% amphiphile.[21]

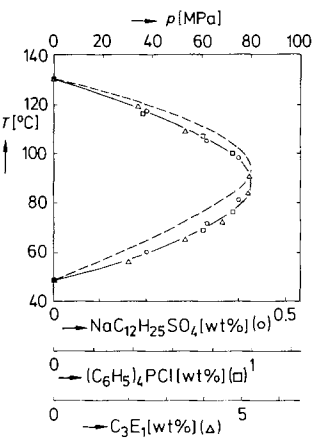


Fig. 9. Profile of the $H_2O-C_4E_1$ nose at 30 wt% C_4E_1. Dashed line: Increase of mutual solubility by increasing the pressure [20]. Full line: Increase of mutual solubility by adding a more hydrophilic amphiphile (C_3E_1), a hydrotropic non-surfactant salt [$(C_6H_5)_4PCl$], and an ionic surfactant ($NaC_{12}H_{25}SO_4$) (after [21]).

The effect of an added electrolyte on the mutual solubility between H_2O and amphiphile was first studied systematically by *Hofmeister*[22] in 1888. He chose the system H_2O–globulin, and employed mainly inorganic electrolytes. *Neuberg*[23] extended these studies to electrolytes with an organic and an inorganic ion. The results of these authors also hold for mixtures of H_2O and nonionic amphiphiles. In the following we shall, for historical reasons, call all electrolytes which decrease the mutual solubility between H_2O and nonionic amphiphiles 'lyotropic', and all electrolytes which increase the mutual solubility 'hydrotropic'.

If one applies the *HSAB* (*H*ard–*S*oft–*A*cid–*B*ase) principle,[24] the results may be summarized as follows:[21] Salts of hard acids and hard bases are lyotropic, i.e. they widen the upper loop, whereas salts of soft acids and hard bases and of hard acids and soft bases are hydrotropic, i.e. make the loop shrink. Salts of soft acids and soft bases appear to be weakly hydrotropic. Accordingly, salts like NaCl, $CaCl_2$, or Na_2SO_4 decrease the mutual solubility between H_2O and amphiphile, whereas salts like $(C_6H_5)_4PCl$, and sodium alkylsulfates ($NaC_kH_{2k+1}SO_4$) increase the mutual solubility. One major exception is the ClO_4^- ion, which, although classified as a hard base, increases the mutual solubility when combined with a hard acid ($NaClO_4$).

At constant salt concentration, the effect decreases with increasing 'dipole moment' of the amphiphile, i.e. with increasing amphiphilicity. Of particular interest is the effect of ionic surfactants. Experiments shows that the hydrotropic effect of such salts increases gradually with increas-

ing carbon number, k, of the alkyl chain,[21,25] and reaches a plateau at high k values. From this point of view, ionic surfactants can be regarded as very efficient hydrotropic salts which differ from the rather effective hydrotropic $(C_6H_5)_4PCl$ only insofar as they are surface active, whereas the latter is not. Adding a hydrotropic salt is, accordingly, equivalent to adding a more hydrophilic nonionic amphiphile (Fig. 9). The profiles of the noses for both $(C_6H_5)PCl$ and $NaC_{12}H_{25}SO_4$ are almost identical with the profile for C_3E_i, if one chooses the concentration units on the abcissa such that the tips of the three noses coincide. Adding a lyotropic salt, on the other hand, is equivalent to adding a more hydrophobic amphiphile. Accordingly, binary systems $H_2O-C_iE_j$ which do not show an upper loop at 1 bar separate into two phases after addition of a sufficient amount of lyotropic salt: the lurking nose shows up. For an example, we refer the reader to the investigation of the system $H_2O-C_3E_0$ (1-propanol)–KCl by *Schneider* and *Russo*[26] (see also [21]).

One may thus push the nose into the phase prism by either adding a more hydrophobic nonionic amphiphile or by adding a lyotropic salt. On the other hand, the nose may be pushed out of the prism by either adding a less hydrophobic amphiphile, by adding a hydrotropic salt, or by increasing the pressure. This property of the nose will be of importance when it comes to discussing the effect of electrolytes on the phase behavior of the ternary system **A–B–C**. With this information at hand we are now in a position to discuss the phase behavior of the ternary system in detail.

5. Phase Behavior of the Ternary System A–B–C

Let us assume for a moment that the binary **A–C** system does not show an upper loop, not even a lurking nose. In this case, the body of heterogeneous phases within the phase prism has a shape resembling that of an apse (Fig. 10). The critical line, connecting the plait point, starts at the upper critical point of the (lower) **B–C** gap, ascends on the oil-rich side of the prism, and finally terminates at the upper critical point of the **A–B** gap. According to *Winsor*'s classification, such a system shows a phase diagram of type I in the entire temperature range between melting and boiling point of the mixture.

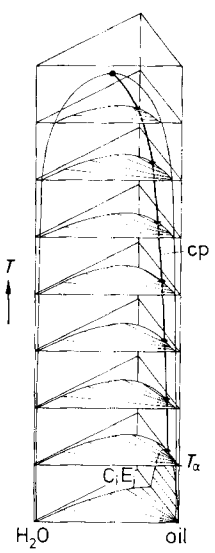


Fig. 10. Phase prism of a ternary system without upper loop between H_2O and amphiphile (schematic). The critical line ascends from the (upper) critical point of the binary **B–C** gap on the oil-rich side to the (upper) critical point of the binary **A–B** gap.

Let us now replace component **C** by a nonionic amphiphile which shows a nose lurking behind the **A–C**–T side of the prism. Since the position of the plait point indicates which of the binary mixtures would separate, if the entropy does not prevent this, the critical line will, at low temperatures, again ascend on the oil-rich side of the prism. With rising temperature, however, the system gradually approaches the lurking nose. Accordingly, the amphiphile will gradually dislike water more than the oil. As a consequence, the critical line will change from the oil-rich side around the surface of the apse to the water-rich side of the prism (Fig. 11). Such a system thus shows a phase diagram of type I at low temperatures which changes to one of type II at high temperatures.

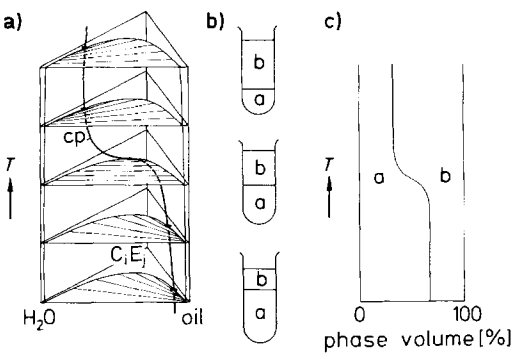


Fig. 11. (a) Phase prism of a ternary system with 'lurking' upper **A–C** nose but connected critical line (schematic). The critical line changes from the oil-rich to the water-rich side as temperature approaches the nose. (b) and (c) Phase volume ratio with $H_2O/oil = 1:1$ [wt%] versus temperature (schematic). At low temperatures, the amphiphile is dissolved mainly in the aqueous phase (type I), at high temperatures mainly in the oil-rich phase (type II). a and b denote aqueous phase and oil phase, respectively.

This change of the critical line from the oil-rich to the water-rich side can be readily demonstrated by measuring the phase volume ratio of the two phases as a function of temperature. At low temperatures, the amphiphile dissolves mainly in the lower aqueous phase, whereas at high temperatures, it dissolves mainly in the upper oil phase (Fig. 11b). Accordingly, the phase volume ratio—if measured at an appropriate composition—shows a sigmoidal dependence on temperature (Fig. 11c), the inflection point indicating that temperature at which the influence of the upper lurking **A–C** nose on the phase behavior overcomes that of the lower **B–C** gap. For an experimental demonstration see, e.g., Figure 4 in Ref. [5c]. This phase volume ratio curve (Fig. 11c) should not be mistaken for the projection of the critical line (Fig. 11a) from the **A–B**–T plane of the prism onto some parallel plane in the rear, although the two curves look rather similar.

The critical line can be looked upon as an elastic spring. Its bending tension can now be increased by either pushing the upper critical point of the **B–C** gap upwards, i.e. by increasing the hydrophobicity of the oil, or by pushing

the lurking **A**–**C** nose closer to the prism by either increasing the amphiphilicity of the amphiphile or by adding a lyotropic salt. The increase of the bending tension of the critical line manifests itself by the observation that the tangent at its inflection point becomes increasingly horizontal—until it eventually breaks (Fig. 12c). The point at which the critical line breaks is called a 'tricritical point'.[27]

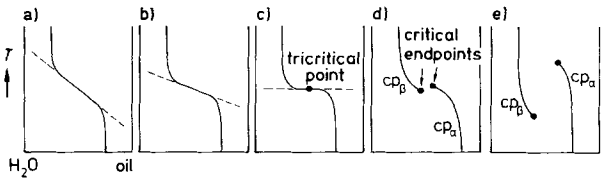


Fig. 12. Transition from a connected critical line, (a) and (b), to a broken critical line, (d) and (e): projection of the critical lines from the **A**–**B**–T plane of the prism onto some parallel plane in the rear (schematic). With increasing 'bending tension' the tangent at the inflection point of the connected critical line tends more and more to the horizontal, until the critical line breaks at a tricritical point (c).

In a ternary system the tricritical point is defined by temperature, pressure, and composition, i.e. by four parameters. To find a tricritical point in a truly ternary system at fixed pressure (e.g. 1 bar), is thus a 'lucky accident'.[28] Either the oil is not sufficiently 'oily' (Fig. 12b), or it is too oily (Fig. 12d), or the amphiphile is not sufficiently amphiphilic (Fig. 12b), or too amphiphilic (Fig. 12d). Therefore, to reach the tricritical point at a pressure of 1 bar, one has to mix either an oil of the type in Figure 12b with one of the type in Figure 12d, or an amphiphile of the type in Figure 12b with one of the type in Figure 12d. Another way to reach a tricritical point is to push the nose of an amphiphile of the type in Figure 12b into the prism by adding a lyotropic salt, or to push the nose of an amphiphile of the type in Figure 12d out of the prism by adding a hydrotropic salt, or—by increasing the pressure.

In a system with a connected critical line (Fig. 11), the amphiphile is transferred continuously from the water-rich to the oil-rich phase as the temperature rises. In a system with a broken critical line, this is achieved by means of a three-phase triangle (Fig. 13). At low temperatures, the amphiphile is dissolved mainly in the water-rich phase. As one raises the temperature, the system approaches the **A**–**C** nose. If the nose is sufficiently close to the prism or even shows up as upper loop on the **A**–**C**–T plane, H_2O and amphiphile separate into two phases on the water-rich side of the prism at the (lower) 'end point' of the critical line cp_β, which descends (or ascends) from the lower critical point of the loop into the prism. As one raises the temperature, the **A**–**C** loop widens. Consequently, the aqueous phase (a) and the 'surfactant' phase or middle phase (c) move further apart. The aqueous phase moves on an ascending line towards the H_2O-edge of the prism, whereas the surfactant phase moves on an ascending line around the surface of the central gap towards the oil-rich side. The oil phase (b), on the other hand, moves on an ascending line counterclockwise towards the surfactant phase until both merge on the oil-rich side of the prism at the (upper) end point of the critical line cp_α, which ascends from the upper critical point of the **B**–**C** gap into the prism. The surfactant phase thus acts like a 'ferry', transporting the amphiphile from the water-rich to the oil-rich side. The three-phase triangle appears as a 'lower critical tie line' at temperature T_l and disappears as an 'upper critical tie line' at T_u. In this temperature range from T_l to T_u, the triangle changes its shape such that the top of the triangle, phase (c), moves clockwise from the end point of cp_β to the end point of cp_α (Fig. 14, top). According to *Winsor*'s classification, such a system thus shows a phase diagram of type I below T_l, one of type III between T_l and T_u, and one of type II above T_u. If one measures its phase volume ratio at an appropriate composition versus temperature, one accordingly finds the behavior shown schematically in Figure 13c. The position and width of the three-phase temperature interval (T_u–T_l) on the temperature scale depends on the chemical nature of both the oil and the amphiphile. For a given oil, the three-phase interval lies the lower the more hydrophobic the amphiphile, i.e., the lower T_β, whereas—for a given amphiphile—it lies the higher the more hydrophobic the oil, i.e., the higher T_α. As a consequence, for some systems the three-phase interval may lie even below the melting or above the boiling point of the mixture.

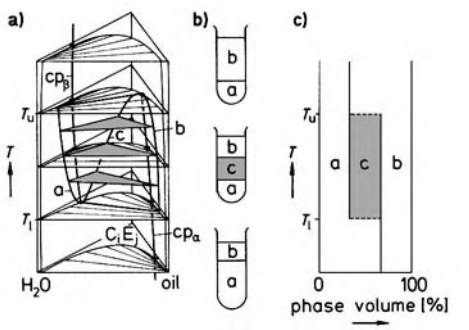


Fig. 13. (a) Phase prism of a ternary system with broken critical line and three-phase body (schematic). For discussion see text. (b) and (c) Phase volume ratio as a function of temperature (schematic). Between type I and type II one finds type III in the three-phase temperature interval T_u–T_l.

The fact, that the three-phase triangle emerges from the end point of the critical line cp_β and disappears at the end point of the critical line cp_α can be readily demonstrated by measuring the dynamic light scattering of the corresponding phases (for experimental details see Ref. [5a]): If one prepares a solution of the composition U of the intersection of the projections of the two critical lines (Figure 11 in Ref. [5b]) and approaches T_l from below, the water-rich solution shows an increasing critical opalescence which reaches its maximum at T_l (black circles in Fig. 14b, left). At T_l, the solution separates into the aqueous and the surfactant phase. A little above T_l, these solutions are still 'near critical'. Accordingly, they still show critical opalescence. If one now follows the opalescence in the surfactant phase (white circles in Fig. 14b), the composition of which is, at each temperature, well defined, the opalescence first decreases with rising temperature, i.e., increasing distance of phase c from the critical line cp_β. However, as soon as the composition of phase c has passed '12 o'clock' on its way around the central gap, opalescence increases again as

phase c starts to approach the critical line cp_α. As the temperature approaches T_u, both the oil phase and the surfactant phase become near critical, because they are to merge at the end point of cp_α. Consequently, both phases show increasing critical opalescence which reaches its maximum at T_u (as shown for the surfactant phase in Fig. 14b). At T_u the two phases merge at the end point of cp_α. With further rising temperature, this now homogeneous solution shows a decreasing opalescence as its distance from the end point of cp_α increases (black circles in Figure 14b, right). From this, it follows that the light scattering frequently observed in such systems must not necessarily stem from aggregates (e.g. microemulsions), but may also stem from critical fluctuations, provided the composition of the corresponding solutions lies sufficiently close to either one of the critical lines.

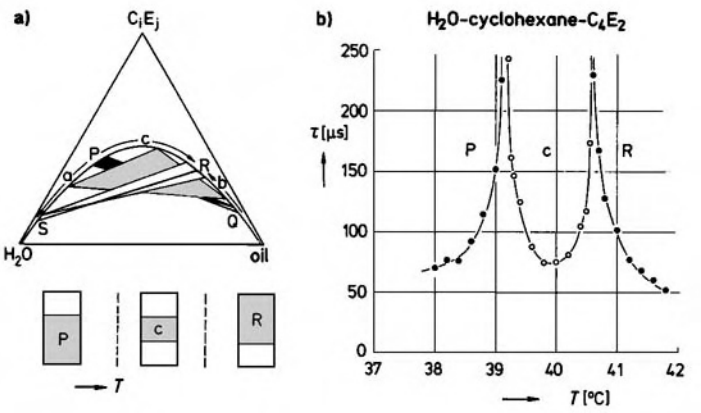


Fig. 14. (a) Change of shape of the three-phase triangle with rising temperature (schematic). The amphiphile-rich middle phase (c) moves clockwise from the (lower) end point (P) of critical line cp_β to the (upper) end point (R) of critical line cp_α. (b) Divergence of the correlation length, determined by dynamic light scattering in the homogeneous solutions of the system H_2O–cyclohexane–C_4E_2: correlation time constant τ versus temperature. (For details see text.)

Another important consequence concerns the temperature dependence of the interfacial tensions between the aqueous phase and the surfactant phase (a/c) and the oil phase and the surfactant phase (b/c). Since phase a and phase c emerge from the end point of critical line cp_β, the interfacial tensions (a/c) will rise from zero at T_l according to the scaling law for the interfacial tension between near critical phases (Fig. 15c). The oil phase and the surfactant phase, on the other hand, merge at the end point of the critical line cp_α. Consequently, interfacial tension (b/c) will vanish at T_u according to the scaling law. The very low interfacial tensions between these phases are, therefore, an inevitable consequence of the phase behavior of the ternary system, irrespective of the particular microstructure of the solutions.

We have thus learned that the phase behavior of a ternary system is determined by its 'distance' from a tricritical point. If its components are such that it lies 'beyond' a tricritical point, it will not show a three-phase body, whereas, if it lies 'this side' of a tricritical point, it will. The three-phase body emerges from the tricritical point on the surface of the central gap. With systems close to the tricritical point, the three-phase body is small, being located close to the surface of the central gap (Fig. 15a). Correspondingly,

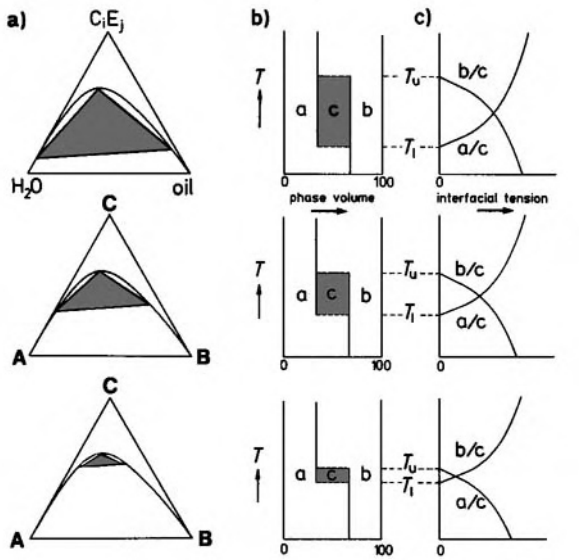


Fig. 15. Alteration of (a) the three-phase triangle, (b) the phase volume ratio, and (c) the interfacial tension with increasing distance from a tricritical point (schematic). (For details see text.)

the three-phase temperature interval is narrow and the interfacial tension between the phases low. With increasing distance from the tricritical point, the three-phase body grows into the central gap and the relative area covered by the three-phase triangles increases, as does also $(T_u - T_l)$ and the interfacial tension (Fig. 15b, 15c).

If one wishes to have a large three-phase triangle and a wide temperature interval, one has to pay with relatively high interfacial tensions. On the other hand, if one wishes to have very low interfacial tensions, one has to pay with relatively small triangles and a narrow interval. Hence, for a given temperature (or temperature range) and a given oil (or oil mixture) the problem is to optimize these properties by choosing the appropriate amphiphile (or combination).

6. Concentration-Temperature Diagrams

An instructive procedure to learn more about the shape of the central miscibility gap and the three-phase body within this gap is to draw vertical sections through the phase prism, i.e. so-called *c-T* diagrams (Fig. 16), as they are frequently employed by metallurgists. Among the

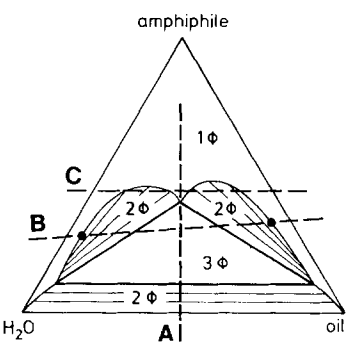


Fig. 16. *c-T* diagrams: vertical sections through the phase prism. (For details see text.)

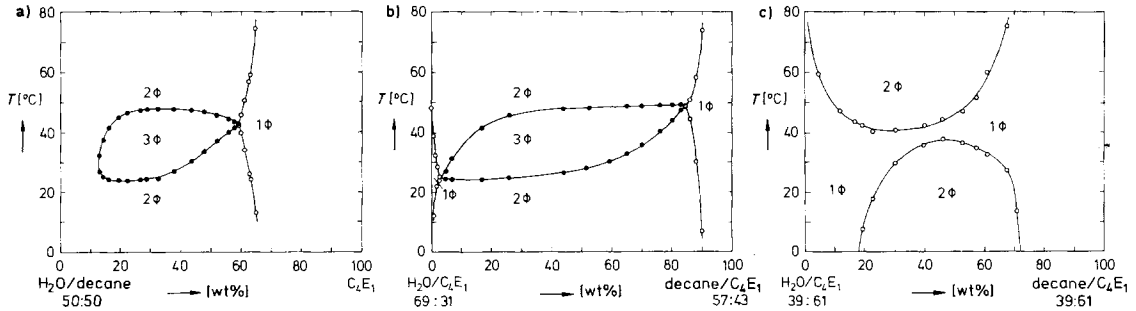


Fig. 17. (a) Section A, (b) section B, and (c) section C through the phase prism of the system H_2O–decane–C_4E_1 with three phase bodies (sections A and B), and homogeneous channel from the water-rich to the oil-rich side (section C).

many possible sections the following are particularly instructive.

Section A: erected on the center line of the Gibbs triangle, i.e. on the line connecting the point H_2O/oil = 1 : 1 on the **A**–**B** side with the **C** corner.

Section B: erected on the line connecting the end point of the critical line cp_β with that of cp_α.

Section C: erected on a line passing the 'groove' close to the surfactant phase c in its '12 o'clock' position (for details see below).

Figure 17 shows these sections for the system H_2O–*n*-decane–C_4E_1. Looking at section A from the **B**–**C** side of the prism, one can see the profile of the central miscibility gap as well as a section through the three-phase body floating within that gap like a 'fish' (Fig. 17a). The 'tail' of this fish, i.e. the groove at that point at which the three-phase body touches the surface of the central gap is a consequence of Schreinemakers' rule, which requires that—for thermodynamic reasons (!)—the boundaries of each homogeneous phase must intersect at the corner of the three-phase triangle in such a way that both their extensions either pass into the triangle (Fig. 18a) or into the adjacent two-phase regions (Fig. 18b).[29]

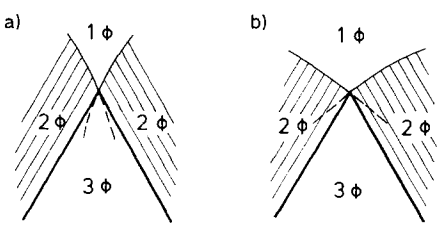


Fig. 18. Origin of *Schreinemakers'* grooves on the body of heterogeneous phases (schematic). For details see text.

Looking at the B section from the **A**–**B** side of the prism (Fig. 17b), one can see a section cutting through the three-phase body more or less parallel to the **A**–**B**–*T* plane. It again shows Schreinemakers' grooves at the end points of the critical line cp_β (on the left) and cp_α (on the right).

On its way from the end point of cp_β to that of cp_α the surfactant phase c thus cuts a groove into the body of heterogeneous phases, which ascends like a 'waist' from the water-rich to the oil-rich side. It is in this waist where one finds the highest mutual solubility of H_2O and oil in the presence of an amphiphile, and it is the groove in the A section from which the data in Table 1 were taken. Figure 19 shows the model of the body of heterogeneous phases of a 'simple' system.

This waist enables one to find an isotropic homogeneous channel from the water-rich to the oil-rich side of the prism, passing along the groove of the central gap (section C) and, like the waist, ascending with temperature from T_l on the water-rich to T_u on the oil-rich side (Fig. 17C). This channel offers a unique possibility to study the microstructure of the homogeneous solution close to the body of heterogeneous phases as it changes from an 'oil in water' to a 'water in oil' emulsion. This does not only hold for systems

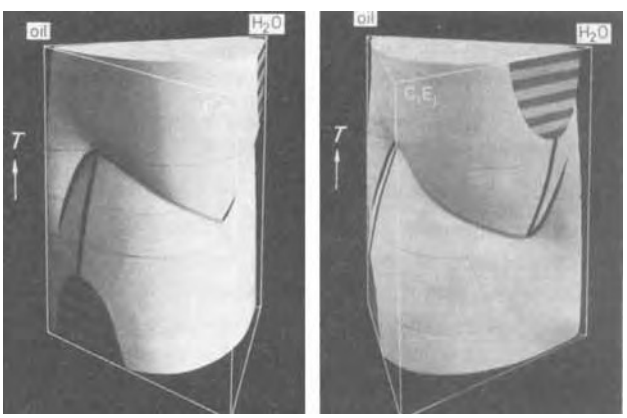


Fig. 19. Model of the body of heterogeneous phases for a 'simple' system with 'waist'. Left: seen from the **B**–**C** side with lower miscibility gap and ascending critical line cp_α; right: seen from the **A**–**C** side with upper gap and descending critical line cp_β.

with 'simple' amphiphiles, but also for systems with long chain amphiphiles (see below).

We shall now discuss some representative experimental examples: The first example demonstrates the transition from a connected to a broken critical line. The system chosen is H_2O–phenylalkane $(C_6H_5)(CH_2)_kH$–C_4E_2. The binary system H_2O–C_4E_2 shows no upper loop at 1 bar, but a lurking nose. Figure 20 shows the A sections of these systems, in which only the hydrophobicity of the oil was increased by increasing the carbon number k. The critical line is thus fixed by the lurking nose of the H_2O–C_4E_2 sys-

tem on the water-rich side, and by the upper critical point of the oil–C_4E_2 gap on the oil-rich side. For the less hydrophobic oils with low k, one finds a connected critical line, with no three-phase body within the prism. If one increases k, i.e. makes the oil more oily, one pushes the upper critical point of the oil–C_4E_2 gap upwards (see Fig. 6). This increases the bending tension of the critical line, until it breaks between k = 6 and k = 7. The tricritical point of this particular system thus lies at about 52 °C and 1 bar, with an oil having k between 6 and 7.

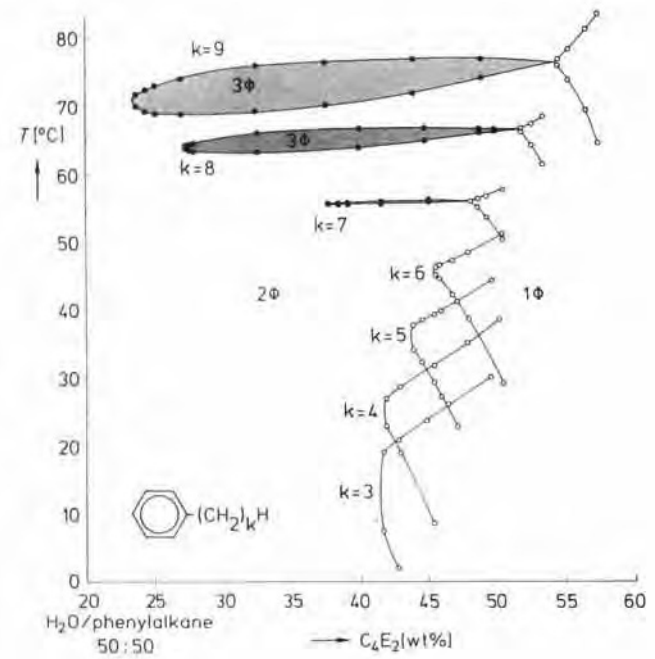


Fig. 20. Section A through the phase prisms of the systems H_2O–phenylalkanes $(C_6H_5)(CH_2)_kH$–C_4E_2. Transition from a connected (k = 3, 4, 5, 6) to a broken (k = 7, 8, 9) critical line by increasing the hydrophobicity of the oil. The three-phase body grows with increasing distance from the tricritical point (between k = 6 and k = 7) (see Fig. 12).

Interestingly, even the connected critical lines cut a groove into the central gap, which becomes increasingly sharper as one approaches the tricritical point. As expected, a system shows the highest mutual solubility between H_2O and oil at that temperature at which either the connected critical line changes from the water-rich to the oil-rich side, or the broken critical line causes the formation of a three-phase body. As further expected, this temperature rises—for a given amphiphile—with increasing hydrophobicity of the oil, i.e. increasing carbon number k.

This general feature is again demonstrated in Figure 21, which shows the change of the three-phase temperature interval $(T_u - T_l)$ for four classes of C_iE_j (i = 4, 6, 8, 12) with the carbon number k of *n*-alkanes. It also demonstrates again that the interval $(T_u - T_l$ shrinks with decreasing carbon number, shaping a 'cusp' which appears to originate in the common tricritical point of each of the series at low carbon numbers.

Unfortunately, due to the high vapor pressure of these short chain alkanes it is not possible to reach these tricritical points at 1 bar; to do so, one would have to increase the pressure (see Figure 11 in [5d]). Nevertheless, these results again suggest considering the tricritical point as a kind of pivot point from which the phase behavior of a system evolves. If this were an approach to reality, the phase behavior would be governed by universal scaling laws for 'near tricritical' systems in more or less good approximation. The closer a system to its tricritical point, the better the description—the further apart, the poorer. This would also explain why the phase behavior of all these systems is qualitatively similar, irrespective of their microstructure: amphiphiles of class C_4E_j form neither micelles nor lyotropic mesophases, those of class C_6E_j apparently only micelles, whereas the higher classes form both. The universal scaling laws, on the other hand, are independent of the particular microstructure, since that is what makes them 'universal'.

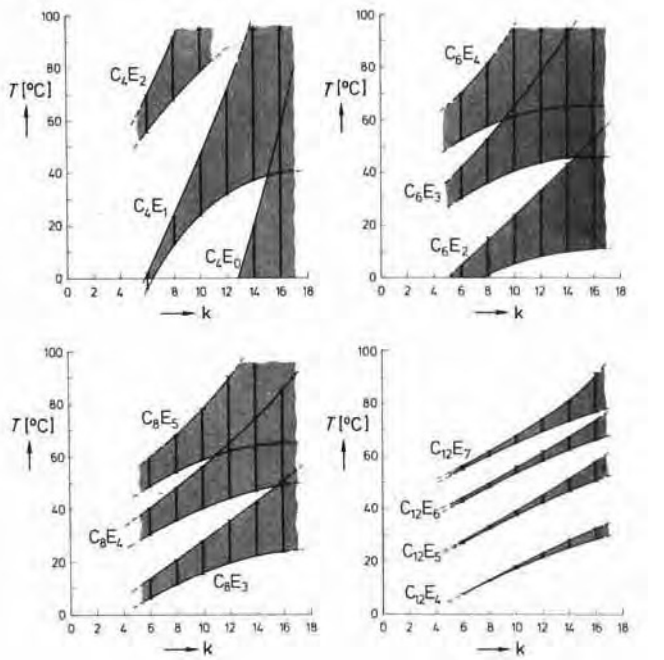


Fig. 21. Three-phase temperature intervals $(T_u - T_l)$ for the systems H_2O–*n*-alkanes C_kH_{2k+2}–C_iE_j (i = 4, 6, 8, 12). Each homologous series shapes a cusp, the tricritical point of which appears to be located at the short-chain alkanes.

Accordingly, the difference between short-chain and long-chain amphiphiles manifests itself not so much in the phase behavior but rather in their efficiency in solubilizing H_2O and oil. This is demonstrated in Figure 22, which shows the change of shape of the three-phase triangles with temperature for the three systems: H_2O–decane–C_4E_1, H_2O–decane–C_8E_3[30] and H_2O–tetradecane–$C_{12}E_5$.[31] The evolution of the three-phase triangles is quite similar.

But, the more amphiphilic the amphiphile, the closer the triangles to the **A**–**B**–*T* plane of the prism and the deeper the grooves, i.e., the less amount of amphiphile needed to achieve a homogeneous solution. This holds, however, only for the groove (!). Below and, in particular, above the three-phase temperature inverval the solubilization efficiency of the amphiphiles differs much less (Fig. 23). This is not surprising, since, at higher temperatures, the central gap merges with the upper loop of the binary H_2O–C_iE_j system. Below the groove, short chain amphiphiles show a rather wide central gap, whereas with long chain amphi-

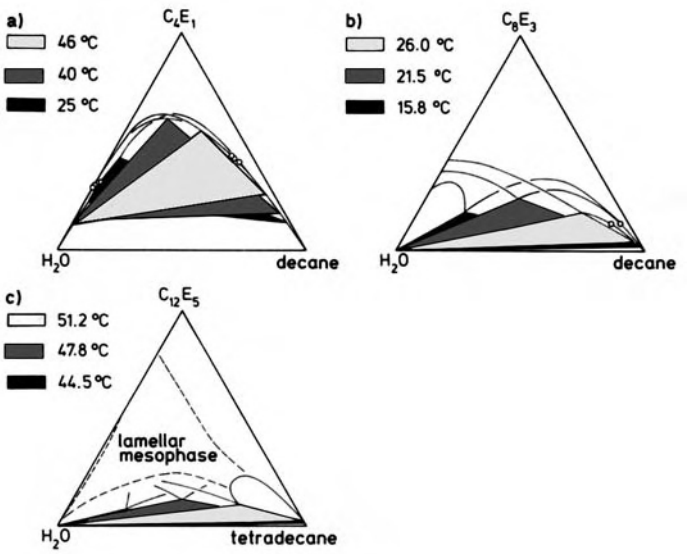


Fig. 22. Change of shape of the three-phase triangles for the system (a) H_2O–decane–C_4E_1, (b) H_2O–decane–C_8E_3, and (c) H_2O–tetradecane–$C_{12}E_5$ with rising temperature: The phase behavior is quite similar, and apparently independent of the particular microstructure of the solutions.

philes part of this gap is somewhat 'replaced' by highly viscous lyotropic mesophases.

The binary **A**–**C** system with long chain amphiphiles shows a number of mesophases (Fig. 24a). On the water-rich side one finds below the upper loop (2Φ) isotropic micellar solutions. With increasing concentration of the amphiphile, first a cubic (I_1), then a hexagonal (H_1), then a viscous isotropic (V_1), and finally, a lamellar (L_α) mesophase appear. All these mesophases extend into the narrow region of an optically isotropic though opalescent homogeneous phase. The existence of this region enables one to find a narrow isotropic homogeneous channel from the water-rich to the oil-rich side of the phase prism (section C in Fig. 23; cf. section C in Fig. 17). *Nilsson* and *Lindman*[34] were apparently the first to recognize the significance of these channels for the investigation of the microstructure of such systems.

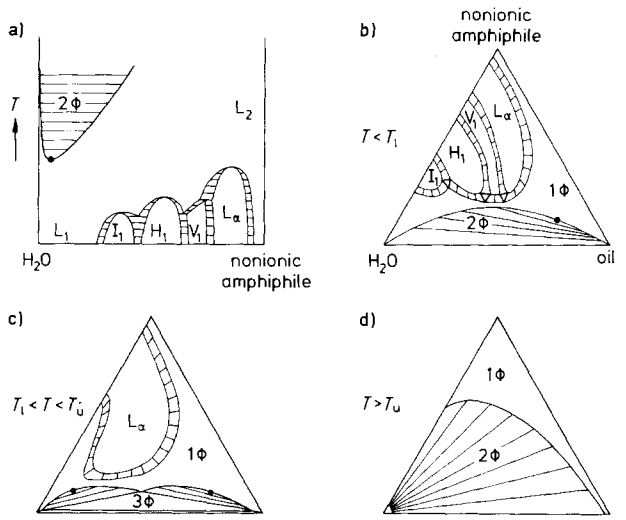


Fig. 24. (a) Lyotropic mesophases in the binary system H_2O–C_iE_j (schematic, notation after ref. [36]; see text, L_1 and L_2 are isotropic phases). (b) Extension of the lyotropic mesophases into the Gibbs triangle below T_l (schematic); (c) extension of the lyotropic mesophases into the Gibbs triangle in the three-phase temperature interval (T_u–T_l) (schematic); (d) phase diagram above T_u (schematic).

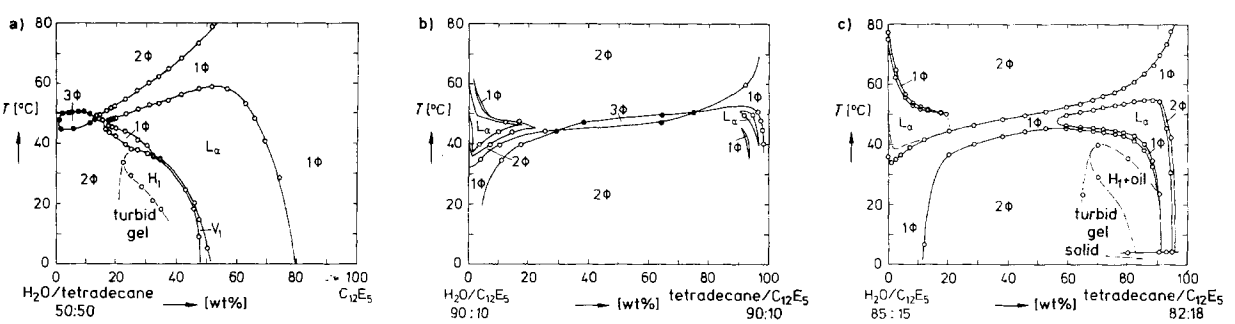


Fig. 23. (a) Section A, (b) section B [32], and (c) section C through the phase prism of the system H_2O–tetradecane–$C_{12}E_5$ with three-phase body (**A** and **B**) and homogeneous isotropic channel from the water-rich to the oil-rich side (**C**). H_1 hexagonal, L_α lamellar mesophase. Section B at 10 wt% $C_{12}E_5$; hence, it does not lie on the line between the two end points of the critical lines but parallel to the **A**–**B** side. The three-phase body, and thus also the groove (c_{min} in Table 1), lie much closer to the **A**–**B**–T plane of the prism than with C_4E_1 as amphiphile (Fig. 17).

A–**B**–**C** prism (Fig. 24b) and may even overlap with the central miscibility gap.[33]

As a rule, the three-phase body within the **A**–**B**–**C** prism appears at a temperature which lies above that for the hexagonal mesophase. Accordingly, in the three-phase temperature interval (T_l–T_u) only the lamellar mesophase is found (Fig. 24c). At sufficiently high temperatures this vanishes and, in general, one finds only isotropic solutions (Fig. 24d). The lamellar phase points at the three-phase body like a signboard (section A in Fig. 23). Between the lamellar phase and the central gap one finds, in general, a

7. Phase Behavior of Quaternary Systems **A**–**B**–**C**–**E**

In this section we shall discuss the phase behavior of quaternary systems **A**–**B**–**C**–**E**, where **E** denotes the fourth component, being either a second oil, a second nonionic amphiphile, or a lyotropic or a hydrotropic salt. The phase behavior of a quaternary system is represented in a phase tetrahedron at constant temperature and pressure (cf. Section 1). As base we choose the Gibbs triangle of the **A**–**B**–**C** system, the phase behavior of which has been

discussed in the preceding sections, and place the fourth component on top of the tetrahedron. Again, the appropriate procedure to discuss the phase behavior of the quaternary system is, first, to consider the phase diagrams of the three other ternary systems **A–B–E**, **B–C–E**, and **A–C–E**. In the following we restrict the discussion to inorganic lyotropic salts as fourth component.

To discuss the phase behavior of the quaternary system as function of the temperature, one has to move the tetrahedron within the **A–B–C–***T* phase prism upwards or downwards like an elevator (Fig. 25). The position of the **A–B–C** base of the tetrahedron then defines the temperature at which the phase behavior of the quaternary system is discussed.

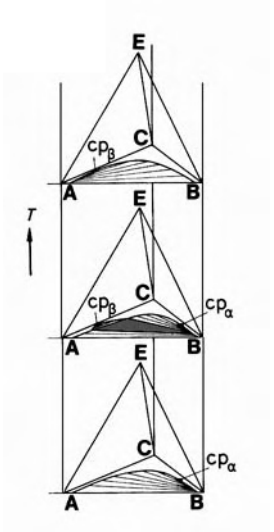


Fig. 25. Illustration of the temperature dependence of the phase behavior of the quaternary system **A–B–C–E**: Alternative positions of the phase tetrahedron **A–B–C–E** within the phase prism **A–B–C–***T* (schematic).

Accordingly, one may place the tetrahedron below, within, or above the three-phase body of the **A–B–C** system. The phase diagram on the base of the tetrahedron will then look like either one of the diagrams shown in Figure 25.

From this, it follows that the phase behavior of a quaternary system crucially depends on the temperature at which it is studied, and, furthermore, that a knowledge of the phase prism of the **A–B–C** system is a prerequisite for an understanding of the quaternary system. The same holds for the phase prisms of the three other ternary systems. Figure 26 shows schematically the unfolded tetrahedron at a temperature below T_l of the **A–B–C** system, i.e. below the temperature of its three-phase body. Accordingly, the base, i.e. the central triangle, shows a phase diagram of type I in *Winsor*'s classification.

Let us now consider the three other triangles:

Triangle **A–B–E**: The miscibility gap **A–B** extends into the **A–B–E** triangle. On the **A–E** and the **B–E** side, one finds homogeneous solutions of **E** in the corresponding mixtures. Since the solubility of a lyotropic salt, e.g. NaCl, is much higher in water than in oil, the tie lines of the two-phase region between the homogeneous regions decline steeply towards the **B** corner. Between this two-phase region and the **E** corner one finds a three-phase triangle with solid **E** as third phase. This phase diagram will change only slightly with temperature.

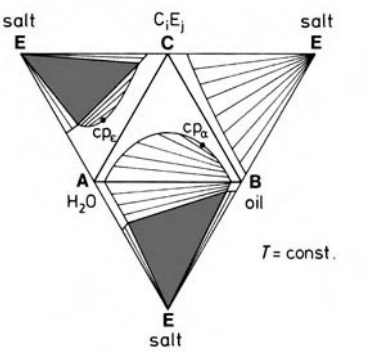


Fig. 26. Unfolded phase tetrahedron for the system H_2O–oil–nonionic amphiphile–lyotropic salt at a temperature below T_l (of the ternary system **A–B–C**). For discussion see text.

Triangle **B–C–E**: If the temperature of the system lies above the critical temperature T_α of the (lower) **B–C** gap, one finds a homogeneous solution along the **B–C** side of the triangle and a two-phase region between this region and the **E** corner with solid **E** as second phase. Since the solubility of the lyotropic salt is higher in the amphiphile than in the oil, the boundary between the homogeneous solution and the two-phase region declines from **C** to **B**.

Triangle **A–C–E**: If the temperature lies below the critical temperature T_β of the upper loop of the **A–C** system, one finds a homogeneous solution along the **A–C** side of the triangle. Since, however, the lyotropic salt enforces a phase separation between **A** and **C** at temperatures below T_β, a two-phase region with two liquid phases is found between the homogeneous region and the **E** corner. The two phases merge at a plait point cp_c. Between this two-phase region and the **E** corner there is a three-phase triangle with solid **E** as third phase.

The phase behavior of such a system can be readily understood on the basis of the considerations presented in the preceding sections,[5b] with the lyotropic salt playing the role of temperature and the plait point cp_c that of the lower critical point of the upper **A–C** loop. The three-phase triangle appears at the salt concentration c_l (instead of T_l) at the end point of the critical line cp_c, which descends from the **A–C–E** triangle into the tetrahedron. With increasing salt concentration, the surfactant phase c moves clockwise around the surface of the central gap to merge at salt concentration c_u (instead of T_u) with the oil phase b at the end point of critical line cp_α, which ascends into the tetrahedron on the oil-rich side. Since the salt is more readily soluble in H_2O than in the amphiphile or the oil, the tie lines as well as the three-phase triangles are not parallel to the **A–B–C** base, but tilted as shown schematically in Figure 27 (top).

Again, one may erect a vertical section A along the center line of the **A–B–C** base, and again one finds the three-phase body floating within the tetrahedron like a fish, now slightly tilted with respect to the base (Fig. 27). If one projects the three-phase triangles from the **E** corner onto the **A–B–C** base, one finds the same change of shape of the triangles with increasing salt concentration as

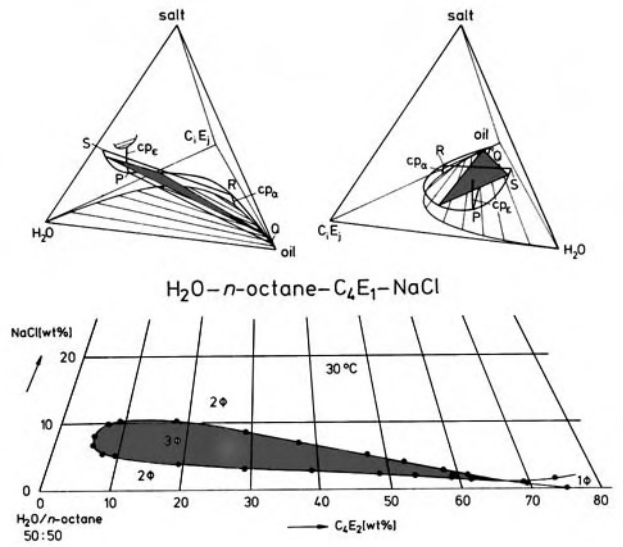


Fig. 27. Top: Position of a three-phase triangle within a phase tetrahedron of the system **A**–**B**–**C**–**E** (schematic). P, Q, R, and S are the endpoints of the two critical tie lines. Bottom: Section A through the phase tetrahedron of the system H_2O–octane–C_4E_2–NaCl at 30 °C.

is found in the ternary **A**–**B**–**C** system with rising temperature (cf. Fig. 22). Figure 28 shows this change of shape for the system H_2O–benzene–C_2E_0(ethanol)–$(NH_4)_2SO_4$ at 21 °C.[35] Accordingly, one finds the same change in the phase volume ratio and interfacial tensions with increasing salt concentration and rising temperature (Fig. 28, bottom; cf. Fig. 15).

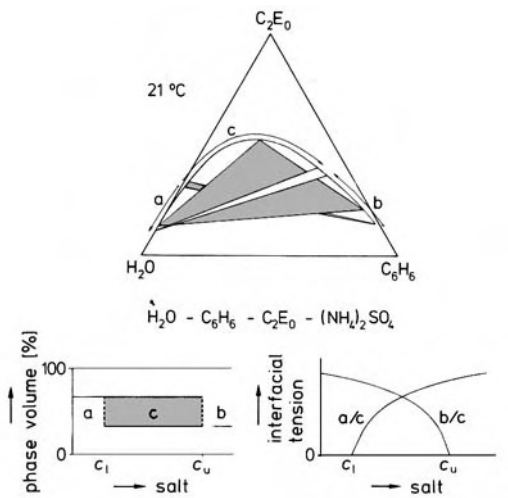


Fig. 28. Top: Change of shape of the three-phase triangle for the system H_2O–benzene–ethanol–$(NH_4)_2SO_4$ with increasing salt concentration at 21 °C (after [35], cf. Fig. 22). Lowest (dark gray), medium (gray), and highest (light gray) concentration. Bottom: Phase volume ratio and interfacial tension as a function of the salt concentration at constant temperature (schematic, cf. Figs. 13 and 15).

Such quaternary systems are frequently represented in pseudoternary phase prisms with H_2O and salt combined as pseudocomponent. The transcription of the phase behavior from a tetrahedron into a prism may lead to considerable quantitative errors insofar as the lower and the upper critical tie lines as well as the three-phase triangles may no longer be parallel to the base of the phase prism as they are in a truly ternary system. Nevertheless, such a representation in a pseudoternary phase prism may simplify the qualitative discussion. It permits, in particular, a rather transparent discussion of the effect of salts on the phase behavior of a ternary system. For this purpose one plots the three-phase temperature interval versus the salt concentration (Fig. 29). At zero salt concentration one finds

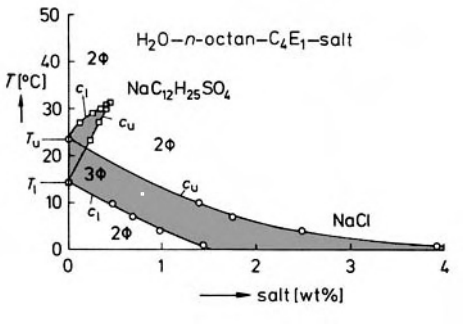


Fig. 29. Three-phase cusps for the system H_2O–octane–C_4E_1–salt (cf. Fig. 21). Lower cusp (○) for NaCl as lyotropic salt with tricritical point at a 'negative' salt concentration. Upper cusp (□) for $NaC_{12}H_{25}SO_4$ as hydrotropic salt with tricritical point within the pseudoternary phase prism.

the interval $T_u - T_l$ of the ternary system. As one adds a lyotropic salt (NaCl), the upper **A**–**C** loop widens. As a consequence, the end points of the two critical lines move further apart (cf. Fig. 12), and $T_u - T_l$ is both lowered and widened. Now consider a temperature below T_l of the truly ternary system. At this temperature the base of the tetrahedron shows a phase diagram of type I (Fig. 25). As one adds salt, one proceeds from the base towards the E corner of the tetrahedron. If the composition of the ternary mixture is properly chosen (for details see Ref. [5b]), one will cross the lower critical tie line of the three-phase body at salt concentration c_l. The three-phase triangle appears. With further increasing salt concentration, one proceeds through the three-phase body until one leaves it at its upper critical tie line at salt concentration c_u. In this representation the three-phase interval has the shape of a cusp, the tip of which lies on the negative salt scale.

Accordingly, one may again visualize a hypothetical tricritical point defined (at 1 bar) by its temperature and a composition with a negative salt concentration, from which the phase behavior of the quaternary system evolves.

In order to move the tricritical point into the pseudoternary prism, one simply has to choose an amphiphile which does not show a three-phase body with that particular oil at zero salt concentration. Such a ternary system shows a connected critical line. If one pushes the **A**–**C** nose into the prism by adding a lyotropic salt, one will eventually break the line: a three-phase body appears (transition from Fig. 12b to 12d). Such an experiment was first performed by *Lang* and *Widom*[35] with the system H_2O–benzene–ethanol–$(NH_4)_2SO_4$. Figure 14 in [5b] shows the cusps with tricritical points found in corresponding experiments with the systems H_2O–*n*-alkanes–NaCl with C_3E_0 or *tert*-C_4E_0 as amphiphile.

Since a connected critical line can be broken by adding a lyotropic salt, one can also mend a broken line by adding a hydrotropic salt or a more hydrophilic nonionic amphiphile (transition from Fig. 12d to 12b). The upper cusp in Figure 29 shows the corresponding experiment with sodium dodecyl sulfate (SDS) as very efficient hydrotropic salt. At zero concentration, one again finds the three-phase temperature interval $T_u - T_l$ of the ternary system. On adding the hydrotropic SDS, the upper **A**–**C** loop shrinks. As a consequence, the end points of the two critical lines approach each other, and $T_u - T_l$ both rises and narrows until the two end points merge at the tricritical point (Fig. 12c): The broken critical line is mended and the three-phase body has, accordingly, disappeared.

Another way of reaching a tricritical point is by decreasing the hydrophobicity of the amphiphile C_iE_j by decreasing i at constant j. Figure 30 shows the result of such an experiment with the system H_2O–hexane–$(C_3E_0 + C_2E_0)$. Here, the **A**–**C** nose is pushed further apart from the prism by gradually replacing pure C_3E_0 by a mixture of C_3E_0 and C_2E_0. Shown are the sections A through the pseudoternary phase prism (cf. Fig. 20).

The system with pure C_3E_0 shows a large three-phase body close to the melting point of the mixture (lowest fish in Fig. 30). On increasing the ratio C_2E_0/C_3E_0, the fish rises and shrinks to disappear at about $C_2E_0/C_3E_0 = 0.05$: The two critical lines cp_α and cp_β have merged at a tricritical point.

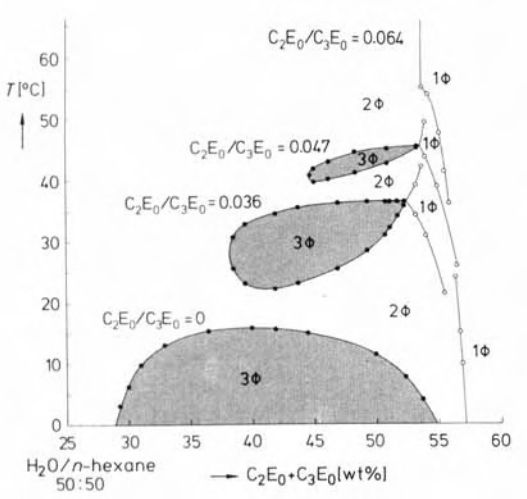


Fig. 30. Transition from a broken critical line ($C_2E_0/C_3E_0 = 0$) to an unbroken critical line ($C_2E_0/C_3E_0 = 0.064$) by increasing the hydrophilicity of the amphiphile: Section A through a pseudoternary phase prism of the system H_2O–hexane–$(C_3E_0 + C_2E_0)$ (cf. Fig. 20).

Neither C_3E_0 nor C_2E_0 show an upper loop with H_2O. On going to long chain amphiphiles C_iE_j with upper loop, one finds that the tricritical point can also be reached by increasing i at constant j, the reason being that with these amphiphiles the lower critical temperature, T_β, of the upper loop drops only slightly with increasing i at constant j, whereas the upper critical temperature, T_α, of the **B**–**C** loop drops steeply. Accordingly, the end points of the two critical lines, cp_β and cp_α, rapidly approach each other.[37]

8. Conclusion

We have shown that the phase behavior of ternary systems of class (1), H_2O–oil–nonionic amphiphile including an electrolyte as fourth component, can be readily understood on the basis of the theory of phase diagrams first developed at the turn of the century. We have, furthermore, suggested that the tricritical points in such systems be regarded as kinds of pivot points from which the phase behavior evolves. This would not only explain the fact that the phase behavior of such systems varies little, irrespective of the chemical nature of the amphiphile, but would also help to systematize its features.

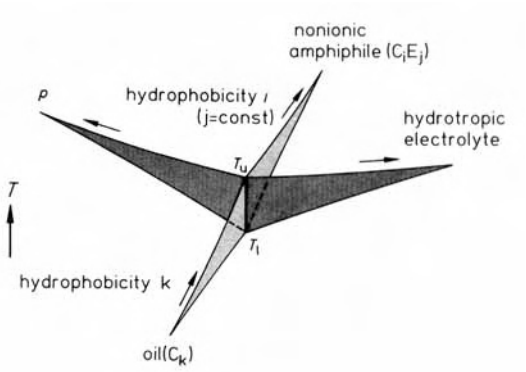


Fig. 31. Three-phase temperature interval ($T_u - T_l$) of a ternary system (center) as evolution from four tricritical points (schematic). For discussion see text.

Figure 31 summarizes our results: It shows in the center the three-phase temperature interval ($T_u - T_l$) of a ternary system of class (1). Its phase behavior evolves from four different tricritical points. These can be reached, at least in principle, by either increasing the pressure, by decreasing the hydrophobicity of the oil within a homologues series, by increasing i at constant j of the amphiphile C_iE_j within a homologues series, or by adding an appropriate hydrotropic salt. Since the thermodynamic properties of the (central) ternary system are functions of state, this suggests that the scaling laws which govern the evolution of its phase behavior from any of these four tricritical points, must be equivalent, if expressed in the appropriate order parameters.

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Selective Reactions Using Organoaluminum Reagents

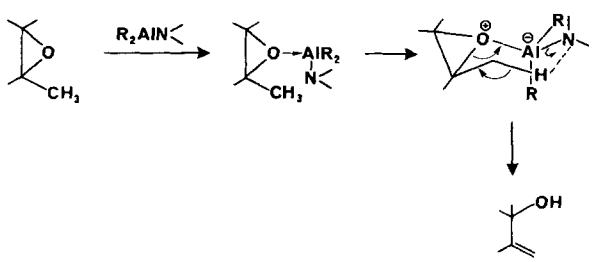
New Synthetic Methods (54)

By Keiji Maruoka and Hisashi Yamamoto*

In addition to their high oxyphilicity, organoaluminum compounds are endowed with ambiphilic character. These properties can be successfully utilized in developing new synthetic reactions with unique selectivities. Especially noteworthy are the organoaluminum-promoted Beckmann rearrangement of oxime sulfonates, new syntheses of polyamino macrocycles via reductive cleavage of aminals and amidines by diisobutylaluminum hydride, the diastereoselective cleavage of chiral acetals by organoaluminum compounds leading to optically active secondary alcohols, allylic alcohols, and β-substituted carbonyl compounds, and biomimetic terpene syntheses. These and other examples, which illustrate the characteristics of organoaluminum chemistry, are used to demonstrate the distinct advantages of organoaluminum reagents in selective organic synthesis.

1. Introduction

During the past seven years since the publication of our first review[1] on organoaluminum compounds, these have found increasing application as reagents for selective organic synthesis.[2] Their chemistry has so far been simply understood in terms of the high Lewis acidity of their monomeric forms, which is directly related to the pronounced tendency of the aluminum atom to build up an octet of electrons. Organoaluminum compounds can interact strongly with various heteroatoms in organic molecules, particularly oxygen, to generate 1:1 coordination complexes. However, in sharp contrast to typical Lewis acids such as $BF_3 \cdot OEt_2$, $AlCl_3$, $SnCl_4$, and $TiCl_4$, they are endowed with a latent nucleophilic character, which can emerge prominently on coordination of an oxygen-containing functional group. The aluminum atom serves primarily as the coordination site for the substrate. The nucleophilic center attached to aluminum can be activated by the formation of the coordination complex, facilitating the nucleophilic attack on the substrate, as illustrated in the isomerization of oxiranes to allylic alcohols by organoaluminum amides.[1]

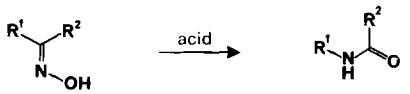


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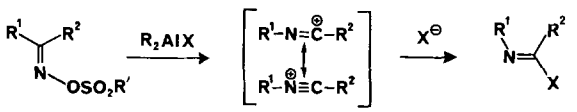
Organoaluminum compounds thus possess both electrophilic and nucleophilic character, and can therefore be viewed as "ambiphilic" reagents rather than as ordinary Lewis acids.[3] These properties are of great value in the design of selective reactions. Our recent studies on the development of new synthetic reactions using organoaluminum reagents are described in this review.

2. Organoaluminum-Promoted Beckmann Rearrangement

The Beckmann rearrangement is the skeletal rearrangement of ketoximes in the presence of certain acids to give amides or lactams.[4] Its mechanism consists essentially of the formation of an electron-deficient nitrogen atom by polarization of the oxygen-nitrogen bond of the oxime with simultaneous intramolecular migration of the group *anti* to the departing hydroxyl group, producing the iminocarbocation, which then reacts with water to give the corresponding amide.



Reexamination of this reaction led us to expect that organoaluminum compounds might be employable as ambiphilic reagents to induce the Beckmann rearrangement of oxime derivatives as well as to capture the intermediary iminocarbocation or alkylidyneammonium ion[5] by the nucleophilic part of the molecule. This proved to be the case.



The realization of this concept opens new synthetic applications of the classical Beckmann rearrangement.[6] Furthermore, it has made possible the highly stereoselective synthesis of naturally occurring alkaloids.

As oxime derivatives, oxime sulfonates are preferred for the following reasons: 1) ready availability from oximes using *p*-toluenesulfonyl chloride (TsCl) or methanesulfonyl chloride (MsCl) in the presence of base in almost quantitative yields; 2) ease of handling because of their fine crystalline properties; 3) high enough reactivity toward organoaluminum reagents to initiate the rearrangement.

2.1. Synthesis of Esters of Thio- and Selenoimidic Acids

The concept discussed in the previous section was first tested using organoaluminum reagents of the type R_2AlX (X = SR', SeR') with the object of developing a new and general approach to thio- and selenoimidic esters,[6] which are an important class of compounds as activated forms of amides in alkaloid synthesis.[7]

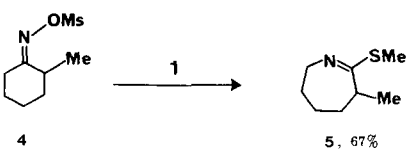
A series of dialkylaluminum thiolates was prepared in situ from diisobutylaluminum hydride (DIBAH) and dimethyl disulfide, or from trimethylaluminum and thiols.[8]

$$2i\mathrm{Bu_2AlH} + \mathrm{MeSSMe} \longrightarrow \underset{\mathbf{1}}{2i\mathrm{Bu_2AlSMe}} + \mathrm{H_2}$$

$$\mathrm{Me_3Al} + \mathrm{RSH} \longrightarrow \mathrm{Me_2AlSR} + \mathrm{CH_4}$$

Reaction of the 2-methylcyclohexanone oxime methanesulfonate **2** with diisobutylaluminum methanethiolate **1** in dichloromethane proceeded smoothly within 1 h at 0 °C to furnish the thioimidic ester **3** in good yield. None of the substitution product at the nitrogen was detected.





By contrast, the isomeric oxime **4**[9] gave exclusively the thioimidic ester **5** under the same conditions. Thus, the regioselectivity of the reaction follows the general rule for the Beckmann rearrangement, which predicts that the group *anti* to the oxime sulfonate migrates preferentially.

Most oxime sulfonates react readily with 1–2 equivalents of organoaluminum thiolates at or below 0 °C to furnish the corresponding thioimidic esters (Table 1); an exception is cyclopentanone oxime *p*-toluenesulfonate **6**,

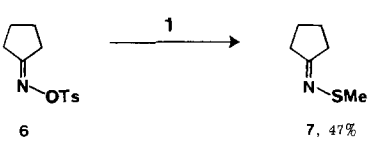
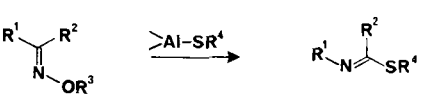


Table 1. Synthesis of thioimidic esters from oxime sulfonates with dialkylaluminum thiolates in CH_2Cl_2.

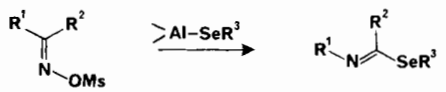


R^1	R^2	R^3	R^4	Yield [%]
$-(CH_2)_5-$		Ms	Me	58
			Et	62
$-CHCH_3(CH_2)_4-$		Ts	Me	66
$-(CH_2)_{11}-$		Ts	Me	97
			allyl	80
			Ph	82
Ph	Me	Ms	Me	90
			*t*Bu	85
			Ph	88

which under the usual conditions gives the unrearranged substitution product **7** as the sole isolable product.

In a similar fashion, selenoimidic esters can be prepared by reaction of oxime sulfonates with dialkylaluminum selenolates ($Me_2AlSeMe$ and $iBu_2AlSePh$)[10] in synthetically useful yields (Table 2).

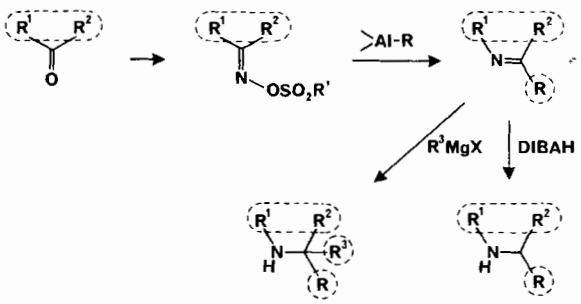
Table 2. Synthesis of selenoimidic esters.



R^1	R^2	R^3	Yield [%]
$-(CH_2)_{11}-$		Me	71
		Ph	57
Ph	Me	Me	49
		Ph	61

2.2. Synthesis of α-Alkylated Amines

Trialkylaluminum compounds were studied in order to find the ultimate methodology for regio- and stereoselective α-alkylation of amines in alkaloid synthesis. Reaction of oxime sulfonates with several equivalents of an alkylaluminum reagent in dichloromethane resulted in the formation of imines, which were directly reduced with excess DIBAH to furnish the corresponding amines.[11] Furthermore, the intermediary imines were directly treated with Grignard reagents producing the α,α-dialkylated amines.[12] The carbon framework of a substrate can thus be elaborated in a flexible manner with regiospecific incorporation of a nitrogen functional group.



This reaction sequence has a wide scope of application as illustrated in Tables 3 and 4. Linear and cyclic oxime sulfonates are equally employable. Diethylaluminum alkynide can be utilized for introduction of the alkynyl moiety into a substrate, leaving the ethyl group intact. Thus, a new entry to propargylic amino derivatives is available in a simple operation. Halogenated hydrocarbons (e.g., dichloromethane, chloroform, or 1,2-dichloroethane) are suitable solvent systems. In tetrahydrofuran (THF), which strongly coordinates to aluminum, little or no α-alkylated amines are formed. Rigorous regioselectivity is also observed here, as in the synthesis of thio- or selenoimidic esters.

Since the discovery of the Beckmann rearrangement/alkylation sequence, we had hoped to apply the reaction to the synthesis of physiologically active alkaloids such as

Table 3. Synthesis of α-alkylamines from oxime methanesulfonates, $R^1R^2C{=}NOMs$, with a trialkylaluminum and DIBAH.

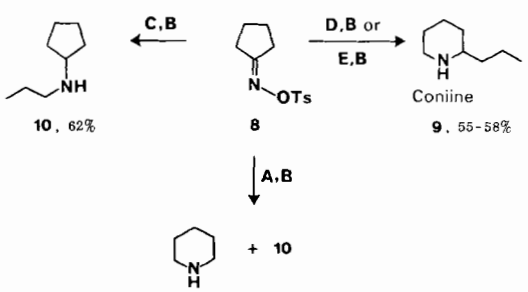
R^1	R^2	Aluminum reagent	Yield [%]
$-(CH_2)_5-$		Me_3Al	70
		nPr_3Al	64
		iBu_3Al	52
		$Et_2AlC{\equiv}CBu$	67
$-CHCH_3(CH_2)_4-$		nPr_3Al	48
Ph	Me	$Et_2AlC{\equiv}CMe$	60
		$Et_2AlC{\equiv}CBu$	83
		$Et_2AlC{\equiv}CPh$	67

Table 4. Synthesis of α,α-dialkylamines from oxime methanesulfonates, $R^1R^2C{=}NOMs$, with a trialkylaluminum and a Grignard reagent, R^3MgBr.

R^1	R^2	Aluminum reagent	R^3	Yield [%]
$-(CH_2)_5-$		Me_3Al	allyl	60
Ph	Me	Me_3Al	propargyl	43
		$Et_2AlC{\equiv}CBu$	allyl	74
$-(CH_2)_{11}-$		Me_3Al	propargyl	61

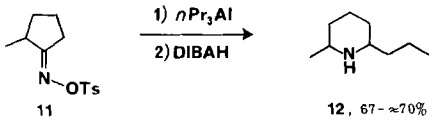
pumiliotoxin C and solenopsin A. Initially, we studied the piperidine ring formation by Beckmann rearrangement in aprotic media and attempted to prepare the simple piperidine alkaloid coniine **9**[12] by reaction of cyclopentanone oxime *p*-toluenesulfonate **8** with nPr_3Al (Scheme 1). This approach, however, was unsuccessful. Thus, treatment of **8** with nPr_3Al at −78 to 0°C followed by reduction with DIBAH gave a mixture of the unrearranged amine **10** (23%) and piperidine in addition to 4% of the desired **9**. Moreover, using hexane as solvent, the amine **10** was produced exclusively. Surprisingly, increasing the initial temperature from −78° to 40–80°C favors the normal rearrangement product **9** at the expense of **10**. The pronounced effect of temperature on the course of the reaction may be attributed to the rapid dissociation of dimeric nPr_3Al at high temperature, which would enhance its Lewis acidity toward **8** (thereby promoting the rearrangement) as well as the nucleophilicity of the *n*-propyl group toward the intermediary iminocarbocation.

In contrast to **8**, 2-alkylcyclopentanone oxime sulfonates cleanly rearrange at initially high temperatures (25–40°C) even in hexane, as exemplified by the synthesis of



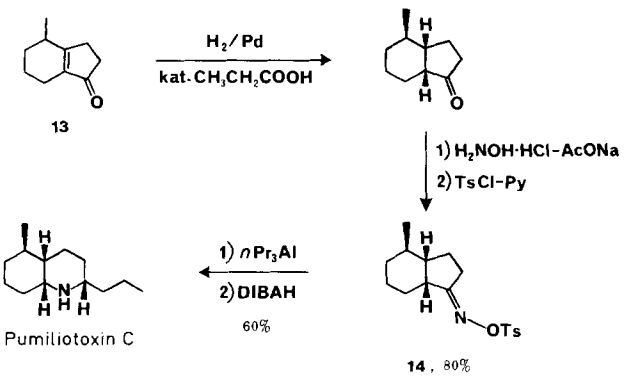
Scheme 1. A: nPr_3Al (2 equiv.) in CH_2Cl_2 (−78°C, 5 min; 0°C, 1 h); B: DIBAH (1.5 equiv.) (0°C, 1 h); C: nPr_3Al (2 equiv.) in hexane (0°C, 1 h); D: nPr_3Al (3 equiv.) in CH_2Cl_2 (40°C, 30 min); E: nPr_3Al (2 equiv.) in $ClCH_2CH_2Cl$ (80°C, 15 min).

dihydropinidine **12** from 2-methylcyclopentanone oxime *p*-toluenesulfonate **11**. The rearrangement of five-membered carbocyclic systems is thus highly dependent on both the nature of the organoaluminum reagents in solution and the substrates.

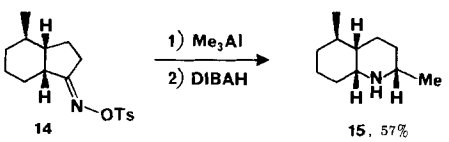


11 **12**, 67–≈70%

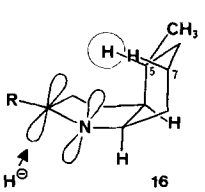
With the modified procedure for the synthesis of α-alkylpiperidine systems in hand, we have successfully developed a simple and highly stereoselective route from the ketone **13**, via the oxime sulfonate **14** as intermediate, to pumiliotoxin C,[12] a physiologically active alkaloid isolated from the skin of the neotropical frogs *Dendrobates pumilio* and *Dendrobates auratus*.



Furthermore, the preparation of other pumiliotoxin analogues was possible. Reaction of **14** with Me_3Al followed by DIBAH afforded the 2-methyl-*cis*-decahydroquinoline **15** in a stereoselective fashion.

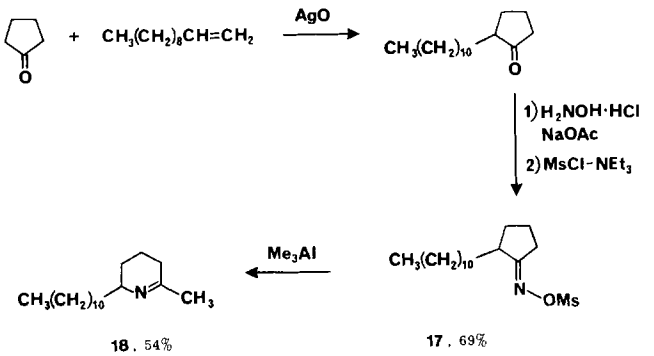


The remarkably high stereoselectivity in the DIBAH reduction of the imine **16**, the precursor of **15**, can be ascribed to steric effects (Scheme 2). In the stable conformation of **16**, the carbocyclic ring, especially its C5 and C7 axial hydrogens, shields one side of the imino group so that *exo* attack by the hydride is preferred.

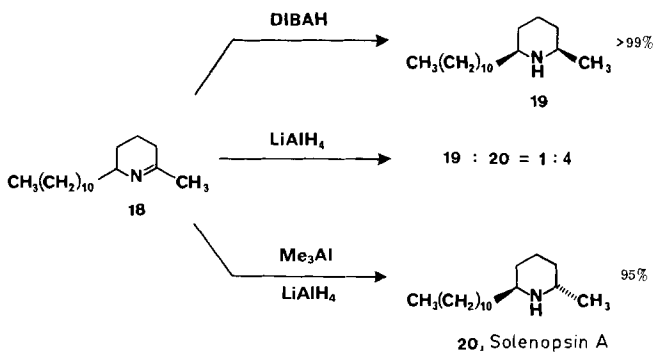


Scheme 2. Preferential *exo* attack $H^{\ominus}$ on **16**.

In addition to the *cis*-2,6-disubstituted piperidine structure in pumiliotoxin C, there are a number of physiologically active alkaloids, such as solenopsin A, that possess a characteristic *trans*-2,6-disubstituted piperidine unit. Nevertheless, none of the existing methodologies is generally applicable for synthesizing the *trans*-2-alkyl-6-methylpiperidine structure in solenopsin A, simply because specific introduction of an alkyl group to form the *trans* structure is not easy to achieve. For example, reduction of imine **18** (prepared by a multi-step synthesis from cyclopentanone and 1-undecene via the oxime methanesulfonate **17** with

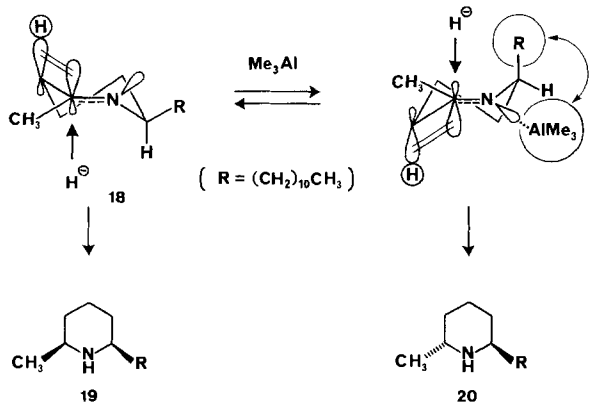


DIBAH gave the *cis* isomer **19** exclusively. Reaction with $LiAlH_4$ in ether produced a mixture of **19** and **20** in a ratio of 1:4. In contrast, coordination of the imino nitrogen atom in **18** to the Lewis acid Me_3Al followed by reduction of the resulting 1:1 complex with $LiAlH_4$ in THF afforded solenopsin A **20** in 90–95% yield with excellent stereoselectivity.[13]



The high degree of stereoselectivity observed for the reduction of the imine using the Me_3Al-$LiAlH_4$ system can be rationalized by the theory of *Houk* et al.[14] as well as by the theory of charge-transfer stabilization of the transition state for nucleophilic addition to a carbonyl group.[15] Both theories predict the strong preference for antiperiplanar attack of the hydride ion with respect to the σ_{C-H} bond vicinal to the imino functional group (Scheme 3).

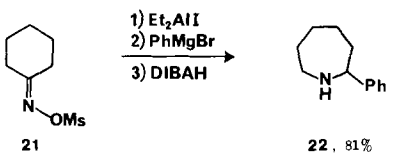
Thus, in the hydride reduction of **18**, the underside approach of the incoming hydride ion toward the π bond is preferred by the stabilization of the σ* orbital (low-lying unoccupied orbital of the imine) through electron delocalization from the σ_{C-H} bond (stereoelectronic control), producing the *cis* isomer **19**. On the other hand, in the presence of Me_3Al as Lewis acid, the alkyl group R of **18** would occupy the axial position because of the stereic repulsion between R and Me_3Al coordinated to the nitrogen



Scheme 3. Stereoselective reduction of **18** with DIBAH or $Me_3Al/LiAlH_4$.

lone-pair electrons ($A^{(1,2)}$ strain).[16] Such a conformational change should facilitate the stereoelectronically favored topside approach of the hydride ion toward the π bond to furnish the desired *trans* isomer **20**.

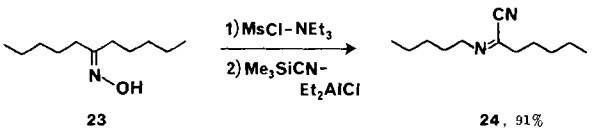
The Beckmann rearrangement/alkylation sequence cannot be utilized for introduction of less reactive nucleophiles containing sp^2-hybridized carbon such as aryl or vinyl groups. A route to α-arylated amines via imidoyl iodides was found to be promising,[17] since these are highly susceptible toward nucleophilic attack.[18] Thus, reaction of cyclohexanone oxime methanesulfonate **21** in dichloromethane with diethylaluminum iodide (2 equivalents) furnished the imidoyl iodide, which was directly arylated by the use of phenylmagnesium bromide (3 equivalents) and then reduced with DIBAH (4 equivalents), producing the α-phenylated amine **22** in high yield. Other oxime derivatives such as cyclohexanone oxime carbonate and acetate gave less satisfactory yields (0–17%).



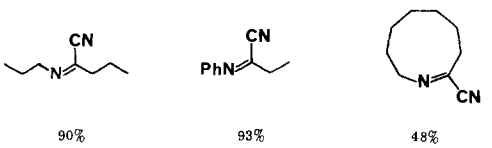
2.3. Synthesis of Schiff Bases Containing an α-CN Group

As a result of extensive investigations into the introduction of other nucleophiles by organoaluminum-promoted Beckmann rearrangement, the combination of diethylaluminum chloride with trimethylsilyl cyanide (*Utimoto*'s method as a substitute for diethylaluminum cyanide)[19] was found to provide a new method of preparing Schiff bases containing α-CN groups from oxime sulfonates.[6] These compounds are viewed as a masked form of α-amino acids, and the presence of the sp^2-prochiral center (the C=N bond) could be used to prepare optically active α-amino acids.[20] Thus, 6-undecanone oxime **23** was converted in the usual manner into its methanesulfonate, which was treated successively with Et_2AlCl and Me_3SiCN at −78 °C to afford the Schiff base **24** in high yield.

Similarly, several other oxime sulfonates were transformed into the corresponding Schiff bases (Scheme 4).



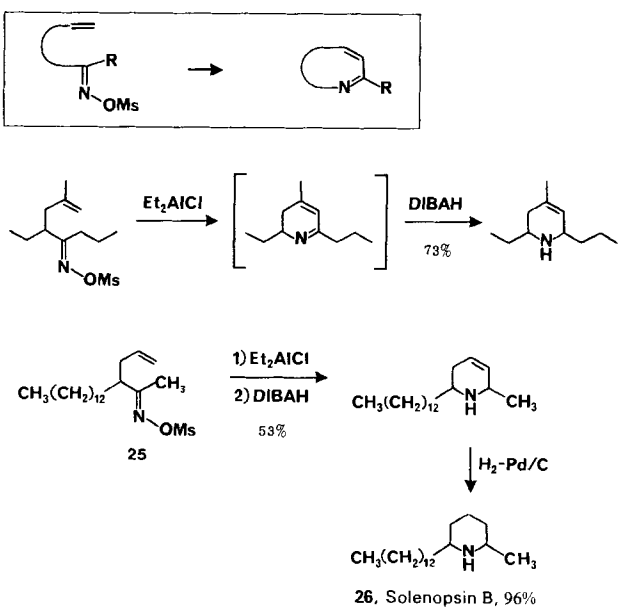
Other Lewis acids, such as $SnCl_4$, $BF_3 \cdot OEt_2$, or trimethylsilyl trifluoromethanesulfonate (Me_3SiOTf), failed to give the desired Schiff bases in the presence of Me_3SiCN.



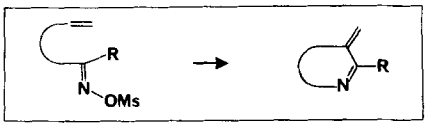
Scheme 4. Schiff bases with α-CN groups, obtained analogously to the reaction **23** → **24**.

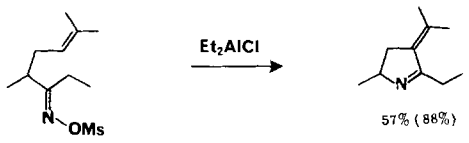
2.4. Olefinic Cyclization Promoted by Beckmann Rearrangement of Oxime Sulfonates

The efficient activation of oxime sulfonates by organoaluminum reagents[21] offers the opportunity to explore the intramolecular cyclization of olefinic oxime methanesulfonates, which involves the electrophilic addition of the intermediary iminocarbocation to the double bond.[22] This would result in the direct formation of a wide variety of structurally diverse carbocyclic as well as heterocyclic systems. A priori, four distinct cyclization modes are possible in these systems. Since the Beckmann rearrangement proceeds by endocyclic or exocyclic migration of the group "*anti*" to the departing sulfonate group, we refer to these as *endo*(B) and *exo*(B) rearrangements, respectively. Furthermore, we denote the endocyclic and exocyclic relationship of the bond being broken to the ring being formed by the suffixes *endo* and *exo*, respectively. Thus, the four possible cyclization modes are *endo*(B)-*endo*, *endo*(B)-*exo*, *exo*(B)-*endo*, and *exo*(B)-*exo*, as depicted in Schemes 5–8, each of which also illustrates representative examples. The values in parentheses refer to the yields obtained using $SnCl_4$.

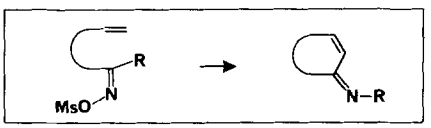


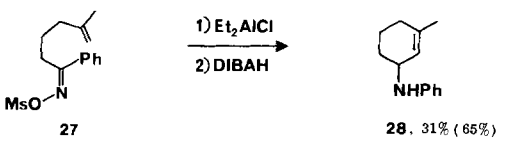
Scheme 5. *endo*(B)-*endo* cyclization.



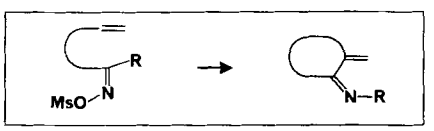


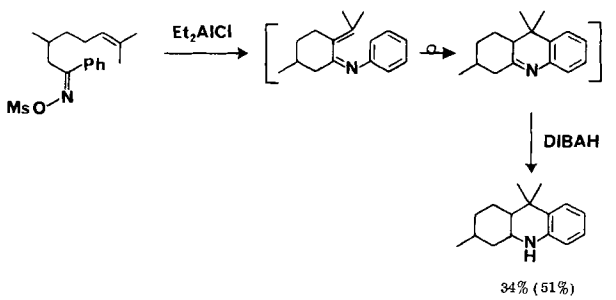
Scheme 6. *endo*(B)-*exo* cyclization.





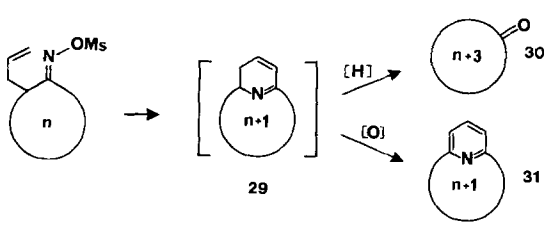
Scheme 7. *exo*(B)-*endo* cyclization.





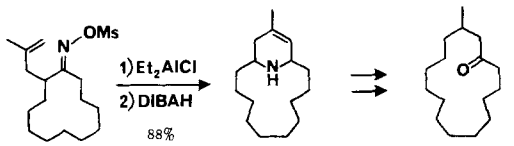
Scheme 8. *exo*(B)-*exo* cyclization.

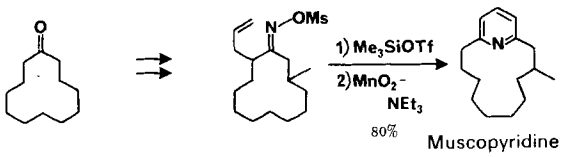
Solenopsin B **26** can be prepared via the *endo*(B)-*endo* cyclization in two steps from the simple acyclic precursor **25** (Scheme 5). Moreover, analogous *endo*(B) cyclizations were found to be key steps in synthetically important ring transformations.[23] Thus, the enimine **29** that is formed



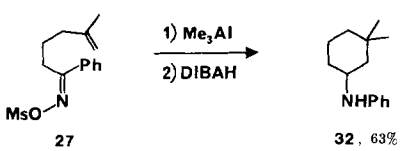
might be reductively cleaved to the ring-expansion product **30**, or oxidized to the heterocycles **31**, as illustrated in the facile syntheses of muscone and muscopyridine, respectively.

It is noteworthy that Me_3SiOTf was the reagent of choice for a new pyridinophane synthesis,[24] and that Et_2AlCl was less satisfactory in the following oxidation step.



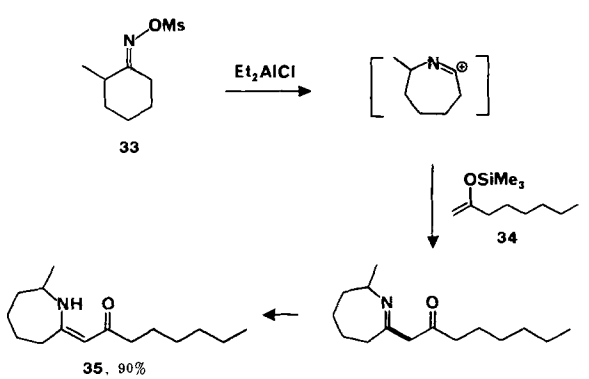


The cyclizations in the reactions described above were terminated by deprotonation, yielding α,β-unsaturated imines. The intermediary cations, however, may also be captured by carbon nucleophiles to afford saturated imines.[25] For example, treatment of the oxime methanesulfonate **27** with Me_3Al followed by reduction with DIBAH produced the methylated product **32** (63%) along with the product of deprotonation **28** (8%).



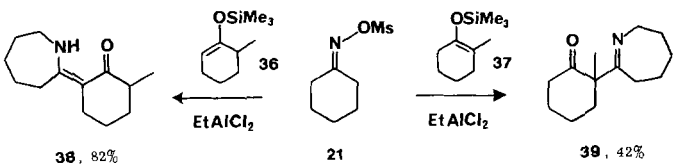
2.5. Synthesis of Enamino Ketones

In the reaction of oxime methanesulfonates with olefinic groups, silyl enol ethers **34** are extremely useful for efficient trapping of the intermediary iminocarbocation as well as for the termination of the reaction. This finding has led to a facile entry to a variety of enamino ketones (N–C=C–C=O),[26] which are useful as building blocks for the preparation of fused carbocycles and polyheterocycles.[27] Thus, in the presence of Et_2AlCl at −78 to 25 °C, the oxime methanesulfonate **33** reacted with 2-(trimethylsiloxy)-1-octene **34** in methylene chloride to give the enamino ketone **35** in high yield. Of all the Lewis acids examined, Et_2AlCl and $EtAlCl_2$ (2–3 equivalents) were the most effective; for other Lewis acids ($AlCl_3$, $SnCl_4$, $FeCl_3$,

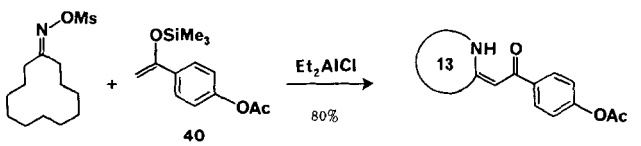


$TiCl_4$, Me_3SiOTf, Me_3SiI, etc.), the yields were between 0 and 35%.

Notably, this condensation takes place with retention of regiochemical integrity in both substrates. Reaction of 6-methyl-1-(trimethylsiloxy)-1-cyclohexene **36** and 1-methyl-2-(trimethylsiloxy)-1-cyclohexene **37** with **21** furnished **38** and **39**, respectively, as the sole isolable products.



Another striking feature of the reaction is the high chemospecificity. The condensation of the silyl enol ether **40** derived from *p*-acetoxyacetophenone occurred in a chemospecific fashion with oxime methanesulfonates, the acetoxy moiety remaining intact.



Oxime sulfonates of aromatic ketones and cyclopentanones are not employable, since complex reaction mixtures are formed.

2.6. Reductive Arylation of Enol Esters

In analogy to the electrophilic addition of the cationic center generated by Beckmann rearrangement of oxime sulfonates to olefins, reductive arylation of enol esters, a new Friedel-Crafts-type reaction, is also possible.[28] Reaction of enol phosphate **41** in an aromatic solvent with excess $EtAlCl_2$ (10 equivalents) at room temperature gave the product of reductive arylation **42** in high yield (Table 5).

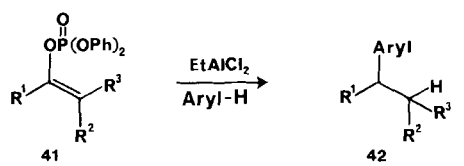
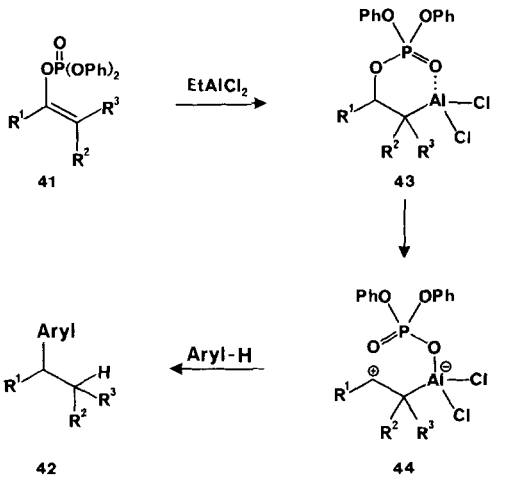


Table 5. Selected reductive arylation reactions of enol phosphates **41** in aromatic solvents in the presence of excess $EtAlCl_2$ at room temperature.

R^1	R^2	R^3	Solvent	Yield [%]
$-CH_2CH_2CHtBuCH_2-$		H	benzene	82
			toluene	97
$-CHCH_3(CH_2)_3-$		H	toluene	86
Ph	H	H	benzene	54
			toluene	90

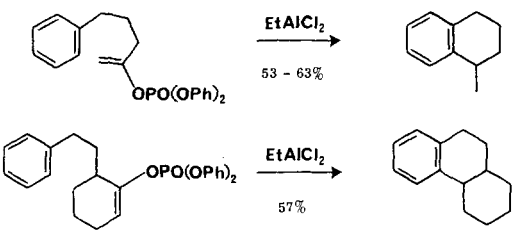
This method is advantageous over typical electrophilic aromatic substitutions in that no polyalkylation is observed. The reaction is also highly regioselective: arylation takes place exclusively at the O-substituted carbon atom.

A possible mechanism is outlined in Scheme 9. The initial step of the reaction is probably hydroalumination of the double bond to form the adduct **43**, which in turn rearranges to the intermediate **44**. Electrophilic addition of the carbocation in **44** to the aryl group then takes place to give the product **42**.



Scheme 9. Mechanism of the reductive arylation of enol esters.

Intramolecular reductive arylation has also been achieved using enol phosphates of aliphatic ketones possessing a phenyl group in the γ or δ position.



2.7. Reduction of Oximes

Oxime sulfonates have been utilized so far as activated oximes. However, the pronounced reactivity of DIBAH enables the smooth cleavage of the N–O bond in the parent oxime, thereby providing a simple, yet highly convenient procedure for obtaining rearranged secondary amines from oximes (Table 6).[29]

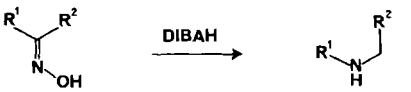
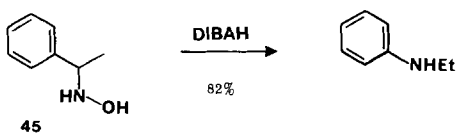


Table 6. Reduction of the oxime $R^1R^2C{=}NOH$ with DIBAH in CH_2Cl_2 at 0°C to room temperature.

R^1	R^2	Yield [%]
Ph	Me	92
$CH_3(CH_2)_4-$	$CH_3(CH_2)_4-$	85
$-(CH_2)_{11}-$		70
$PhCH_2$	$PhCH_2$	71

Dichloromethane is the solvent of choice for the exclusive formation of the secondary amines: use of ethers affords a mixture of primary and isomeric secondary amines.[30]

Two mechanisms can be tentatively proposed for this reductive rearrangement: 1) initial reduction of the C=N bond and subsequent rearrangement of the resulting hydroxylamine; 2) Beckmann rearrangement promoted by cleavage of the N–O bond, followed by reduction of the imine. In order to determine the reaction mechanism, we prepared hydroxylamine **45** and reduced it with DIBAH, producing *N*-ethylaniline exclusively. Exposure of the corresponding oxime to trialkylaluminum produced none of the rearranged products. These results support the first mechanism.[31]

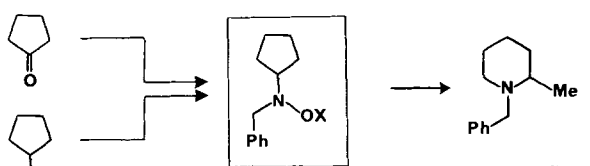


45

2.8. Rearrangement of Hydroxylamine Derivatives

Since the hydroxylamine **45** rearranges to *N*-ethylaniline in the presence of DIBAH, it seemed logical to expect that other hydroxylamines might also undergo rearrangement under these conditions.[32]

The required hydroxylamines were conveniently prepared from a series of carbocyclic ketones, amines, or their precursors. The ethyl carbonate **47** of benzylcyclopentyl-

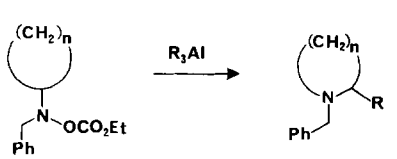


46, X = H
47, X = COOEt

48, 79%

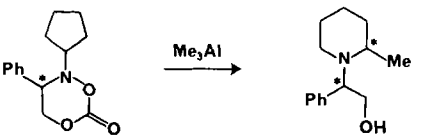
hydroxylamine **46** reacts with Me_3Al in dichloromethane to give exclusively the α-methylated piperidine **48** in high yield. The reaction is applicable to a variety of carbocyclic hydroxylamines (Table 7).

Table 7. Rearrangement of hydroxylamine carbonates using trialkylaluminum in CH_2Cl_2.



n	R	Yield [%]
3	Me	71
	C≡CSiMe$_3$	98
4	Me	74
	C≡CBu	89
	C≡CSiMe$_3$	71
7	Me	62

In contrast to the Beckmann rearrangement of oxime sulfonates, this method opens up the possibility of introducing a new carbon-carbon bond in a diastereoselective manner at the α position of amines, thus allowing the asymmetric synthesis of α-alkylated amines. A simple illustration of the potential of the reaction for asymmetric synthesis is shown by the rearrangement and subsequent alkylation of the cyclic carbonate **49**, in which the conformational mobility is reduced and the free energy difference between diastereomeric transition states in the reaction is increased. Thus, reaction of **49** with excess Me_3Al (6 equivalents) in dichloromethane at 0°C for 10 h afforded the desired amine **50** in 22% diastereomeric excess.

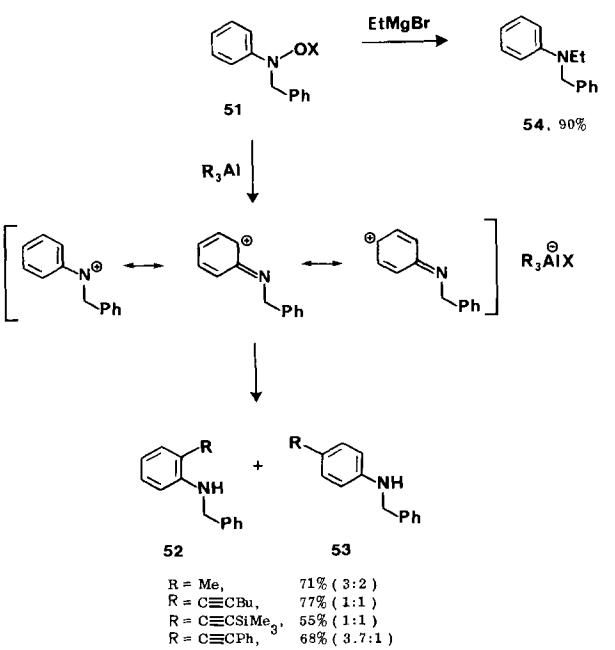


49

50, 61%

2.9. Nucleophilic Aromatic Substitution

Arylhydroxylamines behave in a completely different manner from alkylhydroxylamines on reaction with organoaluminum compounds.[33] For instance, reaction of the phenylhydroxylamine derivative **51** (X = Ac, $SiMe_3$) with trialkylaluminum in dichloromethane gave a mixture of *ortho*- and *para*-substituted methylanilines **52** and **53**, respectively, in high yield. The more nucleophilic Grignard reagent EtMgBr afforded mainly the *N*-alkylation product **54**.



51

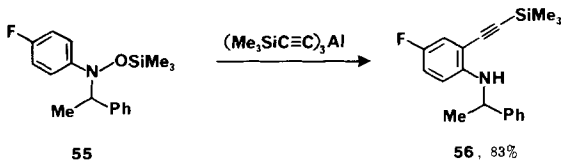
54, 90%

52 **53**

R = Me, 71% (3:2)
R = C≡CBu, 77% (1:1)
R = C≡CSiMe$_3$, 55% (1:1)
R = C≡CPh, 68% (3.7:1)

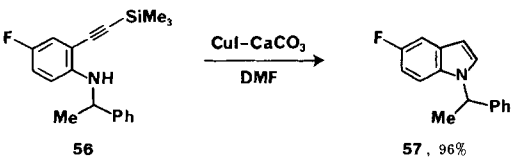
Accordingly, the highly oxyphilic organoaluminum reagent is capable of cleaving the N–O bond heterolytically to yield a phenylaminyl cation,[34] which is readily susceptible toward nucleophilic attack of trialkylaluminum at either the *ortho* or *para* position of the phenyl group. Dou-

ble alkylation products were not detected. This represents a distinct advantage over the classical Friedel-Crafts reaction. The *para*-substituted arylhydroxylamine **55** yielded solely the desired *ortho* alkylation product **56** in high yield.



55 **56**, 83%

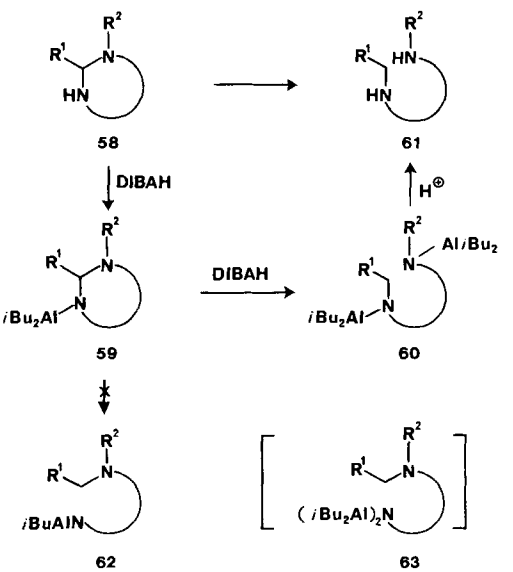
The availability of aromatic amines bearing an *ortho* alkynyl moiety allowed the development of a convenient synthesis of indoles. Reaction of **56** with copper(I) iodide (0.5 equivalents) and calcium carbonate (1 equivalent) in dimethylformamide (DMF) at 120 °C for 2 h[35] led to a smooth cyclization with concurrent elimination of the trimethylsilyl group to furnish indole derivative **57** in excellent yield.



56 **57**, 96%

3. Reductive Amination by DIBAH

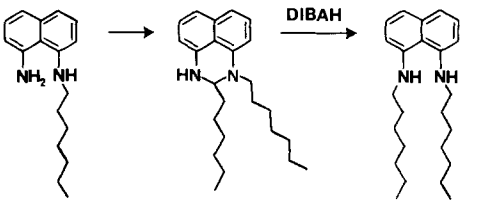
The high reduction potential of DIBAH (see Section 2.7) has also played an important role in the reductive cleavage of cyclic aminals, which provides a new and mild approach to selective *N*-alkylation of polyamines.[36] The general type of transformation is summarized in Scheme 10.[37]



58 **61** **59** **60** **62** **63**

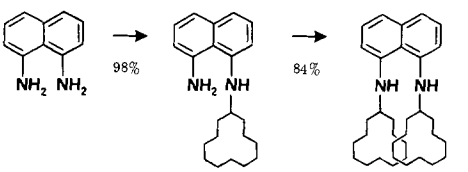
Scheme 10. Mechanism of the reductive cleavage of cyclic aminals.

DIBAH is an effective and selective reducing agent that cleanly converts the diisobutylaluminio compound **59**, prepared from the animal **58** with DIBAH, to the bis(diisobutylaluminio) compound **60**, which, in turn, gives the diamine **61** after hydrolysis. The reaction should proceed regioselectively since the formation of **62** or **63** is energetically much less favorable.

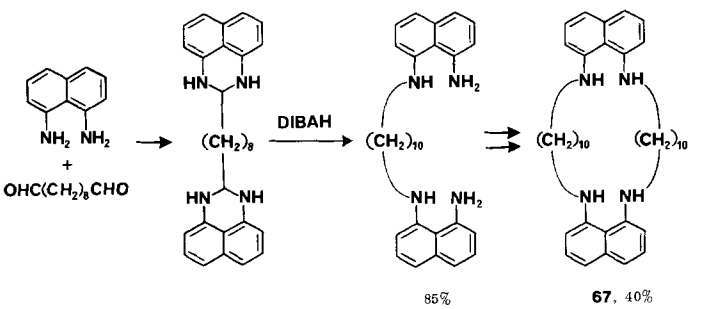


64 **65** **66**, 88%

The conversion of 8-(heptylamino)-1-naphthylamine **64** to 1,8-bis(heptylamino)naphthalene **66** is a typical example of this reaction. Reaction of **64** in benzene with heptaldehyde (1 equivalent) gave the 1-heptyl-2-hexyl-2,3-dihydropyrimidine **65** in quantitative yield.[38] Reduction of **65** with DIBAH (6 equivalents) in refluxing hexane for 1 h afforded the diamine **66** in high yield. Even bulky cyclododecyl moieties can be cleanly introduced with rigorous regioselectivity.

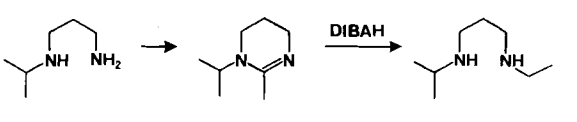


An application of this novel reductive cleavage process is the selective synthesis of the macrocyclic polyamine **67**.



85% **67**, 40%

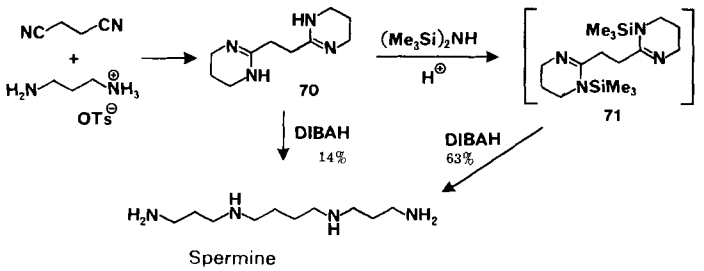
Since DIBAH is an effective reducing agent for conversion of imines to amino derivatives, the new process can be readily extended to the reductive cleavage of the amidine system.[37] Reaction of 1-isopropyl-2-methyltetrahydropyrimidine **68** with DIBAH in hexane at 25 °C for 24 h and under reflux for 30 min gave *N*-ethyl-*N'*-isopropyl-1,3-diaminopropane **69** in almost quantitative yield.



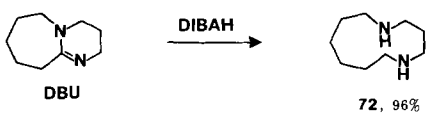
68 **69**, 97%

This method was employed in a facile synthesis of spermine, which is widely distributed in the animal kingdom

and in microorganisms and forms the basic skeleton of spermine plant alkaloids.[39] The direct transformation of 1,2-bis(tetrahydro-2-pyrimidinyl)ethane **70**[40] into spermine did not proceed smoothly under vigorous reaction conditions (neat DIBAH, 150 °C, 11 h). However, protection of the amino function with the trimethylsilyl group,[41] which can be easily introduced and removed, enabled **70** to be converted in situ into the disilylated species **71**. After evaporation of excess hexamethyldisilazane, **71** was directly subjected to reductive cleavage by DIBAH (20 equivalents) in refluxing xylene for 3 d to furnish spermine in good yield.



In the case of bicyclic amidine systems, the reaction should result in a ring expansion, thus providing a selective and suitably mild approach to cyclic polyamines.[37] This is exemplified by the transformation of commercially available 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU) to the eleven-membered cyclic diamine **72** by reaction with excess DIBAH (6 equivalents) in refluxing toluene for 7 h.



Other examples presented in Table 8 illustrate the generality and flexibility of this new approach. Indeed, this reaction was recently utilized to synthesize medium-ring

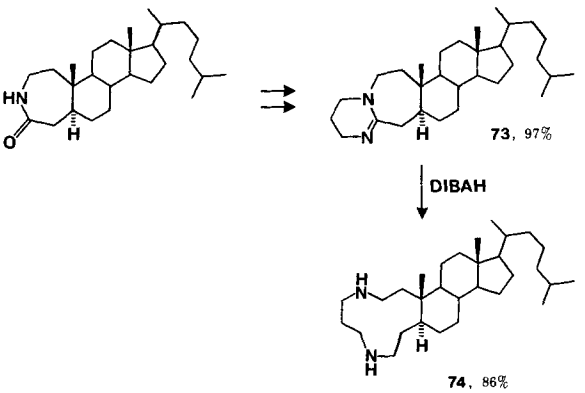
Table 8. Synthesis of cyclic polyamines from bicyclic amidines with DIBAH.



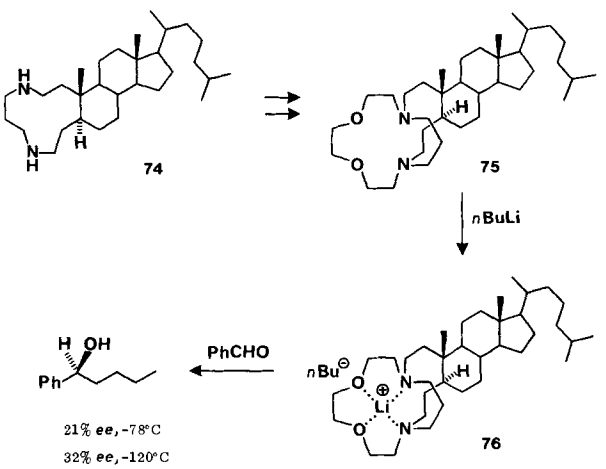
m	n	Yield [%]
4	2	79
7	2	90
7	3	74
11	2	92
11	3	83

bicyclic bridgehead diamines[42] and to confirm the structure of the product of the chemical or enzymatic oxidation of spermine.[43] In addition, the optically active cyclic diamine **74** is readily accessible from the tetrahydropyrimidine derivative **73** using this procedure.

Although a large number of interesting guest compounds are available,[44] the synthesis of the corresponding host structures (e.g., macrocyclic polyethers and polyamines)[45] is rendered difficult by the limited utility of most



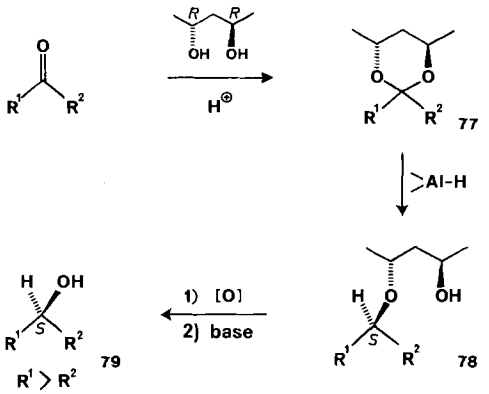
of the existing methods. The introduction of new synthetic methodology for chiral host molecules could be of crucial importance for the development of asymmetric synthesis. Accordingly, we have set out to investigate briefly the synthesis of the chiral ligand **75** and the chemistry of its metal-cation inclusion complexes.[46] Addition of *n*-butyllithium to a solution of **75** in *n*-pentane at low temperature produced the 1 : 1 complex **76**, which, on treatment with benzaldehyde, gave (*S*)-1-phenyl-1-pentanol in moderate optical yield.[47]



4. Cleavage of Chiral Acetals

The selective reducing ability of DIBAH observed in the reductive cleavage of aminals and amidines (Section 3) led us to expect that the optically active acetals might be cleaved regio- and stereoselectively by organoaluminum reagents under appropriate conditions.[48] Were this found to be the case, this might provide a new methodology for asymmetric reduction of prochiral ketones. Indeed, reduction of the chiral acetal **77** derived from (−)-(2*R*,4*R*)-2,4-pentanediol with DIBAH (5 equivalents) gave the hydroxy ether **78** diastereoselectively.[49] Removal of the chiral auxiliary by Swern oxidation[50] followed by β-elimination with methanolic K_2CO_3 afforded the optically active alcohol **79**.

Reagent, temperature, and solvent, the three variables in the reductive cleavage process, were explored in detail. Among the readily available aluminum hydrides tried, only DIBAH, Cl_2AlH,[51] and Br_2AlH gave satisfactory re-

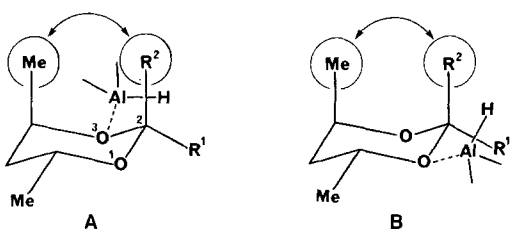


sults. Tetrahydrofuran and other basic solvents were not satisfactory. Lower reaction temperatures resulted in better diastereoselectivities. Table 9 summarizes the results obtained with four different ketones. Since one of the major

Table 9. Selective reduction of chiral acetals 77 with aluminum hydrides.

R^1	R^2	Aluminum reagent	Yield [%]	Diastereomeric ratio
c-hexyl	Me	DIBAH	88	13 : 1
		Et_2AlH	81	8 : 1
		Cl_2AlH	98	19 : 1
		Br_2AlH	99	23 : 1
n-hexyl	Me	DIBAH	58	3.5 : 1
		Cl_2AlH	73	2 : 1
		Br_2AlH	64	8 : 1
Ph	Me	DIBAH	88	28 : 1
		Br_2AlH	94	57 : 1
Ph	*n*Pr	DIBAH	72	20 : 1

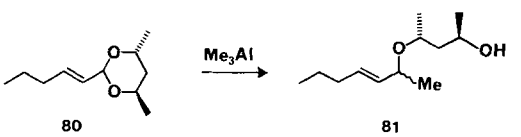
drawbacks of most existing methods for asymmetric reduction of ketones is that they are limited to aromatic or α,β-unsaturated ketones,[52] the present method serves as a practical solution to the asymmetric reduction of saturated ketones. The use of chiral 1,3-dioxanes as acetal substrate is essential for obtaining excellent diastereoselectivity. Reduction of 1,3-dioxolane systems with $LiAlH_4/AlCl_3$ was previously reported to give the corresponding hydroxy ethers with lower diastereoselectivity.[53]



Scheme 11. Complexes **A** and **B** formed from the acetal 77 and an aluminum reagent.

Scheme 11 shows the two complexes **A** and **B** formed between the aluminum reagent and the acetal **77**. Steric effects should influence the reactivity of the acetal oxygen atoms and hence their relative ease of coordination to aluminum. Accordingly, the least sterically conjested structure, the complex **A** should be favored. Due to the steric relief from the severe 2,4-diaxial interaction between methyl and R^2 as well as the anomeric effect in the 1,3-dioxane system,[54] the C2–O3 bond should be longer than a normal C–O ether bond, whereas the C2–O1 bond should have a partial double-bond character because of electron donation from O1. The transient species arising from **A** can undergo smooth cleavage of the C2–O3 bond by attack of aluminum hydride from the direction *syn* to the departing oxygen, leading to the (*S*) configuration at the newly formed ether carbon.

Utilizing a strategy based upon a chiral protecting group that is subjected to activation by ambiphilic aluminum reagents, we next focus our attention on the behavior of organoaluminum reagents toward chiral α,β-unsaturated acetals **80** and **82**. Reaction of the chiral α,β-unsaturated acetal **80** with Me_3Al resulted in formation of the 1,2-adduct **81** without any diastereoselectivity. However, by switching



the chiral auxiliary to optically active tartaric acid diamide,[55] unprecedented regio- and stereochemical control was observed in the addition of organoaluminum reagents to **82**.[56] This finding provides an easy access to optically active β-substituted aldehydes or allylic alcohols. Thus, reaction of **82** ($R^1 = n$Pr) in 1,2-dichloroethane with Me_3Al (5 equivalents) at room temperature for 12 h gave, after acetylation with acetic anhydride-pyridine, the 1,4-adduct **83** ($R^1 = n$Pr, R^2 = Me, X = Ac) preferentially in 84% yield (88% enantiomeric excess *ee*) accompanied by 13% of the

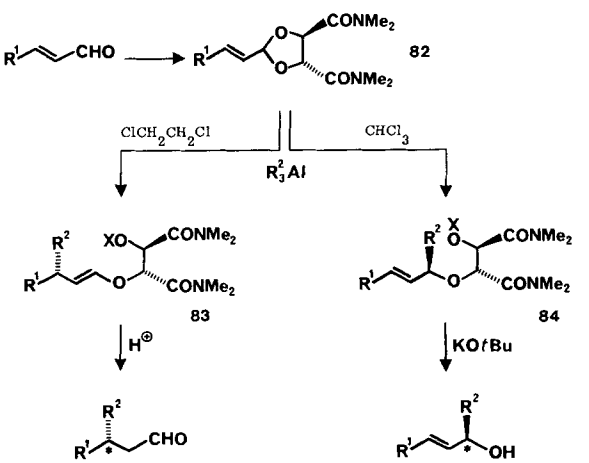


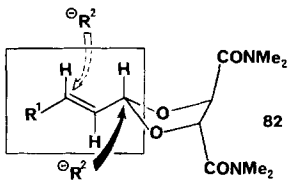
Table 10. Asymmetric 1,4- and 1,2-additions of organoaluminum reagents to α,β-unsaturated acetals **82**.

R^1	R^2	Solvent	*T* [°C]	Yield [%] [a]	*ee* [%]
*n*Pr	Me	$ClCH_2CH_2Cl$	−15	92 (2.8 : 1)	94
		*n*PrCl	RT	96 (6.5 : 1)	91
		CH_2Cl_2	RT	91 (3.3 : 1)	95
		toluene	5	81 (1.7 : 1)	96
Me	*n*Pr	CH_2Cl_2	5	96 (2.1 : 1)	87
		toluene	5	83 (1 : 1)	93
Ph	Me	CH_2Cl_2	5	62 (1 : 0)	94
		toluene	5	91 (5.7 : 1)	98

[a] In parentheses: ratio of 1,4- to 1,2-adduct.

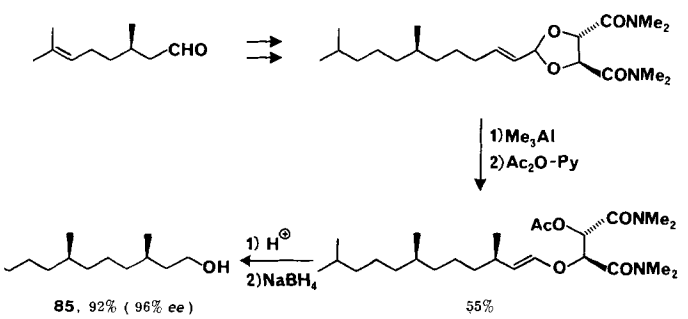
1,2-adduct **84**. In sharp contrast, the use of chloroform as solvent under comparable conditions afforded the 1,2-adduct **84** ($R^1 = n$Pr, R^2 = Me, X = H) exclusively in 85% yield (88% *ee*). The course of the reaction appeared to be strongly influenced by the nature of substrates, solvents, and temperature (Table 10).

Since both (*R,R*)- and (*S,S*)-tartaric acid diamide are readily obtainable in optically pure form,[55] this method allows the synthesis of the two enantiomers of both β-substituted aldehydes and allylic alcohols from α,β-unsaturated aldehydes in a predictable manner (Scheme 12).

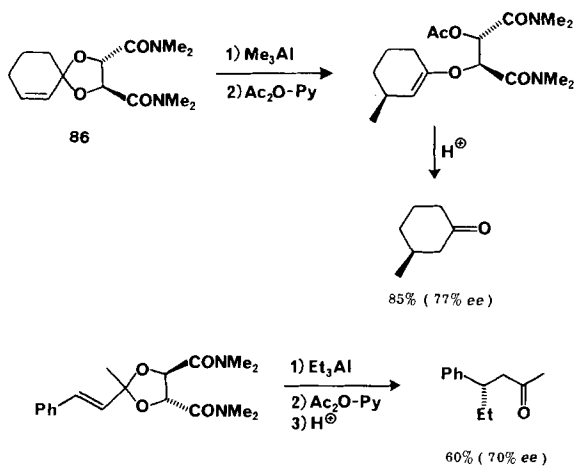


Scheme 12. Addition of the alkyl group R^2 to the chiral α,β-unsaturated acetal **82**.

This reaction has a vast potential in natural product synthesis as illustrated by the short synthesis of the branched alcohol **85**, which is present in the biologically important vitamins E and K.[56]

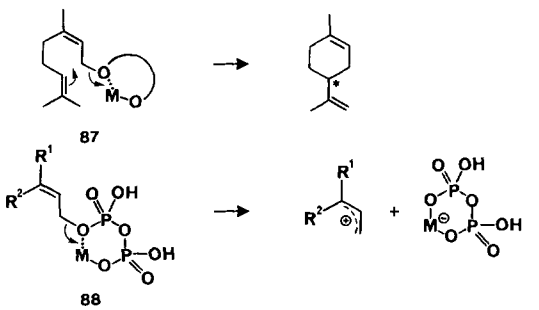


The α,β-unsaturated ketals, on the other hand, exclusively underwent 1,4-addition with moderate diastereoselectivities.[57] Surprisingly, the optical yield tends to decrease upon lowering the reaction temperature (65% *ee* at −15°C in the case of the ketal **86**).

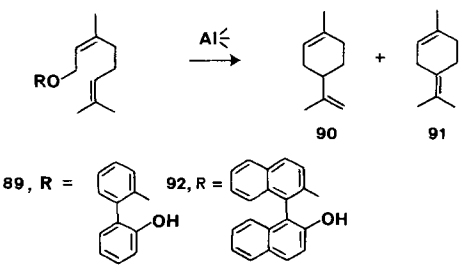


5. Biomimetic Terpene Synthesis

Since organoaluminum compounds have a great tendency to form 1 : 1 complexes, even with neutral bases such as ethers, we have sought to utilize this property ("oxyphilicity") in biomimetic terpene synthesis. Our strategy is based on the anchimerically metal-accelerated cyclization of alkoxide **87** to limonene,[58] for the biochemical transformation of these pyrophosphate derivatives could be profoundly related to the metal-assisted C–O heterolysis of allylic pyrophosphates **88**.

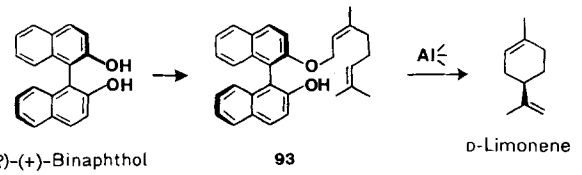


The concept was first examined with ether **89**. It was soon apparent that aluminum compounds can serve as crucial reagents for such allyl-cation-promoted cyclization reactions. When **89** in dichloromethane was treated with DIBAH at −78°C for 30 min and at 20°C for 10 h, limonene **90** and terpinolene **91** were produced in a ratio of 8 : 1 in 81% yield. Similarly, the reaction of **93** with aluminum reagents [DIBAH, 77% (9 : 1); Me_3Al, 72% (7.5 : 1)] produced **90** and **91**.

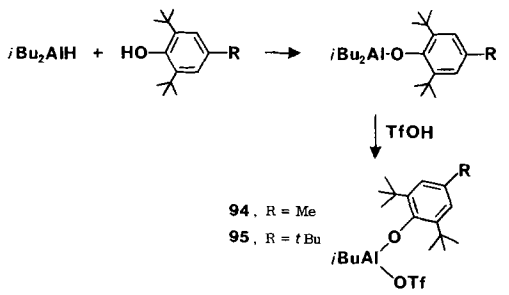


By contrast, the cyclization of neryl phenyl ether proceeds much more slowly than those of **89** and **92** under similar conditions. Thus, the remarkable rate acceleration observed here should be ascribed to the novel metal-anchimeric assistance of the aluminum reagent, which, by binding to the neighboring hydroxyl group, favors the ionization of the allylic substrates.

The enantioselective cyclization of neryl precursors is a reaction that would provide access to a variety of terpenes in enantiomeric form. The reaction of (*R*)-(+)-binaphthol mononeryl ether (**93**) with DIBAH under the conditions described above gave naturally occurring D-limonene and **91** (5 : 1 ratio) in 58% yield with only moderate enantioselectivity (≈ 12% *ee*). Since the optical yield tends to increase by lowering the reaction temperature, we sought to design more "oxyphilic" aluminum reagents than DIBAH in order to conduct the reaction at low temperature. The tri-



fluoromethanesulfonyl group was found to be promising as a ligand that, in organoaluminum reagents, decreases the electron density on aluminum. The bulky, substituted phenoxy group was also incorporated to ensure the formation of a monomeric aluminum species (**94** and **95**) in solution[60] and thus further enhance the oxyphilicity.



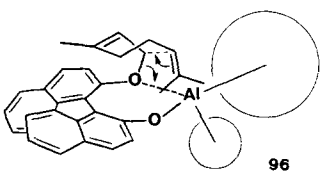
Treatment of **93** with several modified organoaluminum reagents in $CFCl_3$ at low temperature (-130 to -78 °C) produced D-limonene in high optical yield (Table 11).[59]

Table 11. Asymmetric synthesis of D-limonene from **93** with organoaluminum reagents.

Aluminum reagent	Yield [%] [a]	*ee* [%] [b]
iBu_2AlOTf	36 (3 : 1)	39
$iBuAl(OTf)_2$	27 (4 : 1)	40
94	29 (5.2 : 1)	64
95	58 (14 : 1)	77

[a] In parentheses: ratio of limonene to terpinolene. [b] Optical yield of D-limonene.

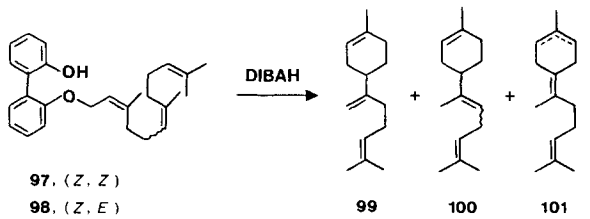
The high asymmetric induction observed here may be rationalized by the intermediacy of **96**, in which the neryl cation cyclizes via a preferential *anti-endo* conformation[61] (Scheme 13).



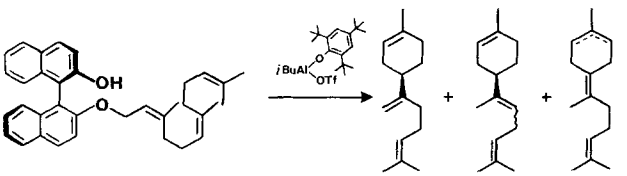
Scheme 13. Postulated intermediate in the asymmetric cyclization of **93** in the presence of an organoaluminum compound.

The present results have been successfully applied to the synthesis of bisabolenes from biphenyldiol (*Z,Z*)-monofarnesyl ether **97** and its *Z,E* isomer **98**. Reaction of the *Z,Z* isomer **97** with DIBAH (-78 °C, 30 min; 20 °C, 4.5 h) furnished β-bisabolene **99** preferentially in 60% yield accompanied by 16% of α-bisabolene **100** and 9% of γ-bisabolene **101**.

On the other hand, the *Z,E* isomer **98**, under similar conditions, was transformed into **99** (34%) and **100** (30%) along with 7% of **101**. Noteworthy is the preferential formation of **99** from the *Z,Z* isomer **97** and not from **98**, since it implies that during deprotonation the aluminum reagent may be responsible for determining the stereochemistry of the farnesyl moiety.

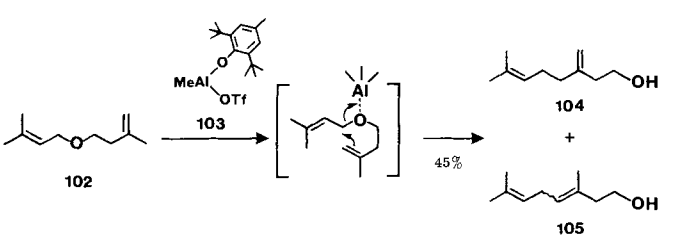


Furthermore, by replacing the biphenyl group with a chiral auxiliary and using other organoaluminum reagents, chiral bisabolenes can be obtained in high optical yields.

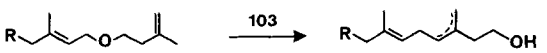


(+)-β-Bisabolene, 92% (76% *ee*)

With oxyphilic aluminum reagents at hand for terpene cyclizations, we have further extended the investigation to an intramolecular version of the prenyl transfer reaction,[62,63] which is accomplished by the rearrangement of isopentenyl prenyl ether **102**.[64] Treatment of **102** with the aluminum reagent **103** in dichloromethane at 25 °C afforded a mixture of the expected C_{10} alcohols **104** and **105** in moderate yield. The choice of catalyst is crucial for the rearrangement. For example, the strong Lewis acids usually used ($TiCl_4$, $SnCl_4$, $BF_3 \cdot OEt_2$, etc.) attack both the ether oxygen and the double bonds in **102**, leading to a number of side products. With weaker acids, it would be difficult to cleave the C–O bond of **102**. Clearly, the oxyphilic aluminum reagent **103** is strong enough to coordinate to the ether oxygen, but not to double bonds; it could thus play a key role in promoting a combined C–O bond fission/rearrangement. In addition, the bulky 2,6-di-*tert*-butyl-4-methylphenoxy group in **103** would assist anchimerically the through-space interaction of the π-electron orbital of the isopentenyl group with a developing empty orbital of the prenyl cation via a six-membered transition state.

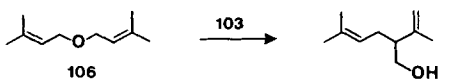


The analogous rearrangements of isopentenyl geranyl ether and isopentenyl farnesyl ether occurred equally well to give the C_{15} and C_{20} alcohols, respectively.



42%, R = Prenyl
33%, R = Geranyl

In addition to the head-to-tail condensation, the alternative head-to-head terpene synthesis was also realized by the organoaluminum-promoted intramolecular rearrangement of diprenyl ether **106**. Thus, reaction of **106** with the reagent **103** at 0°C for 1.5 h furnished only lavandulol.[63]



106

Lavandulol, 33%

6. Closing Remarks

With the aid of selected examples the present review demonstrates that organoaluminum compounds exhibit unique properties, especially their ambiphilic character and their high oxyphilicity, that are capable of considerably extending the scope of organoaluminum chemistry in organic synthesis. In particular, the concept of ambiphilic systems should be applicable to other organometallic compounds such as magnesium, boron, and titanium reagents.[65] However, even with the promising experimental findings so far obtained, it is difficult to predict how many other chemical properties will emerge in the field of organoaluminum chemistry. The synthetic potential of organoaluminum reagents in selective organic synthesis is therefore expected to increase still further.

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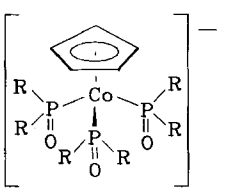
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Tridentate Oxygen Ligands as Cyclopentadienyl Equivalents: Structure and Properties of $[LRh(\mu\text{-}CO)_3RhL]$, $L^- = [(C_5H_5)Co\{P(O)R_2\}_3]^-$**

By *Wolfgang Kläui,* Mario Scotti,* Mauricio Valderrama,* Soledad Rojas, George M. Sheldrick,* Peter G. Jones,* and *Tina Schroeder*

Dedicated to Professor F. Gordon A. Stone on the occasion of his 60th birthday

Complexes of the type L^-, which are anionic tridentate oxygen ligands, are formally isoelectronic with the cyclopentadienide ion.



L^-

$[LRh(CO)_2]$ **1**

$[LRh(\mu\text{-}CO)_3RhL]$ **2**

a, R = OMe; **b**, R = OEt

We have recently observed that the oxygen tripod ligand L^-, R = OEt, can be incorporated similarly to a cyclopentadienyl (Cp) ligand into metal carbonyl complexes of Cr, Mo, W,[1] Mn, Re,[2] and Ru.[3] This is surprising insofar as L^- is a very much weaker ligand according to ligand field spectroscopy and is most closely comparable to the fluoride ion. Since no Rh^I carbonyl complex with three oxygen donors has, to the best of our knowledge, been reported, we have attempted to synthesize complexes of type **1**, which are oxygen analogues of $[CpRh(CO)_2]$.

A reaction is immediately observed on treatment of $[\{Rh(CO)_2Cl\}_2]$ with NaL (R = OMe, OEt) in hexane or dichloromethane at 25 °C; the formation of the dicarbonyl complexes **1a**, **b** can be followed by IR spectroscopy. The $\nu_{C\text{-}O}$ frequencies are observed at 2080 and 1990 cm^{-1} (CH_2Cl_2). The compounds are stable in air but dimerize in solution in a few hours with partial decarbonylation to form the title compounds **2a**, **b**.[4] Crystals of **2b** suitable for X-ray structure determination were obtained by recrystallization from dichloromethane.

2b (Fig. 1) possesses crystallographic twofold symmetry. The three carbonyl groups serve as bridging ligands. It is notable that the formal analogue $[Cp_2Rh_2(CO)_3]$ has only one bridging CO ligand.[5] If the L^- ligand is viewed as the equivalent of three CO groups, the molecule is analogous to "$[(OC)_3Rh(\mu\text{-}CO)_3Rh(CO)_3]^{2+}$," which is isoelectronic with $Fe_2(CO)_9$. Since an Fe–Fe single bond is present in $Fe_2(CO)_9$, the Rh–Rh interaction (254.6 pm) can likewise be viewed as a single bond. Although such bonds normally have lengths of 270–280 pm,[6] Rh–Rh single bonds exist that are appreciably shorter, e.g., 238.6 pm in $[Rh_2(O_2CCH_3)_4(H_2O)_2]$.[7]

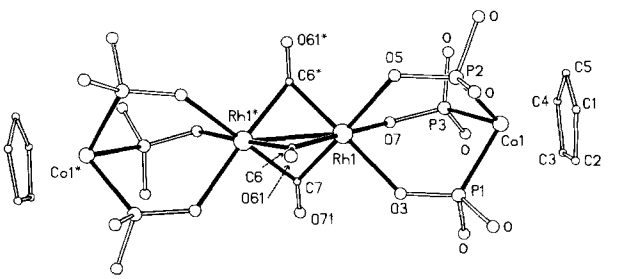


Fig. 1. Crystal structure of **2b**. The ethyl groups of the POEt moieties are omitted for clarity. Space group C2/c, $a = 1013.3(3)$, $b = 1967.0(10)$, $c = 2951.2(6)$ pm, $\beta = 92.71(3)°$, $V = 5.577$ nm^3, $Z = 4$, $\mu(Mo_{K\alpha}) = 2.8$ mm^{-1}; $R_w = 0.055$, $R = 0.078$ for all 3642 absorption-corrected reflections; $Mo_{K\alpha}$ radiation, $2\theta_{max} = 45°$. Two ethyl groups are disordered. C7 and O71 lie on a twofold axis. Important bond lengths [pm]: Rh1–Rh1* 254.6(2), Rh1–O3 218.1(5), Rh1–O5 217.2(5), Rh1–O7 217.7(5), Rh1–C6 199.4(7), Rh1–C7 198.9(9), Rh1–C6* 199.3(7), Co1–P1 216.9(3), Co1–P2 216.6(3), Co1–P3 215.9(3). The asterisk indicates symmetry-equivalent atoms. Apart from the RhRh bond, the coordination geometry at rhodium is nearly octahedral. Further details of the crystal structure investigation are available on request from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2, by quoting the depository number CSD 51411, the names of the authors, and the journal citation.

Preliminary experiments have shown that **1** and **2** form compounds of the type $[LRh(CO)PR'_3]$ with tertiary phosphanes PR'_3, R' = Et, *c*-C_6H_{11}, Ph. **2** reacts in refluxing dichloromethane over several hours, more slowly than $[Cp_2Rh_2(CO)_3]$.[8] Such differences in reactivity have also been observed for $[(C_4H_4)_2Fe_2(CO)_3]$[9] and $[(C_4Ph_4)_2Fe_2(CO)_3]$,[10] which differ similarly in the arrangement (bridging, terminal) of the CO ligands. The CO substitution in **1**, on the other hand, proceeds very fast, more rapidly than in the isoelectronic cyclopentadienyl complex $[CpRh(CO)_2]$.[11] This means that, since the CO substitution in both dicarbonyl complexes takes place via an associative mechanism, the intermediary transition from tridentate to bidentate coordination is energetically more favorable for the oxygen tripod ligand L^- than the "slipping reaction" η^5-Cp/η^3-Cp.[12] An interesting aspect of the chemistry of this rhodium complex is the fact that the oxygen tripod ligands remain bonded to rhodium. It is completely atypical for oxygen ligands to form inert complexes with metals in low oxidation states. This complex opens up the possibility, therefore, of studying the effect of a type of ligand that, in its steric and electronic properties, clearly differs from the isoelectronic C_5H_5 and C_5Me_5 ligands that are ubiquitous in organometallic chemistry.

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[4] Experimental procedure: **2a**: A solution containing NaL (131 mg, 0.28 mmol) in 5 mL of chloroform was added to a suspension of $[\{Rh(CO)_2Cl\}_2]$ (35 mg, 0.09 mmol) in 25 mL of chloroform. The reaction mixture was stirred for 24 h at 25°C and then evaporated in vacuum, and the residue was washed several times with distilled water. After drying in high vacuum, the product was recrystallized from dichloromethane. Yield 66 mg (61%) yellow, air-stable crystals.—^{1}H-NMR (100 MHz, $CDCl_3$): $\delta = 3.75$ (virt. q, 18H, OCH_3), 5.07 (s, 5H, C_5H_5).—IR (KBr): 1838 (s, ν(CO)), 1115 cm^{-1} (s, ν(P=O)).—M_r (osm. CH_2Cl_2), 1184 (calcd. 1192).—Correct C,H analysis.—**2b**: Prepared from $[\{Rh(CO)_2Cl\}_2]$ (78 mg, 0.20 mmol) and NaL (246 mg, 0.44 mmol) in 30 mL of hexane and worked-up as described above. Yield 214 mg (78%) yellow, air-stable crystals.—^{1}H-NMR (100 MHz, $CDCl_3$): $\delta = 1.26$ (t, 18H, CH_3), 4.10 (m, 12H, OCH_2), 5.00 (s, 5H, C_5H_5).—IR (KBr): 1835 (s, ν(CO)), 1120 cm^{-1} (s, ν(P=O)).—M_r (osm. CH_2Cl_2) 1342 (calcd. 1360).—Correct C,H analysis.
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Extremely Long-Wavelength Charge-Transfer Absorptions of Binuclear Complexes with Azo-Modified 2,2′-Bipyridyl Ligands**

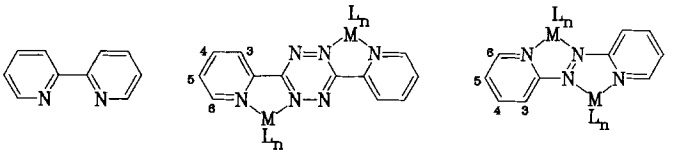
By *Stephan Kohlmann, Sylvia Ernst,* and *Wolfgang Kaim**

The controlled synthesis of complexes with very long-wavelength charge-transfer absorptions is of interest owing to their potential applications in the chemical use of solar energy, since a major fraction of the solar radiation that reaches the earth's surface is in the near-infrared (NIR).[1] In view of the advantageous photophysical properties of complexes containing α-diimines of the 2,2′-bipyridine (bpy) type,[2] we have modified this system by introducing coordinatively bifunctional π-acceptor moieties, which should allow coordination of more than one π-electron-rich metal fragment and thus produce particularly strong effects.[3]

We chose the bridging bis(chelate) ligands 3,6-bis(2-pyridyl)-1,2,4,5-tetrazine **1**[4] and azo-2,2′-bipyridine **2**,[5] which incorporate the π-electron-deficient azo function $-N=N-$,[6] and report here the binuclear complexes **1a–d** and **2a**, **d** containing low-spin d^6 metal-complex fragments[7] (see Table 1).

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bpy **1, 1a–d** **2, 2a, d**

Table 1. Long-wavelength absorption maxima λ [nm] and reduction potentials E_{red} [V vs. SCE] [a] of the ligands **1** and **2** and their binuclear d^6 metal complexes.

Comp.	ML_n	λ(toluene)	λ(acetonitrile)	E_{red}
1	—	546	540	−0.72
1a	$Mo(CO)_4$	909	819	−0.07
1b	$W(CO)_4$	905	814	−0.06
1c	*fac*-$Mn(CO)_3Br$	903	762	[b]
1d	$[Ru(bpy)_2]^{2\oplus}$	[c]	688	−0.03 [d]
2	—	466	460	−0.96
2a	$Mo(CO)_4$	918 [e]	815	+0.04
2d	$[Ru(bpy)_2]^{2\oplus}$	[c]	790	+0.27 [d]

[a] Measurements in dimethylformamide/0.1 M $Bu_4N^{\oplus}ClO_4^{\ominus}$, cyclovoltammetry at a glassy carbon electrode. [b] Irreversible step. [c] Measurements not possible because of insolubility. [d] Measurements in acetonitrile/0.1 M $Bu_4N^{\oplus}ClO_4^{\ominus}$. [e] Absorption maximum at 952 nm in isooctane.

The long-wavelength absorption maxima, which, for the ligands, are already in the visible region due to n→π* transitions and lie between 550 and 700 nm for the mononuclear complexes,[8] reach the NIR region in the binuclear complexes (Fig. 1, Table 1).

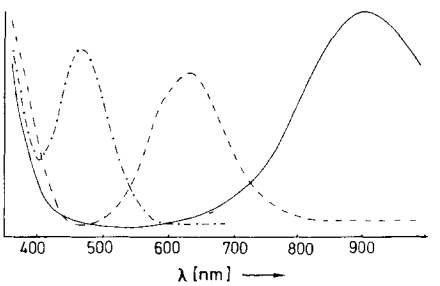


Fig. 1. Absorption spectra of the ligand **2** (·–·–·), the mononuclear complex [**2** $Mo(CO)_4$] (– – –), and the binuclear complex [**2** $\{Mo(CO)_4\}_2$] **2a** (——) in toluene (arbitrary intensity units). Solutions of the mononuclear complex are deep blue, solutions of **2a** have a faint green color because of the absorption gap in the visible (band tails from the NIR and UV regions).

Both the extinction coefficients ($\varepsilon = 10^4 - 10^5$ M^{-1} cm^{-1}) and the characteristic solvent dependence (negative solvatochromism[9]) indicate metal-to-ligand charge-transfer (MLCT) transitions; ESR studies of reduced species[10] confirm the π* character of the lowest unoccupied molecular orbital (LUMO) for the complexes **1a**, **d**.

The extremely low energy levels of the complex LUMOs are illustrated by electrochemical data (Table 1). The binuclear complexes **1a**, **b**, **d**, and **2a** are reduced at ca. 0 V relative to the saturated calomel electrode, and the binuclear ruthenium(II) complex **2d** is an even stronger acceptor than tetracyanoethylene (TCNE, $E_{red} = +0.24$ V[11]) and thus clearly superior to all known polyazine ruthenium(II) complexes.[3, 12]

The redox potentials suggest how to obtain further complexes with even smaller energy differences between the frontier orbitals and correspondingly longer-wavelength charge-transfer absorptions. On the one hand, the ligands must be easily reducible, while, on the other hand, the oc-

cupied metal d levels should be energetically destabilized by the loss of ligands capable of back-bonding. In the complexes **1** and **2**, this strong charge-transfer interaction is possible through coordination to the azo nitrogen centers; chelate coordination via the basic but less strongly back-bonding 2-pyridyl substituents stabilizes the complex toward dissociation.

The steric crowding in the coordination-induced *trans* conformation of the ligand **2** has several interesting consequences. Thus, mononuclear[8] but no binuclear complexes of this ligand could be obtained containing tetracarbonyltungsten or bromo(tricarbonyl)manganese; examination of models as well as the marked low-field ^{1}H-NMR shift for the pyridyl protons H-3 in **2a**[7] indicate non-bonded interactions between these protons and the equatorial substituents L in binuclear complexes with coplanar conformation of the ligand **2**.

Also remarkable is the similarity of the complexes **1a** and **2a** and the fact that the π-acceptor level of **2d** is lower than that of **1d** even though the ligand **1** is more easily reduced than **2** (Table 1). One reason is that the smaller system **2** exhibits a stronger reaction upon *N*-coordination;[13] on the other hand, it is also important to note the relative proximity of the two metal centers in binuclear complexes of **2**. Application of the model of *Richardson* and *Taube*[14] to this case yields an even smaller metal-metal distance (ca. 460 pm) than for N_2-bridged binuclear systems ($d_{M-M} = 500$ pm[14]).

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CAS Registry numbers:
1a, 97374-20-4; **1b**, 97374-21-5; **1c**, 97374-22-6; **1d**, 97374-24-8; **2a**, 97374-25-9; **2d**, 97374-27-1; [(thf)W(CO)$_5$], 36477-75-5; BrMn(CO)$_5$, 14516-54-2; *cis*-[Ru(bpy)$_2$Cl$_2$], 19542-80-4; tetracarbonyl(norbornadiene)molybdenum, 12146-37-1.

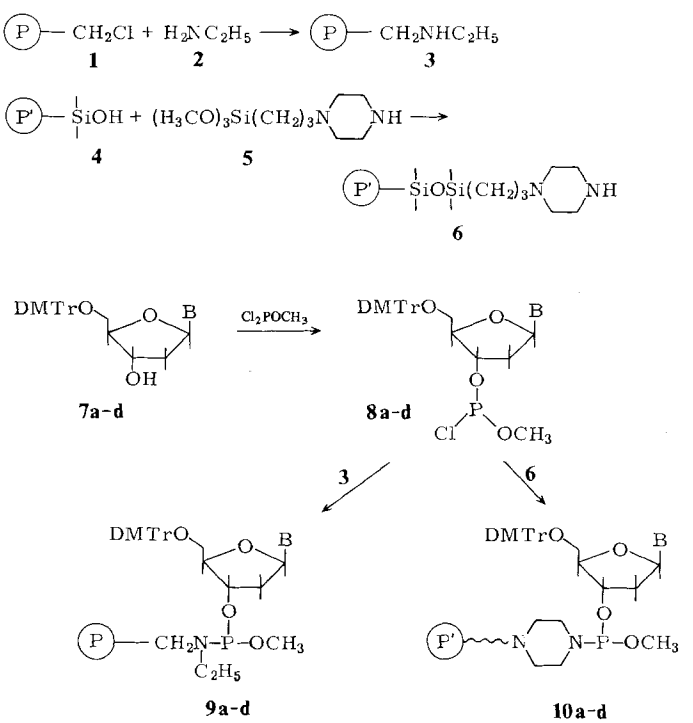
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[7] **1a** and **2a** were prepared by reaction of excess tetracarbonyl(norbornadiene)molybdenum with **1** and **2**, respectively, in toluene. After removal of the solvent, olefin, and olefin complex in vacuum (and purification of **2a** by column chromatography on florisil), the products were recrystallized from toluene/hexane. Yields: 76% (**1a**) and 5% (**2a**), dark crystals, correct elemental analysis. IR (THF; ν(CO) [cm^{-1}]): **1a**: 1995, 1940 (br), 1875; **2a**: 1985, 1945, 1908, 1872. ^{1}H-NMR (CDCl$_3$, 270 MHz): **1a**: $\delta = 7.62$ (dd, H-5), 8.08 (dd, H-4), 8.81 (d, H-3), 9.06 (d, H-6); $^2J_{3,4} = 8$ Hz, $^2J_{4,5} = 7$ Hz, $^2J_{5,6} = 5$ Hz; **2a**: $\delta = 7.53$ (dd, H-5), 7.98 (ddd, H-4), 9.04 (dd, H-6), 9.17 (d, H-3); $^2J_{3,4} = 8.6$ Hz, $^2J_{4,5} = 7.3$ Hz, $^2J_{5,6} = 5.5$ Hz, $^3J_{4,6} = 1.5$ Hz.—**1b** was prepared from photochemically generated [(thf)W(CO)$_5$] and **1** at 0°C in tetrahydrofuran. The unstable complex was purified as for **1a**; yield 3%; dark crystals. IR (THF; ν(CO) [cm^{-1}]): 1979, 1935 (br), 1872.—**1c** was prepared from BrMn(CO)$_5$ and **1** in toluene and purified by column chromatography on florisil; yield 35%, dark crystals, correct elemental analysis. IR (CH_2Cl_2; ν(CO) [cm^{-1}]): 2022, 1965, 1945. ^{1}H-NMR (CDCl$_3$, 270 MHz): $\delta = 7.78$ (H-5), 8.20 (H-4), 8.84 (H-3), 9.14 (H-6), all signals broad.—**1d** and **2d** were prepared from **1** and **2**, respectively, and *cis*-[Ru(bpy)$_2$Cl$_2$]·2 H$_2$O in refluxing water/ethanol (2:1). The products were precipitated as the tetrakis(hexafluorophosphates) and purified by column chromatography (Al_2O_3, CH_3CN). The analytically pure complexes **1d** and **2d** were obtained as the tetrahydrates in 23 and 5% yield, respectively.
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Three-Phase Synthesis of Oligonucleotides**

By *Hartmut Seliger** and *Kailash Chand Gupta*

In the synthesis of oligonucleotides via phosphite triesters[1] using the solid-phase method,[2] the nucleoside *N,N*-dimethylphosphoramidites[3] activated by tetrazole have proved particularly useful as highly reactive intermediates. However, since they are relatively unstable, we have investigated polymeric reagents of the nucleoside phosphoramidite type. We describe here their preparation and their application to the synthesis of oligonucleotides.

The polystyrene **3**, substituted with *N*-ethylaminomethyl groups, was prepared from the commercially available



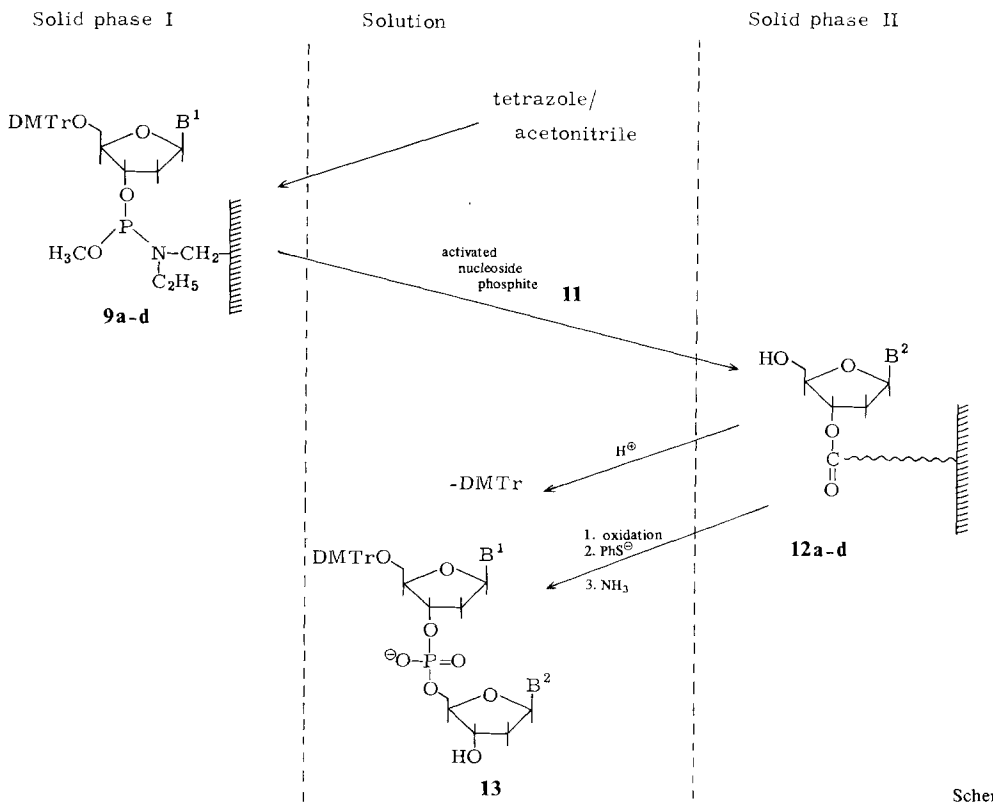
Scheme 1. P = Merrifield resin, P' = silica gel; DMTr = dimethoxytrityl. **a**, B = N^6-Benzoyladenin-9-yl; **b**, B = N^4-benzoylcytosin-1-yl; **c**, B = N^2-isobutyrylguanin-9-yl; **d**, B = thymin-1-yl.

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[**] Carrier Syntheses, Part 11. This work was supported by the Deutsche Forschungsgemeinschaft. *K. C. G.* thanks the Deutscher Akademischer Austauschdienst for a fellowship.—Part 10: [16].

Merrifield resin **1**; piperazino-substituted silica gel **6** was synthesized according to a reported procedure.[4] We reacted **3** with the phosphorochloridite esters **8a—d** (prepared from **7a—d** according to a known route[1]) to give **9a—d**; **6** was analogously converted into **10a—d** (Scheme 1).

The solutions of the activated nucleoside phosphites **11**, which were prepared by treatment of **9** with tetrazole in anhydrous acetonitrile, were reacted with the immobilized nucleosides **12** followed by the usual[5b] oxidation and detritylation. The intense red-orange color of the solution showed that, in every case, a nucleoside transfer from **9** to **12** had occurred. Work-up[5b] gave the dinucleotide **13** (Scheme 2).



Scheme 2. For abbreviations see Scheme 1.

After these preliminary experiments, the solution prepared from **9d** with tetrazole/CH_3CN was used in an automatic synthesizer[6] for fourfold chain extension[5b] of **12a**; the sequence dTTTTA was thus obtained in a yield of 77%. Similarly, dT_8 could be synthesized in a total yield of 68% from **10d** and **12d**. In both cases, the individual condensation steps must have occurred with >95% average yield (taking into consideration losses during work-up). Both nucleotides were characterized by the "wandering spot" method.[7]

9 and **10** are thus excellently suitable as reagents for the chemical synthesis of oligonucleotides. Since sensitive low-molecular-weight compounds are known to be stabilized by immobilization,[8b] **9** and **10** should be more stable upon storage than the low-molecular-weight nucleoside *N,N*-diisopropylphosphoramidite esters or the corresponding morpholides.[9, 10] Accordingly, their in-situ preparation would no longer be necessary.[11, 12] Indeed, **9d** still reacts after 15 months in the same yield; less than 10% of the bound nucleoside was lost during this period by hydrolysis or oxidation. In this respect, **9** and **10** undergo "self-purification" since no oxidation or hydrolysis products appear in **11**; the former remain bound to the carrier, the latter are removed by prewashing.

Analogously to the concept of three-phase catalysis,[13] our results demonstrate that, in the synthesis of oligonucleotides via phosphoramidite ester intermediates, tetrazole not only serves as a proton donor[14] but also reacts with **9** and **10** with formation of an intermediate (**11**). Whether the highly reactive **11**, which is stable for hours, is the postulated[15] tetrazolylphosphane or instead a subsequent product remains to be clarified.

Experimental Procedure

3: **1** (5 g; 2% divinylbenzene, 2.3 mmol Cl/g) was refluxed for ca. 15 h with **2** (100 mmol), filtered, and then shaken an additional 24 h with 150 mL of dioxane/triethylamine (1:1). **3** was washed three times with 100 mL each of dioxane, dioxane/H_2O (3:1), dioxane, toluene, and methanol, and dried in vacuum.

9a—d: **8a—d** (1 mmol) [1] and ethyl(diisopropyl)amine (5 mmol), dissolved in 10 mL of dry tetrahydrofuran (THF), were added by syringe to **3** (1 g). After 30 min, unreacted **8** was removed by suction filtration under argon, and the polymer was washed with 20 mL each of $CHCl_3$ + 5% triethylamine, dry CH_3CN, and ether, and stored under argon. Load: 0.25—0.3 mmol nucleoside/g reagent (determined by VIS spectroscopy after detritylation [5b]).

Oligonucleotide synthesis

a) Manual experiment: **9** (150 mg) prewashed with 2 mL of CH_3CN was treated in a reaction syringe [16] for 10 s with 1 mL of 0.1 M tetrazole in CH_3CN. The resulting solution of **11** was injected through a septum directly into a sintered glass vessel [5b] containing 100 mg of **12** (40—50 μmol nucleoside/g). After 15 min, the mixture was filtered and the carrier was washed, oxidized, and detritylated according to established procedures [5b].

The cleavage of **13** from the carrier and its work-up were carried out as described in [5b].

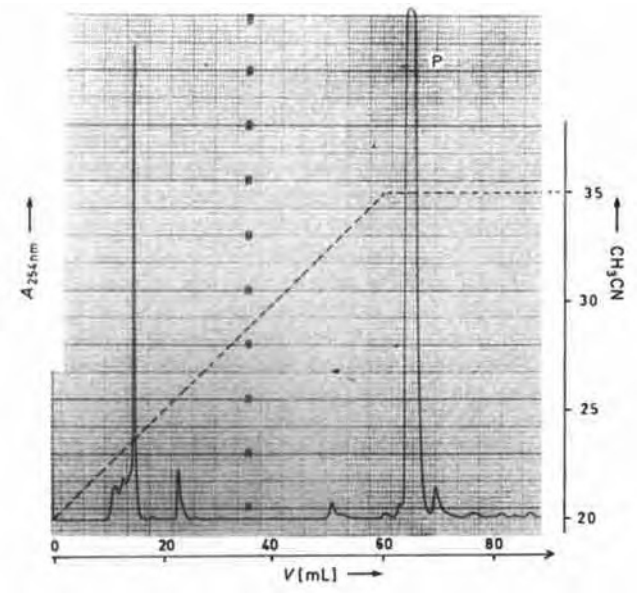


Fig. 1. HPLC separation of the product of the solid-phase synthesis of DMTrdTTTTA. A = absorption; V = elution volume; P = main product. Column: μ-Bondapak C_{18} (Waters; 7.8 × 240 mm); eluent: 0.1 M triethylammonium acetate buffer (pH 7.0) + 20–35% acetonitrile; flow rate: 2 mL/min; detection: UV (254 nm).

b) Experiment with an automatic synthesizer:

9d (1.2 g) prewashed with 15 mL of CH_3CN was treated as described in a) with tetrazole in CH_3CN. The solution of **11** was poured into the reservoir of an automatic synthesizer [6]. Four chain extensions [5b] of **12a** (4.5 μmol dA^{bz}) were carried out (cycle time 23 min). Work-up of the solid phase [5b], HPLC of the product on silica gel C_{18} (Fig. 1), and detritylation and desalting of the product fraction (P in Fig. 1) [5b] gave dTTTTA (174 $O.D._{254}$) in a yield of 77%.

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7a, 64325-78-6; **7b**, 67219-55-0; **7c**, 68892-41-1; **7d**, 40615-39-2; **8a**, 78635-96-8; **8b**, 78635-95-7; **8c**, 78635-97-9; **8d**, 74855-51-9; dTTTTA, 80703-91-9; dT_8, 1270-05-9; Cl_2POCH_3, 3279-26-3.

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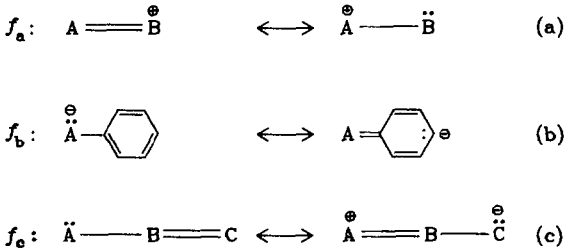
Calculation of the Charge Distribution in Conjugated Systems by a Quantification of the Resonance Concept**

By *Johann Gasteiger** and *Heinz Saller*

Dedicated to Professor Rolf Huisgen on the occasion of his 65th birthday

The resonance theory has become a fundamental part of the basic training in organic chemistry.[1] Although it has a quantum mechanical basis in the valence bond method, it has remained only a qualitative concept in the hands of the organic chemist. Even though individual resonance structures are assigned different weights, there has been no simple method so far to express these weights quantitatively.

We have now developed an empirical procedure that does just this and enables the charge distribution in π-systems to be calculated on the basis of the assignments of weights to the resonance structures. From these charges, predictions can then be made as to the physical and chemical properties of compounds. The weight w of each resonance structure consists of a formal (topological) part and an electronic part. In order to assign the topological weight w_t, the resonance structures are classified according to whether (a) a reduction in the number of covalent bonds, (b) a decrease in the number of aromatic systems, or (c) a charge separation occurs.



Each of these formal situations is assigned a factor, whose value was determined as described below. The total topological weight w_t of a resonance structure is given by Equation (d).

$$w_t = f_a \cdot f_b \cdot f_c \qquad (d)$$

The electronic weight w_e must express how well, for example, the atom A in Equation (c) can donate its lone pair of electrons and how stable a negative charge on atom C is. In order to determine this, we used the electronegativity concept.

According to Mulliken's definition,[2] the electronegativity χ is determined by the ionization potential IP and the electron affinity EA [Eq. (e)].

$$\chi = 1/2(IP + EA) \qquad (e)$$

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In order to further refine these ideas, the concept of orbital electronegativity was introduced.[3,4] According to this concept, the electronegativity is no longer a purely atomic property, but is also dependent on the type of orbital. An sp orbital, for example, has a higher electronegativity than an sp^3 orbital. Furthermore, the orbital electronegativity is dependent on the occupation number of the orbital;[4,5] an unoccupied orbital attracts electrons more strongly than a singly or doubly occupied orbital. We selected a second degree polynomial [Eq. (f)] to express the dependence of the orbital electronegativity on the occupation of an orbital (or, equivalently, on the charge q).

$$\chi_v = a_v + b_v \cdot q + c_v \cdot q^2 \qquad \text{(f)}$$

The coefficients a_v, b_v, and c_v could be calculated[6,7] from published data on valence-state ionization potentials and electron affinities.[3,4]

On the basis of the partial equalization of orbital electronegativities, we had already developed a procedure for the calculation of charge distribution in σ-bonded molecules,[6] which has proved suitable for the reproduction of a variety of physical and chemical data.[6,8,9]

The two resonance structures in each of the equations (a) to (c) differ by electron transfers between the π orbitals of two atoms. The availability of the electrons in these orbitals is characterized by the corresponding π-orbital electronegativity χ^π; the coefficients a_v, b_v, and c_v in Equation (f) that are necessary for its determination have been published already.[7] The value of the charge q in Equation (f) is obtained from Equation (g), in which the different effect of σ and π charges must be taken into consideration in determining the factor f_{sp}.

$$q = q_\pi + f_{sp} \cdot q_\sigma \qquad \text{(g)}$$

The determination of the electronic weight w_e is based on the classical idea that those resonance structures are more important ("have lower energy") in which the negative charge is localized on the more strongly electronegative atom. This can be incorporated into the calculation by the use of the difference of the π electronegativities of the two atoms i and j, which have differing formal charges, e.g., A and B in (a) or A and C in (c). In addition, the second term of Equation (h) takes into consideration the electrostatic potential of the neighboring atoms N_i of the atom i and N_j of the atom j. This potential is assumed to be proportional to the sum of the charges q_k, q_l on these neighboring atoms.

$$w_e = (\chi_i^\pi - \chi_j^\pi) + f_e \cdot \left(\sum_k^{N_i} q_k - \sum_l^{N_j} q_l \right) \qquad \text{(h)}$$

The total weight of each resonance structure is calculated from the topological weight and from the electronic weight according to Equation (i).

$$w = w_t \cdot w_e \qquad \text{(i)}$$

By adding the changes in charge of the individual resonance structures and taking into consideration the scaling factor f_s, which is the same for all resonance structures, the charge distribution is obtained. The two terms in Equation (h), however, are themselves dependent on the charge distribution [cf. Eq. (f)]. In order to take this into consideration, the charge transfer was distributed over several cycles, n_c, so that only a certain part of the charge, q_c, is displaced per cycle. New electronegativity values χ [Eq. (f)] are calculated in the next cycle using the resulting charges.

$$q_c = \frac{1}{n_c} \cdot w \cdot f_s \qquad \text{(j)}$$

Eight cycles have proved to be a good compromise between computing accuracy and computing time; the computing times are then always extremely short.

The six factors f were fixed using properties that directly depend on the charge distribution. This is true, for example, of ^{13}C-NMR shifts as long as one class of compounds is used (constant mean excitation energy[10]), or of ESCA shifts, which can be easily interpreted using a potential model.[11] Three sets of physical data were used to optimize the factors by the Simplex procedure:[12] A) the ^{13}C-NMR shifts of the *para* C atom in twelve monosubstituted benzenes; B) the ^{13}C-NMR shifts of twelve C atoms in nine substituted pyridines; C) the C 1s ESCA shifts of eleven C atoms in seven fluorinated olefins.

This gave the following factors: $f_a = 0.65$; $f_b = 0.30$; $f_c = 0.133$; $f_e = 1.00$; $f_{sp} = 0.50$; $f_s = 0.33$. The charge values calculated from them reproduced these three sets of data well (r = correlation coefficient; s = standard deviation): A) r = 0.986, s = 1.04 ppm (see Fig. 1); B) r = 0.991, s = 1.36 ppm; C) r = 0.987, s = 0.34 eV.

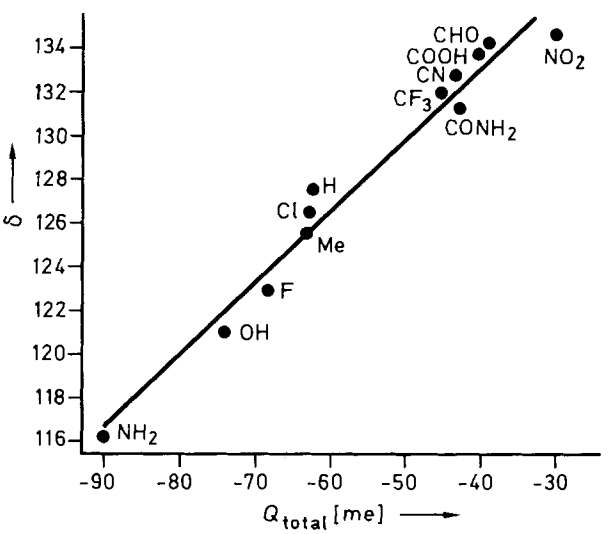


Fig. 1. ^{13}C-NMR shifts (δ values) of the *para* carbon atom in monosubstituted benzenes versus the total charge, Q_{total}, of this carbon atom.

The charge values are also helpful for the calculation of other physical data. Thus, for example, a good correlation was found between the charge of the *para* C atom of monosubstituted benzene derivatives and the chemical shift of the protons bonded to it. Furthermore, for a large data set of molecules (48 points) comprising conjugated olefins, acetylenes, and carbonyl compounds, a linear relationship between charges and C 1s ESCA shifts was obtained. In addition, good agreement between experimental and calculated dipole moments was observed (see Table 1). This emphasizes the broad general significance of the charge values.

The accuracy of the charge values has been demonstrated here on the basis of physical properties. Resonance theory is most important, however, for the interpretation of chemical reactivity, in particular, of aromatic substitution.

Table 1. Experimental and calculated dipole moments (in Debye).

a	μ(exp.)	μ(calcd.)
$H_2C{=}O$	2.34	2.48
$H_2C{=}CHF$	1.46	1.61
$H_2C{=}CF_2$	1.39	1.63
$H_2C{=}CH{-}CH_3$	0.37	0.09
$H_2C{=}CH{-}CH{=}O$	3.11	3.75
C_6H_5OH	1.28	1.16
C_6H_5F	1.60	1.63
C_6H_5Cl	1.58	1.49
$C_6H_5NH_2$	1.15	1.18
$C_6H_5C{\equiv}N$	3.93	3.77
$C_6H_5CH{=}O$	3.21	3.54
$C_6H_5NO_2$	4.16	4.11
p-$H_2N{-}C_6H_4NO_2$	6.91	6.83
Pyridine	2.19	2.20
Pyrrole	1.80	1.69

The weighting of the resonance structures now enables quantitative statements to be made. They are used in the program system EROS[13] for the prediction of reactions and the planning of syntheses. Use of the procedure presented here, along with methods to determine the inductive effect[14] and the polarizability,[15] allows the reactivity of complex organic molecules to be estimated automatically. The course of organic reactions can thereby be predicted.

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$(NEt_4)_2[Cl_3Mo(\mu\text{-}S_2)(\mu\text{-}Cl)_2MoCl_3]$, a Paramagnetic Molybdenum(IV) Compound with a Metal-Metal Bond

By *Ulrich Müller,* Paul Klingelhöfer, Claus Friebel,* and *Jürgen Pebler*

Many compounds are known in which two transition-metal elements are joined via sulfur or halogen atoms and which further contain metal-metal bonds.[1] The metal-metal bond is recognized, apart from its length, by the existence of diamagnetism or only a very weak paramagnetism. Paramagnetic species occur when an odd number of electrons are present—e.g., in **1**–**3**,[2–4] in which the metal atoms have two different oxidation states.

$[(NC)_4Mo(\mu\text{-}S_2)(\mu\text{-}SO_2)Mo(CN)_4]^{5\ominus}$ **1**[2]

$[Cl_3W(\mu\text{-}SPh)_2(\mu\text{-}Cl)WCl_3]^{2\ominus}$ **2**[3]

$[Mo_2Cl_9]^{2\ominus}$ **3**[4]

We have now obtained the title compound, a paramagnetic compound with an even number of electrons, in which a Mo–Mo single bond is present and in which, at the same time, each molybdenum atom possesses an unpaired electron.

When a suspension of molybdenum pentachloride in CH_2Cl_2 is added to an equimolar solution of NEt_4SH in CH_2Cl_2 frozen at 77 K, and the mixture is allowed to thaw, the following reaction occurs with formation of HCl.

$$(MoCl_5)_2 + 2\,SH^{\ominus} \longrightarrow \underset{\mathbf{4}}{[Cl_3Mo(S_2)Cl_2MoCl_3]^{2\ominus}} + 2\,HCl$$

After ca. 15 h of stirring, an insoluble, greyish green product, which has not yet been identified, is filtered off; after addition of CCl_4 to the filtrate, the tetraethylammonium salt of **4** (27%) crystallizes out at 278 K.

A sulfido complex containing pentavalent molybdenum is not present, in contrast to what the composition NEt_4MoSCl_4 might lead one to suppose. As observed for other thiomolybdates,[5] the sulfido ligand is oxidized to the disulfide and the molybdenum is reduced to Mo^{IV}. The presence of a disulfide in **4** follows from the IR spectrum (ν(SS) = 609 cm^{-1}) and by the X-ray structure determination (Fig. 1).[6] The disulfide group links the two molybdenum atoms, which, in addition, are bridged by two chlorine atoms. If the disulfide group is viewed as only a single ligand, then **4** consists of two face-sharing octahedra; the bond angles Mo–Cl–Mo (68.0°) and Mo–S–Mo (69.2°) are only slightly smaller than the ideal value (70.5°) for regular face-sharing octahedra.

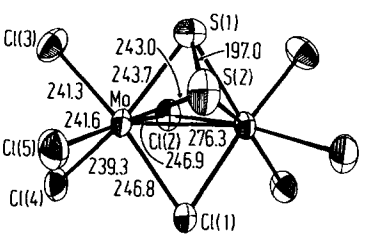


Fig. 1. Structure of **4** in the crystal of $(NEt_4)_2[Cl_3Mo(S_2)Cl_2MoCl_3]$ with ellipsoids of thermal vibration (50% probability at 295 K). Distances [pm]; standard deviations: Mo–Mo 0.2, Mo–Cl 0.3, Mo–S 0.4, S–S 0.7 pm. The ion is situated on a crystallographic mirror plane that intersects the atoms S(1), S(2), Cl(1), and Cl(2).

The Mo–Mo distance (276.3 pm) supports the existence of an Mo–Mo bond. Even though two d electrons are available per molybdenum atom, it can only be a single bond since, according to the magnetic susceptibilities and the electron spin resonance spectrum, each Mo atom still has available an unpaired electron.

Between 4 and 160 K the magnetic susceptibility approximately obeys the Curie-Weiss law. The fitting of the measured data gives a magnetic moment of 1.40 μ_B per

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atom and a Curie-Weiss temperature of $\theta \approx 0$ K. Taking into consideration the spin-orbit coupling constant for molybdenum, the magnetic moment corresponds to a localized $4d^1$ electron. This is in accord with the electron spin resonance spectrum, which was recorded between 130 and 298 K for the powder and for the oriented single crystal at 9.5 and 35 GHz. Although two unpaired electrons are present in **4** no triplet state with recognizable zero-field splitting is observed. The small anisotropy of the ESR powder spectrum, however, indicates a coupling of two molecular g tensors, whose axial components should be oriented parallel to the Mo–S_2 directions. Accordingly, in the direction of the crystallographic b axis, with respect to which all Mo–Mo vectors are directed parallel, the two molecular $g_{\parallel}$ components are seen at an angle of approximately 55°:

$$g_b \approx \tfrac{1}{3} g_{\parallel} \pm \tfrac{2}{3} g_{\perp} = \bar{g}$$

The observed parameter $g_b = 1.94_6$ agrees surprisingly well with the literature values for isolated octahedral Mo^V complexes such as $[MoCl_6]^{\ominus}$ ($\bar{g} = 1.95_0$) and $[MoOCl_5]^{2\ominus}$ ($\bar{g} = 1.94_5$).[7] This result supports the assumption of an Mo–Mo single bond between the two Mo^{IV} centers in **4**, which reduces the paramagnetism to that of two d^1 systems.

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4·$(NEt_4)_2$, 97374-19-1; $MoCl_5$, 10241-05-1; Mo, 7439-98-7; NEt_4SH, 10408-33-0.

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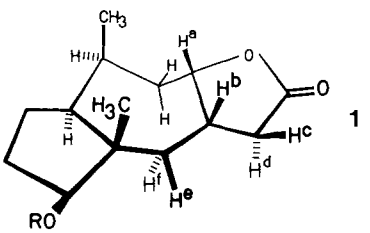
Simplification of Spectra for the Determination of Coupling Constants from Homonuclear Correlated 2D NMR Spectra**

By *Horst Kessler** and *Hartmut Oschkinat*

Indirect spin-spin coupling (J coupling) is one of the most important parameters in NMR spectroscopy. In complicated ^{1}H-NMR spectra it is often difficult to determine the coupling constants of importance for a structure elucidation because the proton signals to be analyzed show a complex multiplet structure or are covered by other signals.

Herein, we will show with the aid of a special method (*D*ifferences and *S*ums COSY spectra, DISCO), how coupling constants can be obtained from phase-sensitive homonuclear-correlated proton spectra (H,H-COSY)[1] without additional measurements having to be made. Difficulties that can occur in conventional methods such as double resonance spectroscopy[2] and 2D-J,δ-spectroscopy,[3] by falsification of the coupling values ("boosting"[2]) or in the assignment of the measured values, are avoided.

As example of the possibility of simplifying complex multiplet structures with the aid of the DISCO technique[4,5] we have investigated the compound **1**, R = tBuMe$_2$Si, formed during a natural product synthesis.[6]



1

Our intention was to use the proton coupling constants together with nuclear Overhauser enhancement values (NOE) for elucidation of the structure at the ring connection site of the seven-membered ring/five-membered ring

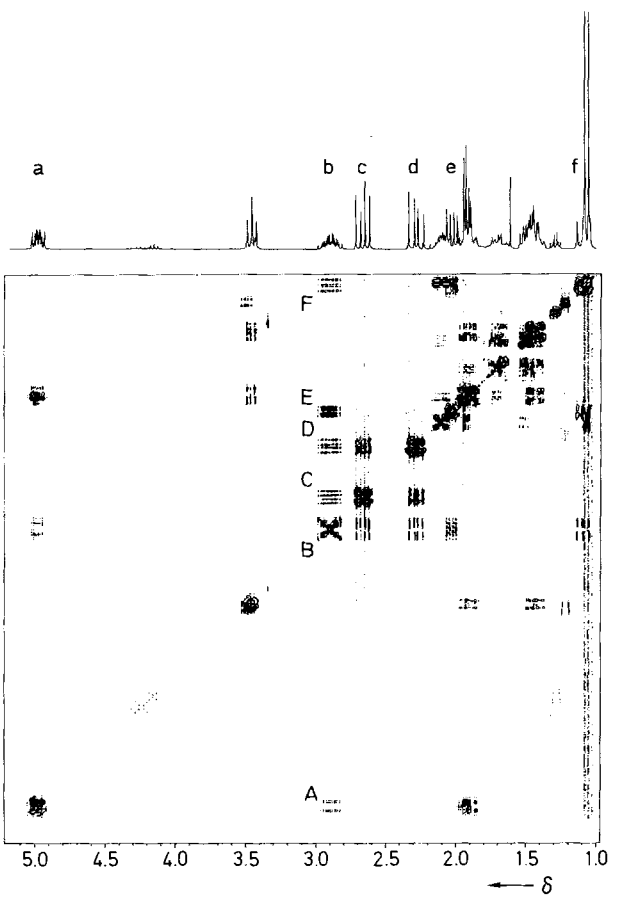


Fig. 1. Section of the phase-sensitive H,H-COSY spectrum (with double quantum filter) [7] of **1** at 300 MHz in $CDCl_3$, recorded via the TPPI method [8]. 616 increments were recorded, each with 16 scans of 8 K in t_2. Before the Fourier transformation, zero-filling to 2 K data points in t_1 was applied. The total recording time was 14 h, the computation time ca. 30 min.

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lactone. For this purpose we were interested in the five coupling constants which are contained in signal b at $\delta = 2.89$. Conclusions about the position of the coupling partners can be drawn from the H,H-COSY spectrum (Fig. 1). All ten of the expected cross peaks due to coupling of b to a, c, d, e, and f are observable. In no case is there a strong coupling to b and between the signals a, c, d, e, and f. The "active" coupling giving rise to an individual cross peak is also responsible for the so-called anti-phase structure of this particular cross peak.[1, 4, 5] This means that lines with positive and negative intensity appear within a cross-section through a cross peak. The difference between the centers of the positive and negative groups of signals within this cross-section is equal to the "active" coupling constant. A direct evaluation, however, is often very difficult or impossible, owing to cancelling effects [Fig. 2 (a–e)].

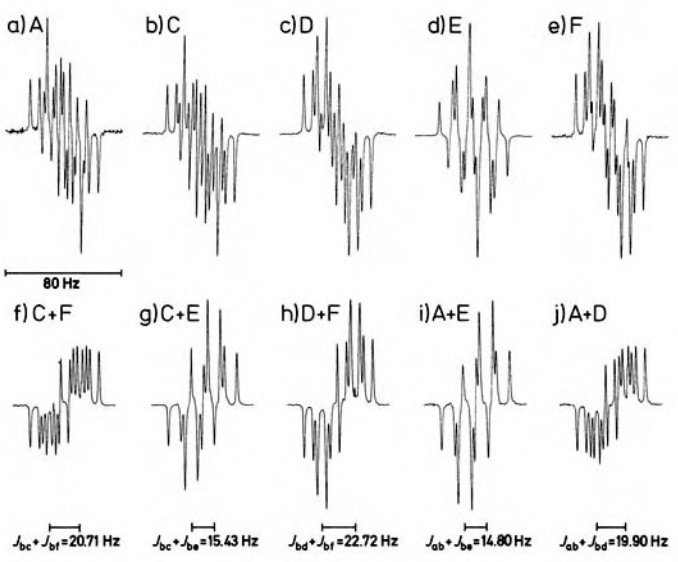


Fig. 2. (a–e). Pseudo one-dimensional spectra from the cross peaks to b. The spectra were obtained by co-addition of the individual traces of the respective cross peaks. Their resolution was improved by retro-Fourier transformation, zero filling to 32 K data points, Lorentz-Gauss transformation, and renewed Fourier transformation. The resolution was 0.4 Hz beforehand and 0.2 Hz afterwards. (f)–(j): DISCO spectra by addition of the untreated 8 K pseudo one-diemensional spectra. The resolution of the spectra thus obtained was improved as described above.

The structure of the pattern in a cross-section can be simplified by a simple trick. When the cross-sections of two different cross peaks are added, a pattern results which contains only half as many lines as originally. The anti-phase structure is still present but less perturbing, since the distance between the two groups of signals with positive or negative intensity is now the *sum* of the two active coupling constants [Fig. 2 (f, g)].

Hence, the desired coupling constants are not obtained directly but by solving a set of linear equations with n unknowns (where n is the number of participating cross peaks). If, for example, there are three cross peaks A, B, C, and they are combined to give A+B, A+C, B+C, then the difference between the centers of the positive and negative groups of signals in the individual DISCO spectra gives the sum of the coupling constants active in both cross peaks. A set of three linear equations with three unknowns is obtained which is just determinate ($J_A + J_B = X$, $J_A + J_C = Y$, $J_B + J_C = Z$) and can be solved. If there are four cross signals, then six DISCO spectra are possible, and the system is already overdeterminate. This makes it possible to minimize the errors and to forgo DISCO spectra in which the position of the centers of the in-phase multiplet cannot be established unequivocally.

To achieve good signal-to-noise ratio of the cross-sections one can add *all* traces of *one* cross peak corresponding to the signs of individual lines such that the intensity for the signals will be maximal and the signal-to-noise ratio correspondingly improved.[9] In this way T_1-noise and dispersional contributions from the diagonal peaks can be reduced. Such "pseudo one-dimensional" spectra were derived from the cross peaks labeled A, C, D, E, F in Figure 1 [see Fig. 2 (a–e)] and appropriately combined. Five of the ten possible combinations are reproduced in Figures 2f–j. Partly occurring cancellation effects do not prevent the localization of the centers of these groups of lines. In Figures 2f–j the values for the sums of the corresponding coupling constants are also quoted; solution of the linear expression with five unknowns gives $J_{ab} = 8.3$, $J_{bc} = 9.2$, $J_{bd} = 11.3$, $J_{be} = 6.2$, and $J_{bf} = 11.4$ Hz. The same values for the coupling constants J_{bc} and J_{bd} are obtained from the one-dimensional spectrum.

An intense cross peak between the signals d and f in the phase-sensitive NOESY spectrum[10, 11] enables assignment of the diastereotopic methylene ring protons e, f and c, d. A large coupling constant of 11.3 or 11.4 Hz, respectively, to signal b is found for these signals, thus proving the antiperiplanar position of their protons to proton b. The coupling of proton b to e lies in the expected range while that to c appears unusually large. The coupling constant between b and a (8.3 Hz) is compatible with an almost eclipsed arrangement. The strong NOE effect between a and b, and of proton a to both methyl groups, unequivocally confirms the *cis* ring coupling. Proton b exhibits a NOE effect only to the methyl group on the quaternary C-atom, thus indicating an incompletely eclipsed arrangement (see formula). Altogether an unambiguous picture of the configuration and conformation at the ring connection site is obtained.

The advantage of the DISCO technique is that the values for the coupling constants can also be taken from a *routinely recorded,* phase-sensitive H,H-COSY spectrum with or without double quantum filter, without other experiments being necessary. In our example, ca. 15 minutes are required for evaluating all the ten possible DISCO spectra using a data station ASPECT 3000 with an array processor. Even when the computation time of ca. 30 min for the Fourier transformation of the stored FID's is added to this, the method is still quicker than conventional experiments on a spectrometer with renewed measurement of the sample. Since only a good resolution in ω_2 is required for the use of the DISCO technique, the necessary better resolution does not demand any increase in recording time. The method can also be used when the signals to be evaluated in a one-dimensional spectrum are covered by other signals. If, however, the diagonal signals are free, the coupling constants can also be determined by DISCO spectra between cross peaks and diagonal signals calculated on the absorption phase.[5]

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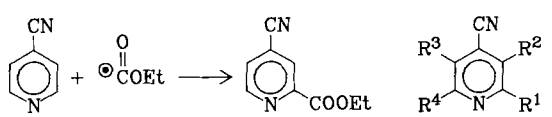
Marked Increase in the Regioselectivity of Radical Substitution: Minisci Reaction in a Two-Phase System**

By *Gottfried Heinisch** and *Gerhard Lötsch*

Dedicated to Professor Franz Vieböck on the occasion of his 85th birthday

Protonated π-electron-deficient N-heteroarenes are attacked by nucleophilic carbon radicals with pronounced regioselectivity (Minisci reaction[1]). This procedure is of great preparative value if the heteroarene has only *one* free position that can be attacked by radicals. Otherwise, unless the first substituent introduced by radical reaction deactivates the ring system, polysubstitution occurs to a significant extent, as observed, for example, in homolytic acylations[2] and, especially, in alkoxycarbonylations.[3,4] We have now found a simple method to significantly increase the regioselectivity of radical ethoxycarbonylation which thus provides an easy access to useful heteroaromatic synthetic building blocks.

According to *Minisci* et al.,[3] 4-pyridinecarbonitrile **1** is attacked by ethoxycarbonyl radicals—employing a ratio of **1** : peroxide = 3 : 1—preferentially at the α-carbon atom; in addition to ethyl 4-cyano-2-pyridinecarboxylate **2**, **3** and disubstitution products, which were not further identified, were observed.[5] Although, by reversing the ratio of **1** to peroxide, the conversion could be increased from 19 to 76% (see Table 1), disubstitution predominated as expected; this is shown by the increased formation of the pyridinetricarboxylic acid derivatives **4**–**6**.[6]



1 **2** **3–6**

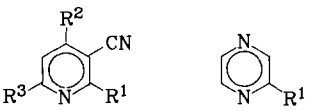
	R^1	R^2	R^3	R^4
3	H	COOEt	H	H
4	COOEt	COOEt	H	H
5	COOEt	H	COOEt	H
6	COOEt	H	H	COOEt

Since, in general, an alkoxycarbonylated heteroarene should exhibit increased lipophilicity and reduced basicity, we investigated (cf. ref. [4]) the homolytic ethoxycarbonylation of protonated **1** in the presence of variable amounts of dichloromethane. In each case, **2** was formed as the main product. As shown in Table 1, it is possible to react **1** practically quantitatively, so that analytically pure **2** can be obtained in >80% yield.[7]

Table 1. Product distribution [mol-%] in the reaction of **1** with the ethoxycarbonyl radical (GLC analysis: 25 m 3% OV 17 WCOT, FID). For reaction conditions, see [7].

Mole ratio **1** : peroxide	3 : 1	1 : 3	1 : 3	1 : 3	1 : 10
Added CH_2Cl_2 [mL]	—	—	30	150	150
1	81	24	6	49	—
2	14	36	80	42	85
Σ **4**, **5**, **6**	3	38 [a]	6	3	4
unidentified products	3	2	9	6	11

[a] 4% **4**, 24% **5** and 10% **6** [6].



7–10 **11, 12**

	R^1	R^2	R^3
7	H	H	H
8	COOEt	H	H
9	H	COOEt	H
10	H	H	COOEt
11	H		
12	COOEt		

Also in the case of 3-pyridinecarbonitrile **7**, it is possible to suppress multiple substitution, even at high conversions, by carrying out the reaction in a two-phase system.[8] The resulting, expected mixture of the three esters **8**,[9] **9**,[10] and **10**[11] can be smoothly separated by chromatography. Similarly, this reaction principle enables the product ratio in the homolytic ethoxycarbonylation of pyrazine **11** (cf. ref. [3]) to be decisively influenced in favor of the monosubstitution; ethyl 2-pyrazinecarboxylate **12**[12] is formed in 80% yield.[8] Furthermore, the reaction of 4-phenethylpyridazine to give ethyl 5-phenethyl-4-pyridazinecarboxylate, which proceeds smoothly under these conditions (70% yield) is noteworthy.[4]

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[7] Experimental procedure: **2**: 30% H_2O_2 (11.3 g, 100 mmol) was added with stirring to ethyl pyruvate (17.3 g, 150 mmol) at −10 to 0°C [3]. This solution was then added with stirring and cooling (−5 to 0°C) to a mixture of **1** (10 mmol), conc. H_2SO_4 (3 g), H_2O (8 g), $FeSO_4 \cdot 7H_2O$ (28 g, 100 mmol), and CH_2Cl_2 (150 mL). After 15 min of further stirring, the resulting mixture was poured into ice water, the phases were separated, and the aqueous phase was exhaustively extracted with CH_2Cl_2. After drying over anhydrous Na_2SO_4, the solvent and excess ethyl pyruvate were removed in vacuo. The spontaneously crystallizing, colorless needles were recrystallized from diethyl ether: Yield: 1.4 g (81%) **2**; mp = 89–93°; correct C,H,N analyses. IR (KBr): 1715 ($\nu_{C=O}$), 2250 cm^{-1} ($\nu_{C\equiv N}$); MS: *m/z* 176 (2%, M^+), 104 (100%); ^{1}H-NMR ($CDCl_3$, 90 MHz): $\delta = 9.00$ (d, 1H, $J = 5$ Hz, H-6), 8.39 (d, 1H, $J \approx 2$ Hz, H-3), 7.75 (dd, 1H, $J = 5$ Hz, 2 Hz, H-5), 4.53 (q, 2H, $J = 7$ Hz, CH_2), 1.48 (t, 3H, $J = 7$ Hz, CH_3).

[8] **8–10**, **12**: 30% H_2O_2 (3.4 g, 30 mmol) was added with stirring to ethyl pyruvate (5.2 g, 45 mmol) at −10 to 0°C [3]. This solution was then added with stirring and cooling (−5 to 0°C) to a mixture of **7** or **11** (10 mmol), conc. H_2SO_4 (3 g), H_2O (8 g), $FeSO_4 \cdot 7H_2O$ (8.3 g, 30 mmol), and CH_2Cl_2 (30 mL).—**8–10**: After a work-up similar to that for **2**, the residue is separated by medium pressure chromatography (Lobar® size B, LiChroprep® Si60, Merck; dichloromethane/ethyl acetate 5:1). Fraction I: 394 mg **10** [11] (22%); fraction II: 580 mg **9** [10] (33%); fraction III: 366 mg **8** [9] (21%).—**12**: After washing the spontaneously crystallizing, pale yellow needles with diisopropyl ether, 1.2 g (80%) of the product is obtained, whose spectroscopic data are identical with those of authentic material [12].

[9] **8**: Structure determination on the basis of the ^{1}H-NMR spectrum [$CDCl_3$, 90 MHz: $\delta = 9.10$–8.90 (m, 1H, H-6), 8.38–8.18 (m, 1H, H-4), 7.83–7.60 (m, 1H, H-5), 4.58 (q, 2H, $J = 7$ Hz, CH_2), 1.49 (t, 3H, $J = 7$ Hz, CH_3)] as well as the hydrolysis in 2N Na_2CO_3 solution to 3-cyano-2-pyridinecarboxylic acid [13].

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Proton Exchange between Arenium Ions and Arenes in the Gas Phase**

By *Dietmar Kuck,* Steen Ingemann, Leo J. de Koning, Hans-Friedrich Grützmacher,* and *Nico M. M. Nibbering*

Proton transfer reactions are known to be extremely fast in general.[1] In the gas phase, they can be studied by modern, time-resolved mass spectrometry. Thus, MIKE spectrometry of metastable ions[2] (time scale 10^{-5} to 10^{-4} s) is used for the investigation of *intra*molecular hydrogen migration reactions, e.g., the proton exchange in protonated α,ω-diphenylalkanes [Eq. (1a)],[3] while, for *inter*molecular exchange reactions,[4] Fourier transform ion cyclotron resonance (FT-ICR) spectrometry[5] is becoming increasingly important (time scale 10^{-3} to 10^{+1} s). We report here on the intermolecular proton exchange [Eq. (1b)] between simple arenium ions and arenes[4c] in the cell of a FT-ICR mass spectrometer[6] (Ar, Ar′ = aryl).

$$ArH^{\oplus}-(CH_2)_n-Ar' \rightleftharpoons Ar-(CH_2)_n-Ar'H^{\oplus} \quad (1a)$$
$$2 \le n \le 20$$

$$ArH_2^{\oplus} + Ar'H \rightleftharpoons ArH + Ar'H_2^{\oplus} \quad (1b)$$

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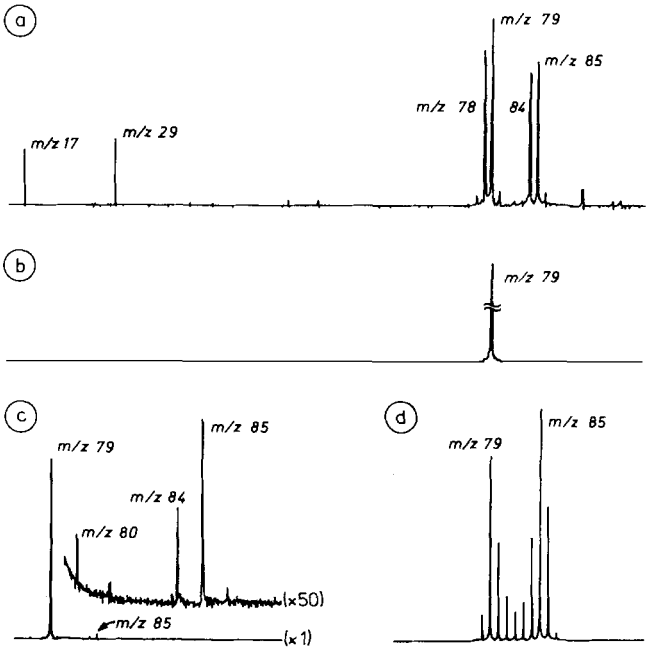


Fig. 1. a) FT-ICR mass spectrum of a mixture of CH_4, C_6H_6, and C_6D_6 [7a]; b) after ejection of all ions except $C_6H_7^{\oplus}$ (*m/z* 79) at the time $t_r = 0$; c) after $t_r = 190$ ms, and d) after $t_r = 6290$ ms.

We generated the benzenium ions $C_6H_7^{\oplus}$ and $C_6HD_6^{\oplus}$ by electron-impact ionization of a mixture of benzene, [D_6]benzene, and methane at 10^{-4} Pa (Fig. 1a).[7a] All ions except $C_6H_7^{\oplus}$ (*m/z* 79) were then removed from the ICR cell by "notch ejection"[8] (Fig. 1b); subsequently, the ion-molecule reactions of the benzenium ions isolated in this way with the C_6H_6/C_6D_6 mixture were followed as a function of time (t_r). Figures 1c and 1d show all ions present in the cell at $t_r = 190$ and 6290 ms, respectively; Figure 2 displays the dependence of the relative abundance of the *product* ions $C_6(H,D)_7^{\oplus}$ on t_r.

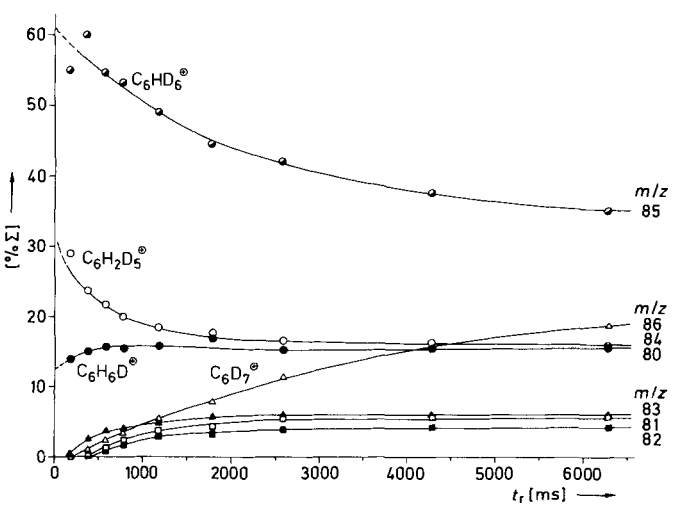


Fig. 2. Relative abundances of the product ions in the system $C_6H_7^{\oplus}/C_6H_6/C_6D_6$ as a function of the reaction time t_r given relative to the sum of all product ions and corrected for naturally occurring ^{13}C.

The measurements allow two conclusions to be drawn:

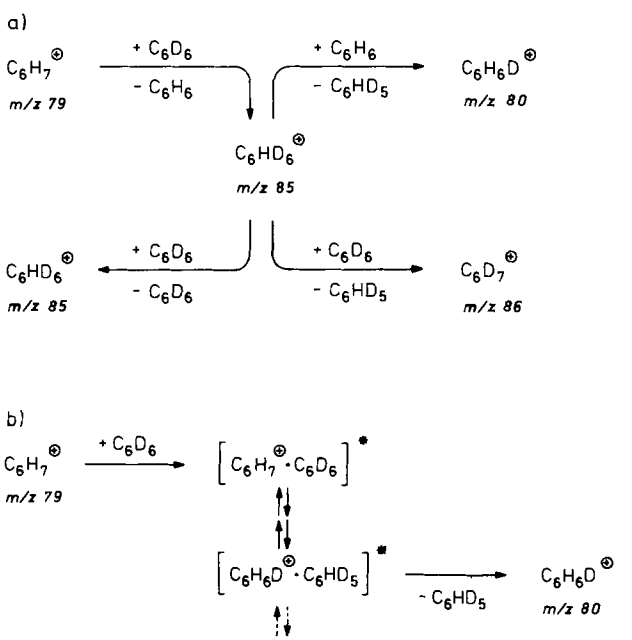
1. The proton exchange between benzenium ions and benzene is a surprisingly slow process (cf., for example, the system $D_3O^{\oplus}/C_6H_6$[4a]). For short reaction times t_r (under

"single collision conditions"), no isotopomers other than $C_6HD_6^{\oplus}$ (simple $H^{\oplus}$ transfer), $C_6H_6D^{\oplus}$ (simple $H^{\oplus}/D^{\oplus}$ exchange), and $C_6H_2D_5^{\oplus}$[9] are formed. The light and the heavy benzenium ions also predominate under "multiple collision" conditions ($t_r \gtrsim 300$ ms).

2. The proton exchange occurs not only by consecutive ion-molecule reactions, but also within the collision complexes (e.g., $[C_6H_7^{\oplus} \cdot C_6D_6]^*$). This follows from extrapolation of the relative abundances of the product ions to $t_r = 0$: The exchange products $C_6H_6D^{\oplus}$ (m/z 80) and $C_6H_2D_5^{\oplus}$ (m/z 84) are already present there (Fig. 2).

Similar results are obtained from the corresponding investigation of the reaction of isolated $C_6HD_6^{\oplus}$ ions with the C_6H_6/C_6D_6 mixture.

A further experiment allows a clear distinction to be made between these two exchange processes (Scheme 1). If the ions $C_6HD_6^{\oplus}$ (m/z 85) are continuously removed from the cell for the entire reaction time,[7b] the formation of all further $C_6(H,D)_7^{\oplus}$ ions is suppressed to the extent that they are formed via $C_6HD_6^{\oplus}$ (Scheme 1a). In contrast, $C_6(H,D)_7^{\oplus}$ ions that arise via $H^{\oplus}/D^{\oplus}$ exchange *within* the collision complexes $[C_6H_7^{\oplus} \cdot C_6D_6]^*$ are *not* suppressed (Scheme 1b). In Table 1 the relative abundances of the ions present in the cell after $t_r = 790$ ms—with and without continuous removal of the ions m/z 85—are compared.



Scheme 1.

Table 1. Ion abundances in the system $C_6H_7^{\oplus}/C_6H_6/C_6D_6$ after $t_r = 790$ ms without (−) and with (+) continuous removal of the ions $C_6HD_6^{\oplus}$ (m/z 85) [a].

m/z	78	79	80	81	82	83	84	85	86
(−)	30	1000	49	8.6	7.9	14.3	70	168	15.8
(+)	30	1000	40	6.4	4.2	10.4	62	0	1.0

[a] ^{13}C-corrected values. The absolute abundance of the ions $C_6H_7^{\oplus}$ (≡ 1000) was constant in both experiments. In order to continuously remove the ions $C_6HD_6^{\oplus}$, a radiofrequency pulse with an amplitude of 2.5 V peak-to-peak was used.

The data confirm that the proton exchange takes place within the collision complex: even upon ejection of the ions m/z 85, all $C_6(H,D)_7^{\oplus}$ isotopomers are formed, albeit in lower absolute abundances. Thus, for example, the abundance of the ions $C_6H_6D^{\oplus}$ (m/z 80) decreases by only a relative 19%; in contrast, the formation of the ions $C_6D_7^{\oplus}$ (m/z 86), which are formed *exclusively* by consecutive ion-molecule reactions (Scheme 1a), is completely suppressed.[10]

The proton exchange between toluenium ions and toluene ($C_7H_8/C_7D_8/CD_4$)[7a] is even slower than that between the lower homologues. Here, too, the exchange takes place partly within the collision complexes (e.g., $[C_7D_9^{\oplus} \cdot C_7H_8]^*$). Thus, a fraction of the $C_7(H,D)_9^{\oplus}$ isotopomers are still formed despite continuous removal of the ions $C_7H_8D^{\oplus}$. A possible reason is that the proton exchange in the collision complex $[C_7H_9^{\oplus} \cdot C_7H_8]^*$ only occurs between positions having the same proton affinity (primarily *para*⇄*para'*), which must lead to a considerable slowing of the reaction compared with the exchange in the collision complex $[C_6H_7^{\oplus} \cdot C_6H_6]^*$.

In fact, no proton exchange is observed for non-degenerate proton-transfer reactions, such as in the system benzene/toluene/methane.[7a] Accordingly, solely proton *transfer* is observed at all t_r in the exothermic direction of the reaction [Eq. (2a)], and no other toluene isotopomers are formed in the endothermic direction of the reaction [Eq. (2b)].[11]

$$C_6D_7^{\oplus} + C_7H_8 \longrightarrow C_6D_6 + C_7H_8D^{\oplus} \quad (2a)$$
$$\not\longrightarrow C_6(H,D)_7^{\oplus} \text{ and } C_7H_7D_2^{\oplus} \text{ etc.}$$
$$C_7H_9^{\oplus} + C_6D_6 \not\longrightarrow C_7(H,D)_9^{\oplus} + C_6(H,D)_6 \quad (2b)$$

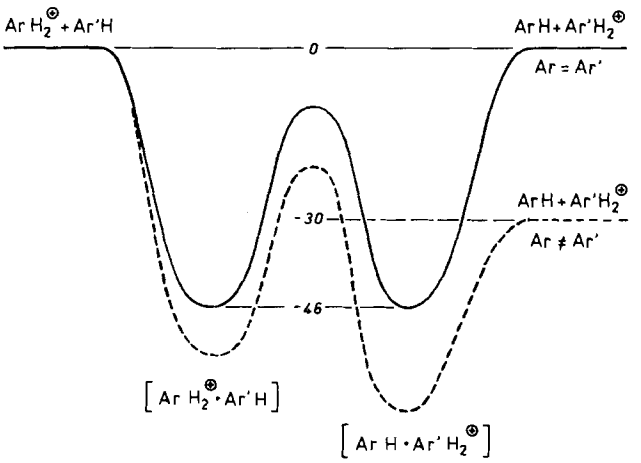


Fig. 3. Energy profiles for the $H^{\oplus}$ transfer between arenium ions and arenes (enthalpy values [11, 13] in kJ/mol^{-1}). (—): thermoneutral $H^{\oplus}$ transfer, $Ar = Ar' = C_6H_5$ or $C_6H_4CH_3$; (---): non-thermoneutral $H^{\oplus}$ transfer, $Ar = C_6H_5$, $Ar' = C_6H_4CH_3$.

These observations can be explained qualitatively by a symmetrical (Ar = Ar') or an asymmetrical (Ar ≠ Ar') double-minimum energy profile[12] (Fig. 3).[13] According to our results, the activation barrier between the minima $[ArH_2^{\oplus} \cdot Ar'H]$ and $[ArH \cdot Ar'H_2^{\oplus}]$ must be relatively high. This is especially noteworthy in comparison with the extremely fast *intra*molecular proton exchange in protonated α,ω-diphenylalkanes and related arenium ions.[3]

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benzenium, 38815-08-6; benzene, 71-43-2; toluenium, 52809-63-9; toluene, 108-88-3.

[1] a) R. P. Bell: *The Proton in Chemistry*, 2nd ed., Cornell University Press, New York 1973; b) M. Eigen, *Angew. Chem. 75* (1963) 489; *Angew. Chem. Int. Ed. Engl. 3* (1964) 1; c) J. E. Crooks in E. Caldin, V. Gold (Eds.): *Proton Transfer Reactions*, Wiley, New York 1975, chap. 6.

[2] a) R. G. Cooks, J. H. Beynon, R. M. Caprioli, G. Lester: *Metastable Ions*, Elsevier, Amsterdam 1973; b) K. Levsen: *Fundamental Aspects of Mass Spectrometry*, Verlag Chemie, Weinheim 1978.

[3] a) D. Kuck, *Int. J. Mass Spectrom. Ion Phys. 47* (1983) 499; b) D. Kuck, W. Bäther, H. F. Grützmacher, *J. Am. Chem. Soc. 101* (1979) 7154; c) D. Kuck, W. Bäther, H. F. Grützmacher, *Int. J. Spectrom. Ion Proc.*, in press.

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[5] a) C. L. Johlman, R. L. White, C. L. Wilkins, *Mass Spectrom. Rev. 2* (1983) 389; b) M. L. Gross, D. L. Rempel, *Science 226* (1984) 261; c) N. M. M. Nibbering, *Nachr. Chem. Tech. Lab. 32* (1984) 1044; d) K. P. Wanczek, *Int. J. Mass Spectrom. Ion Proc. 60* (1984) 11.

[6] The FT-ICR mass spectrometer was built at the University of Amsterdam. a) Electronics: J. H. J. Dawson in H. Hartmann, K. P. Wanczek: *Lecture Notes in Chemistry, Vol. 31*, Springer, Berlin 1982, p. 331; b) software: A. J. Noest, C. W. F. Kort, *Comput. Chem. 6* (1982) 111, 115; c) general methods of measurement: J. C. Kleingeld, N. M. M. Nibbering, *Org. Mass Spectrom. 17* (1982) 136; S. Ingemann, N. M. M. Nibbering, S. A. Sullivan, C. H. DePuy, *J. Am. Chem. Soc. 104* (1982) 6520.

[7] a) Experimental conditions: The magnetic field strength was 1.4 T in all experiments. The cell of the FT-ICR mass spectrometer [6] was filled with $\approx 1 \cdot 10^{-5}$ Pa of each of the two arenes and with $\approx 8 \cdot 10^{-5}$ Pa of methane. $CH_5^{\oplus}$ and $C_2H_5^{\oplus}$ ions, among others, were generated by an electron pulse (20 eV, 5 ms); they protonated the arenes in the following 200 ms to give $ArH_2^{\oplus}$ and $Ar'H_2^{\oplus}$. Subsequently, all ions except $ArH_2^{\oplus}$ (or $Ar'H_2^{\oplus}$) were removed from the cell by "notch ejection" [8] (radiofrequency pulse with a scan length of 10 ms); then, in the following reaction time ($t_r = 0$ to $t_r = 6290$ ms), the ions formed from $ArH_2^{\oplus}$ (or $Ar'H_2^{\oplus}$), ArH and Ar'H were measured. b) By applying a radiofrequency pulse for *m/z* 85 (amplitude 3.5 V peak-to-peak) during the entire reaction time t_r, all $^{12}C_6HD_6^{\oplus}$ ions were removed from the cell within $\lesssim 300$ µs after their formation. During this time, no collisions with molecules of the gas mixture took place (average rate of collision $\approx 10\ s^{-1}$).

[8] a) A. J. Noest, C. W. F. Kort, *Comput. Chem. 7* (1983) 81; b) J. C. Kleingeld, N. M. M. Nibbering, *Tetrahedron 39* (1983) 4193; c) A. G. Marshall, T. C. Lin Wang, T. Lebatnan Ricca, *Chem. Phys. Lett. 105* (1984) 233.

[9] A fraction of the ions *m/z* 84 are $C_6D_6^{\oplus\odot}$ molecular ions formed by charge exchange (cf. *m/z* 78, $C_6H_6^{\oplus}$; Table 1).

[10] The ions $^{13}C^{12}C_5HD_6^{\oplus}$ (*m/z* 86, rel. abundance 0.066 [$^{12}C_6HD_6^{\oplus}$] were *not* ejected and therefore generated ca. 1/16th of the $C_6D_7^{\oplus}$ ions formed without ejection of *m/z* 85.

[11] $PA(C_6H_6) = 777$ kJ mol^{-1}, $PA(C_7H_8) = 808$ kJ mol^{-1} (PA = proton affinity); D. H. Aue, M. T. Bowers in M. T. Bowers (Ed.): *Gas Phase Ion Chemistry, Vol. 2*, Academic Press, New York 1979, p. 33.

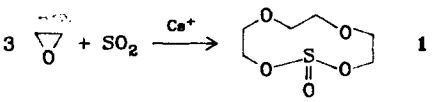
[12] a) M. Jasinski, J. I. Brauman, *J. Am. Chem. Soc. 102* (1980) 2906; b) H. Zimmermann, *Angew. Chem. 76* (1964) 1; *Angew. Chem. Int. Ed. Engl. 3* (1964) 157.

[13] The proton-bound dimer $[C_6H_7^{\oplus} \cdot C_6H_6]$ is more stable by $\Delta H = 46$ kJ mol^{-1} than $C_6H_7^{\oplus}$ and C_6H_6; M. Mautner, P. Hamlet, E. P. Hunter, F. H. Field, *J. Am. Chem. Soc. 100* (1978) 5466.

Reaction of Ethylene Oxide with Sulfur Dioxide in the Presence of Cesium Ions: Synthesis of 1,3,6,9,2λ⁴-Tetraoxathia-2-cycloundecanone

By *Herbert W. Roesky** and *Hans Georg Schmidt*

Cyclic homologues of ethylene oxide have attracted great interest because of their unusual complexation properties in the presence of alkali metal ions and other cations.[1] Their properties can be changed by incorporation of further heteroatoms. Reactions of ethylene oxide and sulfur dioxide in the presence of catalysts have been well documented.[2] Ethylene sulfite is formed. We have now found that the reaction of ethylene oxide, sulfur dioxide,



and cesium salts[3] at room temperature leads to higher membered ring compounds, of which the title compound **1** has been isolated in 20% yield as a white solid.[4]

In the field ion mass spectrum, M^+ of **1** (*m/z* 196) is observed as sole peak. **1** polymerizes on storage at room temperature for several weeks in a sealed flask. Poor quality single crystals were obtained from ethylene oxide and examined X-ray crystallographically.[5]

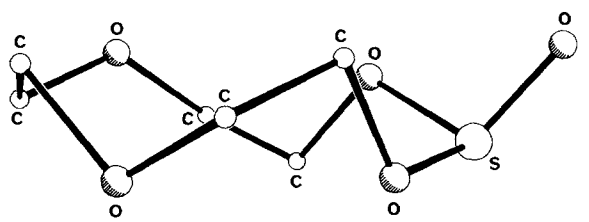


Fig. 1. Crystal structure of **1**.

The structure contains two independent conformationally isomeric molecules of **1** (Fig. 1). A final refinement was not possible owing to disorder and/or thermal motions.[6]

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[1] C. J. Pedersen, *J. Am. Chem. Soc. 89* (1967) 7017; J. Dale, G. Borgen, K. Daasvatn, *Acta Chem. Scand. B 28* (1974) 378.

[2] Review: G. Dittus in *Houben-Weyl, Methoden der Organischen Chemie, Bd. 6/3*, 4th ed., Thieme, Stuttgart 1965, p. 482; Farbwerke Hoechst AG, Brit. Pat. 753872 (August 1, 1956); *Chem. Abstr. 51* (1957) 5821; Chemische Werke Hüls AG, Brit. Pat. 783561 (September 25, 1957); *Chem. Abstr. 52* (1958) 5455; G. M. Gibson, C. R. Heald, D. J. Hartley, Brotherton and Co. Ltd., Brit. Pat. 844104 (August 10, 1960); *Chem. Abstr. 55* (1961) 11308; W. A. Rogers, Jr., J. E. Woekst, R. M. Smith, Dow Chemical Co., U. S. Pat. 3022315 (February 20, 1962); *Chem. Abstr. 57* (1962) 5802; A. J. Shipman, ICI Ltd., Brit. Pat. 898630 (June 14, 1962); *Chem. Abstr. 57* (1962) 13697; H. Distler, G. Dittus, BASF AG, DBP 1217970 (June 2, 1966); *Chem. Abstr. 65* (1966) 7189; H. Distler, BASF AG, DBP 1223397 (August 1966); *Chem. Abstr. 65* (1966) 20008.

[3] F. Vögtle, F. Ley, *Chem. Ber. 116* (1983) 3000.

[4] C_2H_4O (25 g, 570 mmol) and SO_2 (10 mL) were condensed into two 1.5 g (4.65 mmol) batches of $CsAsF_6$ in a Schlenk apparatus under vacuum. The mixtures were allowed to warm to room temperature and stirred for 48 h. The volatile products SO_2, C_2H_4O and dioxane were removed at 20 mbar. Both batches were then combined and distilled in a vacuum. Three fractions were obtained: 1) B.p. 38 °C/0.05 mbar, $C_2H_4SO_3$, yield 1.9 g (1.5%); 2) B.p. 38-65 °C/0.05 mbar, mixture of $C_2H_4SO_3$ and SO_2 with two and three ethylene oxide molecules, 0.8 g; 3) B.p. 95 °C/0.01 mbar, **1**, yield 15 g (20.2%), m.p. 41 °C.—IR (Nujol): $\nu = 1300$, 1248, 1204, 1150, 1130, 1105, 1080, 1015, 905, 870 cm^{-1}, and further bands.

[5] $P2_1/c$, $a = 11.873(4)$, $b = 18.219(6)$, $c = 8.981(3)$ Å; $\beta = 112.11(1)°$; $\rho_{calc} = 1.448$ g/cm^3 with $M = 196.22$ and $Z = 8$; $T = -40$ °C, $2\theta < 40°$, direct methods.

[6] G. M. Sheldrick, M. Noltemeyer, private communication.

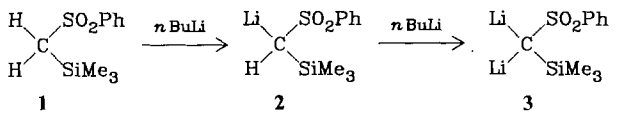
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Dilithio(phenylsulfonyl)trimethylsilylmethane: Synthesis, $^{13}C/^{1}H$-NMR Characterization, and Lithium-Titanium Exchange**

By *Jürgen Vollhardt, Hans-Joachim Gais,** and *Karl L. Lukas*

Dilithioalkyl sulfones of the type $Li_2[C(R^1)SO_2R^2]$ are, as sulfonyl derivatives of n,n-dilithioalkanes,[1] of particular interest, on the one hand because of their structure in solution and in the crystalline state—whereby aggregation, number of Li atoms bound to the C atom, and its coordination geometry are of paramount importance[2]—and, on the other, because of their synthetic potential.[3] The dilithiation of alkyl(aryl) sulfones with *n*-butyllithium (*n*BuLi) has already been repeatedly described,[4] but a direct spectroscopic proof for the formation of the dilithio derivatives has not, as yet, been reported; the formation of α,α-disubstituted alkyl sulfones during the deuteration and alkylation is, according to our findings with α,*o*- and α,α-dilithiated allyl phenyl sulfones,[3] inconclusive. We have now been able to synthesize the title compound **3**, the first crystalline dilithioalkyl sulfone that is soluble in inert solvents. We have also characterized **3** by ^{13}C- and ^{1}H-NMR spectroscopy, and been able to convert it by lithium-titanium exchange into a novel organotitanium compound suitable for carbonyl olefination.[3]

Lithiation of the trimethylsilyl sulfone **1**[5] with one equivalent of *n*BuLi in tetrahydrofuran (THF) at −70°C leads quantitatively to the readily soluble lithioalkyl sulfone **2**[6] (Scheme 1), whose ^{1}H- and ^{13}C-NMR spectra characteristically differ from those of **1** (Table 1). Proof of the structure of **2** is provided, inter alia, by the upfield shift of $\Delta\delta = 1.65$ of the ^{1}H-NMR signal of H-7 and that of $\Delta\delta = 14.7$ of the ^{13}C-NMR signal of C-7;[7] remarkably, the ^{13}C-NMR signal of C-1 is shifted downfield by $\Delta\delta = 10.9$.

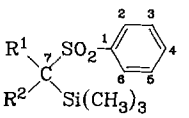


1 **2** **3**

Scheme 1

Further direct lithiation of **2** to the dilithioalkyl sulfone **3** was achieved smoothly with one equivalent of *n*BuLi in THF (−70°C→0°C) without prior *o*-metalation of the phenyl ring and subsequent transmetalation[3,8] (Scheme 1). On cooling the solution, **3** precipitates as pale yellow crystals of the composition $\mathbf{3}(thf)_2$. It is, e.g., readily soluble in THF, and stable under argon at 25°C. The ^{13}C-NMR signal of C-7 at $\delta = 50.5$ (Table 1) is broadened because of dynamic processes[9] and the ^{7}Li-^{13}C coupling;[10] interestingly, it is shifted by $\Delta\delta = 16.7$ downfield compared to that of **2**. The observed change in the ^{13}C chemical shift on going from the H_2- via the H,Li- to the Li_2-compound is found 'qualitatively' in the series methane, lithiomethane, dilithiomethane.[1b] Comparison of the ^{13}C- and ^{1}H-NMR spectra of **1**, **2**, and **3** also reveals an increasing downfield shift of the ^{13}C-NMR signal and an increasing upfield shift of the ^{1}H-NMR signal of the trimethylsilyl group (Table 1). The crystallinity and solubility of **3** should facilitate further investigations of its structure in the crystal and in solution, e.g. by low-temperature ^{13}C- and ^{6}Li-NMR spectroscopy[10,11] on [$^{6}Li_2$/7-^{13}C]-**3**.

Table 1. ^{1}H- and ^{13}C-NMR data of **1**, **2**, and **3**.



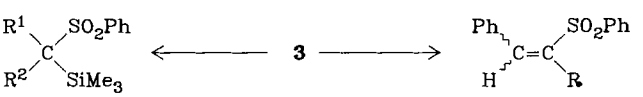
1, $R^1 = R^2 = H$
2, $R^1 = Li$, $R^2 = H$
3, $R^1 = R^2 = Li$

Cpd.	^{1}H-NMR [a]			
	H-2,6	H-3,4,5	H-7	$Si(CH_3)_3$
1	7.85–7.92 (m)	7.48–7.62 (m)	2.85 (s)	0.22 (s)
2	7.94–8.02 (m)	7.18–7.28 (m)	1.20 (s)	−0.05 (s)
3	7.70–8.00 (m)	7.00–7.30 (m)	—	−0.30 (s)

Cpd.	^{13}C-NMR [b]				
	C-1	C-2,3,5,6	C-4	C-7	$Si(CH_3)_3$
1	145.4 (s)	129.8, 127.5 (d)	133.4 (d)	48.5 (t)	−0.3 (q)
2	156.3 (s)	128.0, 126.1 (d)	128.5 (d)	33.8 (d)	2.8 (q)
3	157.5 (s)	127.7, 126.3 (d)	127.6 (d)	50.5 (bs)	4.8 (q)

[a] 300-MHz NMR spectrum in [D_8]THF at ≈25°C with [H,D]THF as internal standard, δ values. [b] 75.47-MHz NMR spectra in [D_8]THF at ≈35°C with [D_8]THF as internal standard, δ values.

Deuteration of **3** with DCl/D_2O/THF (−30°C) affords the D_2-compound **4a** in 95% yield (≥98% deuteration), while alkylation with methyl iodide (THF, −70°C) leads to formation of 2-phenylsulfonyl-2-trimethylsilylpropane, **4b** (86%), and cycloalkylation with 1,4-dibromobutane (THF, 0°C) to formation of the cyclopentyl sulfone **4c** (81%) (Scheme 2); **4c** is desilylated with nBu_4NF in THF to cyclopentylphenyl sulfone (98%). Peterson olefination of **3** with benzaldehyde (−70°C→0°C) and reaction with DCl/D_2O/THF furnishes the styryl sulfone **5a**, deuterated in the 1-position (55%, 95% deuteration); the trimethylsilyl styryl sulfone **5b** is formed as byproduct (4%, Scheme 2).



4a, $R^1 = R^2 = D$
4b, $R^1 = R^2 = Me$
4c, $R^1, R^2 = -(CH_2)_4-$

5a, R = D
5b, R = $SiMe_3$

Scheme 2.

The lithium-metal exchange of **3** with halides of the early transition metals opens up an entry to novel functionalized organometal compounds.[3] Thus, **3** can be titanated with one equivalent of diisopropoxytitanium dichloride in THF (−90°C→−35°C); the organotitanium compound thus formed has hitherto only been generated as a deep-red THF-solution. In the titanation of [7-^{13}C]-**3**, the Li–Ti exchange manifests itself ^{13}C-NMR spectroscopically in the disappearance of the singlet of C-7 at $\delta = 50.5$; a new singlet appears at $\delta = 173$(!).

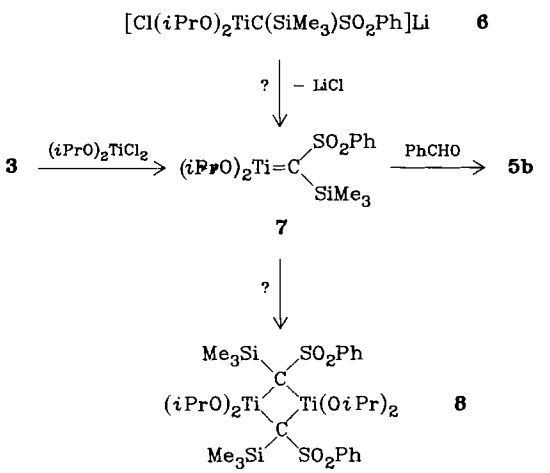
The titanium species undergoes no further reaction with methyl iodide.[3] On the other hand, on reaction with benzaldehyde in THF at −35°C, the product expected to be

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formed in a carbonylolefination, the trimethylsilylated styryl sulfone **5b**[12] is obtained in 85% yield ($E:Z=2:1$). However, the spectroscopic and chemical findings are still inadequate for differentiation between the lithium-titanium compound **6**, the alkylidenetitanium compound **7**, and the dimer **8** (Scheme 3).



Scheme 3.

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CAS Registry numbers:
1, 17872-92-3; **2**, 97351-67-2; **3**, 97351-68-3; **4a**, 97351-69-4; **4b**, 91787-39-2; **4c**, 97351-71-8; **5a**, 97351-70-7; (*E*)-**5b**, 74632-96-5; (*Z*)-**5b**, 74632-95-4; $(i\text{-PrO})_2TiCl_2$, 762-99-2; PhCHO, 100-52-7; cyclopentylphenylsulfone, 14633-46-6.

[1] a) K. Ziegler, K. Nagel, M. Patheiger, *Z. Anorg. Allg. Chem. 282* (1955) 345; b) J. A. Gurak, J. W. Chinn, Jr., R. J. Lagow, H. Steinfink, C. S. Yannoni, *Inorg. Chem. 23* (1984) 3717 (solid-state ^{13}C-NMR spectra of CH_3Li and CH_2Li_2); c) A. Maercker, M. Theis, *Angew. Chem. 96* (1984) 990; *Angew. Chem. Int. Ed. Engl. 23* (1984) 995, and references cited therein.

[2] P. von R. Schleyer, *Pure Appl. Chem. 56* (1984) 151, and references cited therein; S. Wolfe, L. A. LaJohn, D. F. Weaver, *Tetrahedron Lett. 25* (1984) 2863, and references cited therein.

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[6] J. Vollhardt, *Diplomarbeit*, Technische Hochschule Darmstadt 1984; S. V. Ley, N. S. Simpkins, *J. Chem. Soc. Chem. Commun. 1983*, 1281.

[7] G. Chassaing, A. Marquet, *Tetrahedron 34* (1978) 1399.

[8] **1**, which was generated by dilithiation of **4a** and subsequent protonation, does not contain deuterium in the *o*-position of the phenyl ring (cf. also 3).

[9] Detected by temperature-dependent ^{13}C-NMR spectroscopic examination of [$^6Li_2$/7-^{13}C]-**3**; S. Braun, H.-J. Gais, J. Vollhardt, unpublished.

[10] G. Fraenkel, A. M. Fraenkel, M. J. Geckle, F. Schloss, *J. Am. Chem. Soc. 101* (1979) 4745.

[11] D. Seebach, J. Gabriel, R. Hässig, *Helv. Chim. Acta 67* (1984) 1083, and references cited therein.

[12] *Z*-**5b**: m.p. 85–87 °C; ^1H-NMR (300 MHz, $CDCl_3$): $\delta=0.44$ (s, 9H), 7.08–7.20 (m, 7H), 7.26–7.40 (m, 3H), 7.40 (s, 1H, H-2).—*E*-**5b**: m.p. 80–82 °C; ^1H-NMR (300 MHz, $CDCl_3$): $\delta=0.02$ (s, 9H), 7.26–7.35 (m, 2H), 7.36–7.45 (m, 3H), 7.88–7.98 (m, 3H), 8.42 (s, 1H, H-2).

Synthesis and Structure of the $[Ni_{38}Pt_6(CO)_{48}H_{6-n}]^{n-}$ (n = 5, 4) Ions: Ni-Pt Clusters as Models for "Cherry" Crystallites

By *Alessandro Ceriotti, Francesco Demartin, Giuliano Longoni,* Mario Manassero,* Mario Marchionna, Gianluigi Piva,* and *Mirella Sansoni*

We report the synthesis and structural characterization of the series of clusters **1a**—**d** having the general formula $[Ni_{38}Pt_6(CO)_{48}H_{6-n}]^{n-}$. These four compounds have all been isolated in a crystalline state and the structures of two, **1b** and **1c**, have been determined by X-ray diffraction studies. They constitute the highest nuclearity carbonyl clusters that have presently been fully characterized by X-ray analysis, and preliminary measurements suggest an unusual magnetic behavior.

$[Ni_{38}Pt_6(CO)_{48}H_{6-n}]^{n-}$ **1**
a, n = 3; **b**, n = 4; **c**, n = 5; **d**, n = 6

In spite of their molecular complexity, the synthesis of the cluster ions **1** is rather straightforward. Variable mixtures of **1b** and **1c** are obtained by reaction of the nickel cluster **2** in acetonitrile with either $PtCl_2$ or K_2PtCl_4 in a ca. 1:1 molar ratio; their formation probably conforms to the stoichiometry of Equation (1).

$$\underset{\mathbf{2}}{7[Ni_6(CO)_{12}]^{2-}} + 6\,Pt^{2+} \longrightarrow \underset{\mathbf{1d}}{[Ni_{38}Pt_6(CO)_{48}]^{6-}} + 2\,Ni^{2+} + 2\,Ni(CO)_4 + 28\,CO \quad (1)$$

$[Ni_{12-x}Pt_x(CO)_{21}H_{4-n}]^{n-}$ **3** $\qquad$ $[Ni_9(CO)_{18}]^{2-}$ **4**

1d is successively protonated to **1c** and **1b** [Eq. (2)] owing to the intrinsic acidity of the platinum-complex starting material. The clusters **1** can be cleanly separated from impurities (mainly the carbonyl clusters **3**[1] and **4**[2] and unreacted starting material **2**[3]) owing to the differential solubility of their tetrasubstituted ammonium or phosphonium salts in organic solvents. They are generally obtained in up to 80% yield (based on platinum) with the remaining 20% being due to the presence of variable amounts of **3** and **4** as well as some platinum metal. The salts of **1** are readily soluble in acetonitrile, only moderately soluble in acetone, and sparingly soluble or insoluble in tetrahydrofuran, alcohols, and nonpolar organic solvents.

$$\mathbf{1a} \underset{H^+}{\overset{CH_3CN}{\rightleftharpoons}} \mathbf{1b} \underset{H^+}{\overset{CO}{\rightleftharpoons}} \mathbf{1c} \underset{H_2O}{\overset{OH^-}{\rightleftharpoons}} \mathbf{1d} \quad (2)$$

Owing to the occurrence in acetonitrile solution of a rapid protonation-deprotonation equilibria [Eq. (2)], the mixture of the ions **1a**—**d** is easily converted into one of its components by controlled addition of acid or base. The derivatives **1b** and **1c** have been isolated in a crystalline state with several tetrasubstituted ammonium or phosphonium counterions by precipitation with diisopropyl ether from acetonitrile solution.[4] Isolation of **1a** is hampered by ready deprotonation of its salts on dissolution both in acetone and acetonitrile. All the crystalline sam-

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ples examined gave very poor X-ray diffraction patterns and underwent rapid decay, probably owing to loss of clathrated molecules of solvent: the only exception was the $[AsPh_4]_4$ salt of **1b**. Although this sample allowed full determination of the metal framework of the cluster, the carbonyl groups and the cations could be localized only in part and exhibited very high thermal factors. The *R* structure factor progressed to a limiting value of 0.13.[5]

An X-ray analysis of a salt of **1c** containing a mixture of tetraphenylarsonium and tetrabutylammonium counterions gave the stoichiometry $[AsPh_4]_2[NBu_4]_3$ **1c**, and enabled full elucidation of the structure.[6] The combination of spherical $[AsPh_4]^+$ and spider-like $[NBu_4]^+$ counterions gave rise to good diffraction patterns and prevented rapid decay under radiation, probably because the counterions fill the holes left in the crystal lattice by the packing of big anionic molecules such as **1c**.

The unit cell of **1c** contains two independent anion molecules, which have the same structure and, after refinement, show almost identical parameters. The $Ni_{38}Pt_6$ framework in **1c** and **1b** consists of an inner octahedron of six platinum atoms fully encapsulated in a ν_3 octahedron of 38 nickel atoms (Fig. 1). The metal cluster has the same structure as a fragment of a cubic close-packed (ccp) metal lattice, and is closely related to that of the homonuclear cluster ion $[Pt_{38}(CO)_{44}H_x]^{2-}$.[7,8] The twelve Pt–Pt bond distances have a mean value of 2.719 Å; the 48 Ni–Pt bonds connecting the inner Pt_6 to the outer Ni_{38} octahedron are between 2.510 and 2.764 Å (mean value 2.630 Å). The 108 surface Ni–Ni bonds also vary in length (2.393–2.762 Å, mean value of 2.580 Å).

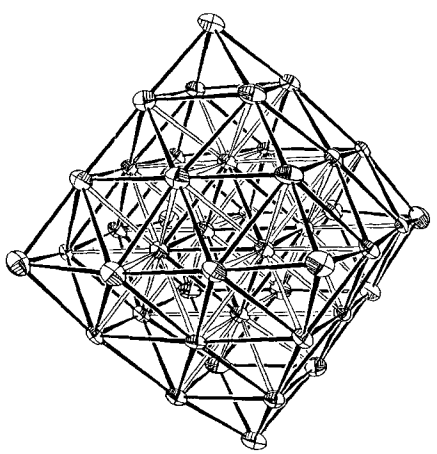


Fig. 1. ORTEP drawing of the structure of the metal framework of **1b** and **1c** in the crystal [5, 6].

The metal framework of both **1b** and **1c** provides a molecular model of bimetallic "cherry" crystallites.[9] This is further supported by the existence of a series of clusters having the more general formula $[Ni_{44-x}Pt_x(CO)_{48}H_{6-n}]^{n-}$ $(x \geqslant 6)$. We have also found an analogous series of dodecanuclear cluster ions, $[Ni_{12-x}Pt_x(CO)_{21}H_{4-n}]^{n-}$ $(x = 2, 3;\ n = 2\text{-}4)$.[1]

In both the independent molecules of **1c** in the crystal, the O_h idealized symmetry of the metal framework is reduced to a D_{3d} idealized symmetry by the presence of the 48 carbonyl ligands (18 terminal, 12 edge-bridging, and 18 face-bridging); as a result, the two opposite ν_3 triangular faces differ from the other six. The cluster **1c** with all its CO groups is shown in Figure 2.

In spite of the fact that the cluster ions **1a–c** have a relatively simple spin system, we have been so far unable to detect any ^{195}Pt- or ^1H-NMR signal due to the Pt_6 metal core or the protons. Preliminary measurements indicate

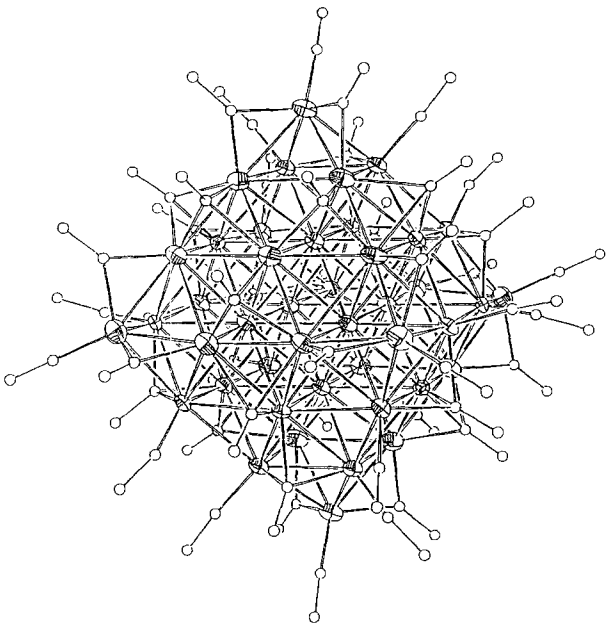


Fig. 2. ORTEP drawing of the structure of **1c** in the crystal of $[AsPh_4]_2[NBu_4]_3$ **1c** [6].

that **1b** and **1c** show peculiar magnetic behavior.[10] Unusual magnetic behavior of small metal particles,[11] and also of an even-electron molecular cluster, $[H_2Os_{10}(CO)_{24}C]$,[12] have already been documented. Such magnetic behavior could be the reason for the present failure in observing ^{195}Pt- and ^1H-NMR signals, as is also the case for platinum crystallites.[13]

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[4] IR (ν(CO)) **1a** (acetone): 2030 (s), 1890 (ms), 1875 (sh); **1b** (acetone): 2010 (s), 1875 (ms), 1858 (sh); **1c** (acetonitrile): 2000 (s), 1860 (ms), 1845 (sh); **1d** (acetonitrile): 1990 (s), 1845 (ms), 1830 (sh) cm^{-1}.
[5] $[AsPh_4]_4$ **1b**: $P2_1/n$, $a = 19.043(6)$, $b = 18.778(7)$, $c = 29.855(12)$ Å, $\beta = 96.32(4)°$, $V = 10611(18)$ Å^3, $Z = 2$, $R = 0.13$, $R_w = 0.19$ for 1924 absorption- and decay-corrected reflections having $I > 3\sigma(I)$. $F(000) = 5988$.
[6] $[AsPh_4]_2[NBu_4]_3$ **1c**: $M = 6241.2$, $P2_1/c$, $a = 30.927(5)$, $b = 31.881(7)$, $c = 19.045(3)$ Å, $\beta = 91.09(2)°$, $V = 18775(10)$ Å^3, $\rho_{calcd.} = 2.208$ g cm^{-3} for $Z = 4$, $\mu(Mo_{K\alpha}) = 86.4$ cm^{-1}, $F(000) = 12064$. The structure was solved by direct methods and refined by block matrix least squares on the basis of 5578 independent absorption and decay corrected reflections having $I \geq 3\sigma(I)$. $R = 0.045$, $R_w = 0.060$. Further details of the crystal structure investigation are available on request from the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW (England) on quoting the names of the authors and the journal citation.
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Reactive Metabolites of Carcinogenic Polycyclic Hydrocarbons: Synthesis and Trapping Reaction of 9-Hydroxybenzo[*a*]pyrene 4,5-Oxide**

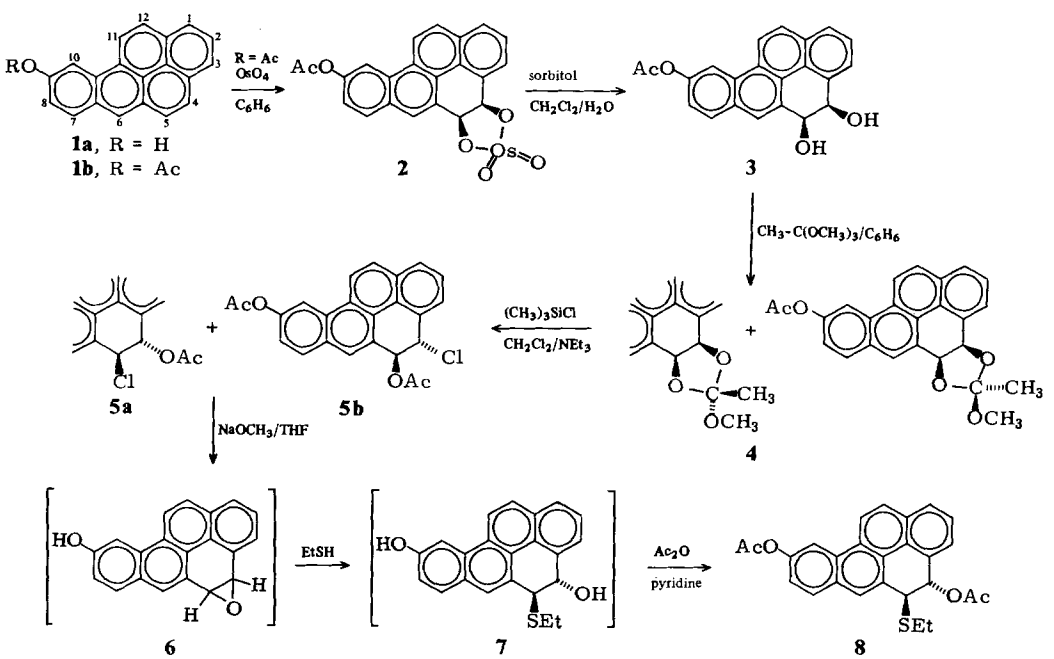
By *Werner Bochnitschek, Albrecht Seidel, Horst Kunz,** and *Franz Oesch*

The carcinogenic activity of benzo[*a*]pyrene is dependent on metabolic activation by cytochrome P-450 monooxygenases[1] and was hitherto directly correlated with the DNA binding products of 7,8-dihydro-7,8-benzo[*a*]pyrenediol 9,10-oxide.[2] However, one other metabolite, 9-hydroxybenzo[*a*]pyrene (**1a**) also showed mutagenic activity in the Ames test[3] and bound with metabolic activation to nucleic acids in vivo.[4] The 4,5-oxide of **1** was regarded as the reactive species.[5] Supporting evidence for this hypothesis however was previously lacking, since all attempts to synthesize this epoxide with a free phenolic hydroxy group failed.[6]

We now describe a method for the synthesis of the ultimate carcinogen, the title compound **6**, and its trapping reaction with ethanethiol (Scheme 1). The acetate **1b** is converted with osmium tetroxide into the osmate **2** (93% yield). Subsequent transesterification with sorbitol in aqueous $NaHCO_3$/dichloromethane gives the enantiomeric *cis*-diols **3** in 54% yield. Remarkably, H-4 and H-5 appear as one singlet ($\delta = 5.15$) in the ^{1}H-NMR spectrum of **3**. Reaction of **3** with trimethyl orthoacetate affords a mixture of the two diastereomers **4**, which are purified by flash chromatography and characterized by UV, mass, and NMR spectroscopy. H-4 together with H-5, as well as the OCH_3- and CH_3-protons, give rise to a singlet for both the *exo*- and *endo*-methyl isomers ($\delta = 5.73$, 2.60, 1.79, and 5.82, 3.67, 1.58, respectively).

Reaction of the orthoacetate **4** with trimethylchlorosilane proceeds smoothly in dichloromethane/triethylamine, affording the isomeric *trans*-acetoxychloro compounds **5a** and **5b** (total yield 74% after flash chromatography). Decisive for the success of the synthesis is that no aromatization occurs in this last step by cleavage of hydrogen chloride or acetic acid. The mixture of the isomers **5a** and **5b** [m.p. 163 °C; MS: *m/z* 404 (M^+)] is characterized by its ^{1}H-NMR spectrum, which shows two doublets at $\delta = 6.59$–6.49 ($J = 3.2$ Hz) for H-4/H-5 geminal to OAc, and two doublets at $\delta = 5.68$–5.58 ($J = 3.2$ Hz) for H-4/H-5 geminal to Cl.

Reaction of **5** with sodium methoxide leads to simultaneous cleavage of the acetate and an intramolecular S_N reaction to give the desired 9-hydroxybenzo[*a*]pyrene 4,5-oxide **6**. The arene oxide **6** is unstable. Its formation is clearly detectable by thin-layer chromatography [color reagent: 4-(*p*-nitrobenzyl)pyridine].[7] Since **6** cannot be isolated as such, it is trapped with ethanethiol. The ensuing nucleophilic ring-opening reaction simulates a natural detoxification reaction for arene oxides.[8] The primary adduct **7** is further converted with acetic anhydride/pyridine into the diacetate **8**, which is isolated chromatographically on silica gel (hexane/ethyl acetate 2 : 1) in 47% yield [m.p. 172 °C, MS: *m/z* 430 (M^+)]. According to the 400-MHz ^{1}H-NMR spectrum only one isomer of 5-ethylthio-4,5-dihydro-4,9-benzo[*a*]pyrenediyl diacetate **8** is present. It follows, therefore, that both "chlorohydrin acetates" **5** react via a common intermediate **6** to give the adduct **7**. The coupling constant ($J_{4/5} = 2.5$ Hz) is consistent with a dipseudoequatorial arrangement of the two benzylic protons H-4 ($\delta = 6.44$) and H-5 ($\delta = 4.74$) in **8** and thus with the subsequent *trans* opening of the epoxide ring of **6**. Furthermore, ^{1}H-NMR NOE difference measurements show



Scheme 1. Synthesis of **6** from the acetate **1b**, trapping reaction of **6** with ethanethiol to give **7** and its conversion into the diacetate **8**. THF = tetrahydrofuran. In each case only one (arbitrarily chosen) enantiomer of the compounds **2**, **3**, **4**, **5a** and **5b**, and **7** and **8** is shown.

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that the thiolate ion attacks only the 5-position of **6**. In contrast, this sulfur nucleophile reacts with unsubstituted benzo[*a*]pyrene 4,5-oxide both in the 4- as well as in the 5-position.[9] The instability and the unequivocal nucleophilic ring-opening of **6** support the hypothesis[10] that arene oxides are selectively activated by phenolic hydroxy functions.

The reaction sequence described here opens the way for the in vivo detection of adducts of **6** (to DNA or detoxifying nucleophiles) and their structural elucidation.

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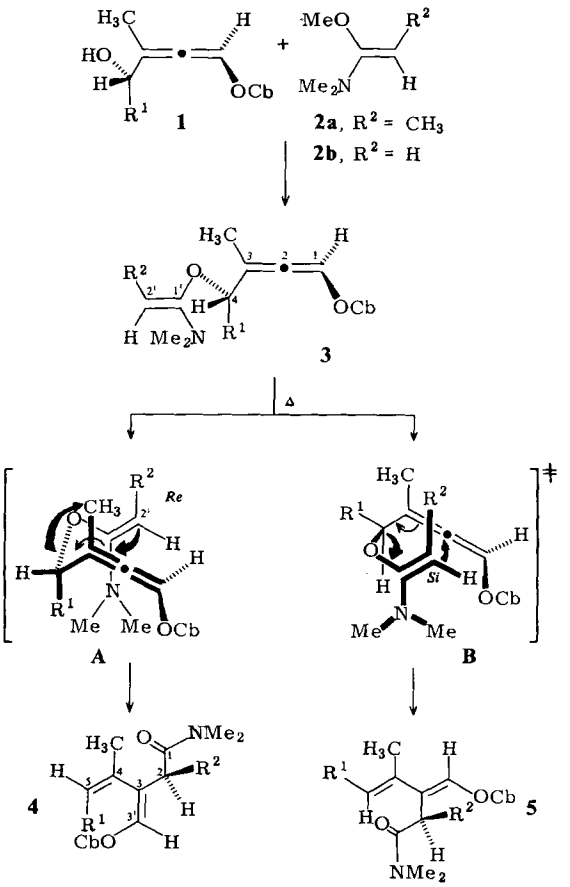
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Allene Claisen Rearrangement with 1,4-Chirality Transfer**

By *Dieter Hoppe,* Charlotte Gonschorrek, Ernst Egert,** and *Dieter Schmidt*

[3,3]-Sigmatropic rearrangements of derivatives of chiral allyl alcohols often proceed with transfer of chirality—and the Claisen rearrangement is no exception; as a rule, the direction of asymmetric induction is predictable from the most favorable chair conformation of the transition state and the given topicity of the target atoms for migration.[1] Claisen rearrangements with α-allenyl alcohols that lead to 1,3-alkadienes are already well documented,[2] yet their stereochemical course has so far never been investigated.

We recently described a highly regio- and stereoselective entry to diastereomerically pure allenes[3,4] such as **1** and have now investigated their amide Claisen rearrangement.[5,6] An allene like **1** and a ketene *N,O*-acetal **2** ($R^2 \neq H$) should react to give the (*Z*)-configurated[6] intermediate **3**, whose [3,3]-sigmatropic rearrangement can proceed via four stereotopically different transition states. Which route is actually followed is revealed by the product: The chair-like transition states **A** and **B** lead to **4** (2*S*,3*Z*,4*Z*) and **5** (2*R*,3*E*,4*E*), respectively, whereas the boat-like transition states (not shown) lead to the enantiomers *ent*-**4** (2*R*,3*Z*,4*Z*) and *ent*-**5** (2*S*,3*E*,4*E*), respectively (Scheme 1).



Scheme 1. Cb = C(=O)N*i*Pr$_2$. R^1 = CH_3.

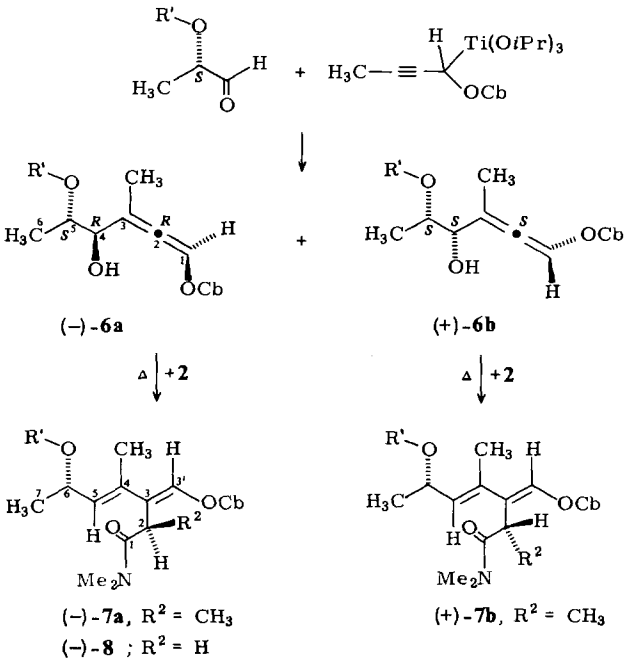
Thus, a knowledge of the absolute configuration of educt and product is indispensable for ascertaining the preferred transition state.[7] We have therefore investigated enantiomerically pure allenes of type **1** and, to simplify the synthesis and analysis, have introduced a further stereogenic, uniformly configurated reference center into the side chain R^1.

Reaction[3] of (*S*)-2-benzyloxypropanal[8] with triisopropoxytitanium *N,N*-diisopropyl-2-butynylcarbamate affords the two chromatographically readily separable, optically active diastereomers (−)-**6a**[9] and (+)-**6b**[9] (yield 71%, 37 : 63). The absolute configuration of the less polar isomer (+)-**6b** was shown by a crystal structure analysis[10] of the *p*-bromobenzoate to be (a*S*,4*S*,5*S*). (−)-**6a** is (a*R*,4*R*,5*S*) configurated, since, owing to the mode of formation[3,4] both diastereomers **6** must have the same *relative* configuration[11] at the axial-chiral and at the centrochiral stereocenter (C-4), but the same *absolute* configuration at C-5 (Scheme 2).

On heating with 20 mole equivalents of **2a** (toluene, 2 h, 50°), (−)-**6a** and (+)-**6b** afford the (*E,E*)-dienes (−)-**7a**[13] (79%) and (+)-**7b**[13] (59%), respectively, each of which contain less than 5% (^{13}C-NMR) of the other diene. According to an X-ray structure analysis (−)-**7a** has (2*R*,6*S*,3*E*,4*E*)-configuration.[14] Since 30% of (−)-(**7a**) is converted via the amide enolate into (+)-**7b** on treatment with lithium diisopropylamide (50 equiv., 1 h at −78°C in tetrahydrofuran), the stereoisomers **7** must differ only in the configuration at C-2.

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[**] Metalated Nitrogen Derivatives of Carbonic Acid in Organic Synthesis, Part 30.—This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.—Part 29: E. van Hülsen, D. Hoppe, *Tetrahedron Lett. 26* (1985) 411.



Scheme 2. Cb = C(=O)NiPr$_2$, R′ = $C_6H_5CH_2$.

Consequently, the rearrangement of (−)-**6a** to (−)-**7a** proceeds via the transition state **B** and that of (+)-**6b** to (+)-**7b** via the enantiomeric transition state.[15] R^1 and the NMe_2 group thus avoid a 1,3-diaxial position, which would be accompanied by repulsion; in **B**, R^1 takes a pseudo-equatorial position. On the other hand, approach of C-2′ towards C-2 from the more strongly shielded side of the allene moiety in **B** also seems unfavorable.[16] The configuration of the two double bonds in **5** is determined by the *relative* configuration of **1** and that at C-2 in **5** by the *absolute* configuration at C-4 (for the same configuration of the enol double bond). Therefore, reaction of a mixture of (−)-**6a** and (+)-**6b** with the (at C-2′ non-prochiral) reagent **2b** affords, as expected, a uniform diene (−)-**8**[13] (70%, *ds* >98%).

This synthesis provides a simple and general entry to highly substituted diastereomerically pure 1,3-alkadienes of the type **5** in only two steps; the C-4–C-5 bond and the C-2–C-3 bond are thereby connected. The method is also well suited for the preparation of enantiomerically pure dienes such as **7**.

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CAS Registry numbers:
2a, 97315-73-6; **2b**, 867-89-0; (−)-**6a**, 97315-72-5; (+)-**6b**, 97371-84-1; (+)-**6b** *p*-bromobenzoate, 97315-75-8; (−)-**7a**, 97336-07-7; (+)-**7b**, 97315-74-7; (−)-**8**, 97336-08-8; (*S*)-$CH_3CH(OCH_2Ph)CHO$, 81445-44-5; $CH_3C{\equiv}CCH(OC(O)N\text{-}i\text{-}Pr_2)Ti(O\text{-}i\text{-}Pr)_3$, 97315-71-4.

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[7] This argument is strictly valid if R^1 in **3** is non-stereogenic. If a stereogenic reference center is incorporated with R^1, then a knowledge of the relative configuration of the participating racemic diastereomers also suffices.

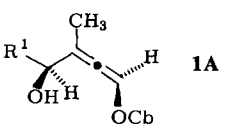
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[9] (−)-**6a**: $[\alpha]_D^{20}$ −22.9 (*c* = 5.4, CH_3OH), R_F = 0.24; (+)-**6b**: $[\alpha]_D^{20}$ +15.0 (*c* = 3.1, CH_3OH), R_F = 0.32.—Selected NMR data (δ values, $CDCl_3$), ^{1}H-NMR: **6a**: 7.42 (qd, $J_{1,3'} = J_{1,4}$ = 2 Hz, 1-H); **6b**: 7.68 (dq, $J_{1,3'}$ = 2 Hz, $J_{1,4}$ = 1.5 Hz); ^{13}C-NMR, **6a/6b**: 114.85/114.49 (C-1), 189.81/190.62 (C-2), 112.78/112.34 (C-3), 76.51/76.36 (C-4), 74.08/75.99 (C-5), 13.71/15.82 (C-6), 17.35/17.04 (3-CH_3).

[10] Crystal structure analysis of the *p*-bromobenzoate of (+)-**6b** ($C_{28}H_{34}BrNO_5$): Space group $P2_1$, *a* = 608.1(1), *b* = 1412.3(1), *c* = 1643.2(2) pm, β = 95.69(1)°, *V* = 1.404 nm^3, *Z* = 2, μ = 1.48 mm^{-1} ($Mo_{K\alpha}$), 4844 measured intensities ($2\theta_{max}$ = 50°) including Friedel pairs, 3949 reflections with $|F| > 3\sigma_F$ classified as observed, empirical absorption correction, Patterson and Fourier methods, non-hydrogen atoms refined anisotropically, H atoms geometrically positioned, *R* = 0.050 (R_w = 0.045), values for the false absolute configuration: *R* = 0.083 (R_w = 0.081); η-refinement gave 1.00(2) [17].

[11] Contrary to our previous assumption [3] the titanium-mediated addition affords *syn*-configurated [12] 4-hydroxy-1,2-alkadienes **1**. Thus, for the racemic acetaldehyde adduct (**1**, $R^1 = CH_3$), the (a*R**,4*S**) configuration was confirmed by crystal structure analysis of the *p*-chlorophenylurethane; reversal of the relative configuration compared to **6** is only due to altered *CIP* priorities. E. Egert, D. Schmidt, C. Gonschorrek, D. Hoppe, unpublished.

[12] a) Analogously to the widely accepted proposal by *Masamune* et al. [12b] for aldol-like diastereomers, we would like to suggest the *syn/anti* notation for the facile assignment of allenes of the type **1** to diastereomeric series, on the basis of the "zig-zag conformation" **1A**. **1** and **6** accordingly belong to the *syn* series and the diastereomers (e.g. 1-H and OCb exchanged) to the *anti* series. However the *CIP* notation [12c] is recommended for the stereochemical assignment of individual compounds.—b) S. Masamune, S. A. Ali, D. L. Snitman, D. S. Garvey, *Angew. Chem.* *92* (1980) 573; *Angew. Chem. Int. Ed. Engl.* *19* (1980) 557; c) D. Seebach, V. Prelog, *ibid.* *94* (1982) 696 and *21* (1982) 654.



1A

[13] (−)-**7a**: $[\alpha]_D^{20}$ −133.1 (*c* = 0.6, CH_3OH), m.p. 66°C, R_F = 0.14. (+)-**7b**: $[\alpha]_D^{20}$ +23.4 (*c* = 0.8, CH_3OH), oil, R_F = 0.13. (−)-**8**: $[\alpha]_D^{20}$ −33.4 (*c* = 0.3, CH_3OH), oil.—Selected NMR data (δ values, $CDCl_3$): ^{1}H-NMR: **7a/7b**: 5.47/5.48 (dq, $J_{5,6}$ = 9/9 Hz, $J_{5,4'}$ = 1/1 Hz, 5-H); **8**: 7.48 (s, 2′-H), 5.38 (d, $J_{5,6}$ = 8 Hz, 5-H).—^{13}C-NMR, **7a/7b**: 171.95/172.84 (C-1), 36.95/37.25 (C-2), 132.00/133.90 (C-3′), 133.19/134.17 (C-3), 125.01/125.84 (C-4), 129.86/130.12 (C-5), 70.59/70.89 (C-6), 15.63/15.84 (C-7), 16.87/17.05 (2-CH_3), 21.41/21.42 (4-CH_3); **8**: 135.49 (C-3′), 134.13 (C-3), 119.39 (C-4), 129.15 (C-5), 71.00 (C-6), 21.49 (4-CH_3).

[14] Crystal structure analysis of **7a** ($C_{26}H_{40}N_2O_4$): Space group $P2_12_12_1$, *a* = 970.7(1), *b* = 1540.7(2), *c* = 1820.6(2) pm, *V* = 2.723 nm^3, *Z* = 4, μ = 0.07 mm^{-1} ($Mo_{K\alpha}$), 2721 measured intensities ($2\theta_{max}$ = 50°), 2104 with $|F| > 3\sigma_F$ significant, direct methods (SHELXTL), C, N, and O atoms refined anisotropically, H atoms geometrically positioned, *R* = 0.065 (R_w = 0.060) [17].

[15] The stereogenic center in R^1, which has no influence on the course of the reaction, is ignored here.

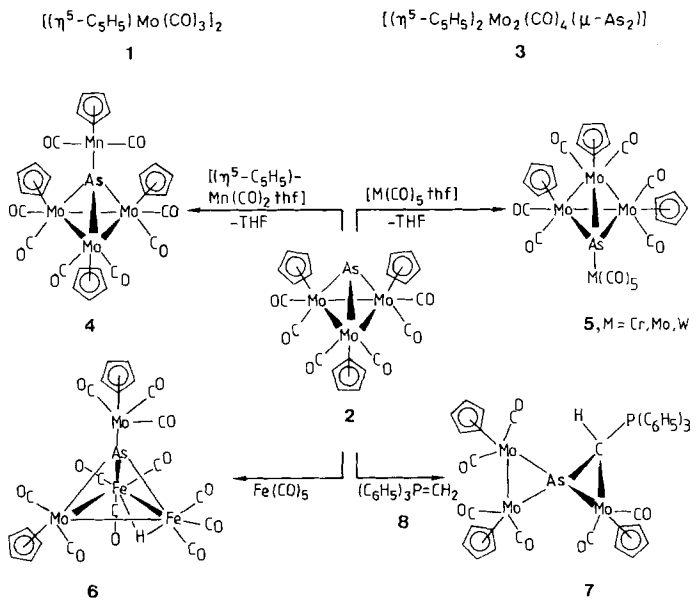
[16] The stereoselectivity of the rearrangement in **3** decreases with increasing bulkiness of the substituents on C-3 ($SiMe_3$ for CH_3) and on disubstitution of C-2′. The configuration of the additional isomers formed at the same time has so far not been elucidated; D. Hoppe, C. Gonschorrek, unpublished.

[17] Further details of the crystal structure investigation are available on request from Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2, on quoting the depository number CSD 51 506, the names of the authors, and the full citation of the journal.

Synthesis and Structure of the Spirocluster $[(\eta^5\text{-}C_5H_5)_3Mo_3As(CO)_6\{CHP(C_6H_5)_3\}]$**

By *Klaus Blechschmitt, Thomas Zahn,* and *Manfred L. Ziegler**

The Mo-complex **1** reacts with elemental arsenic to give the cluster compounds **2**[1] and **3**[2] in good yields. On investigating the reactivity of **2** we have established that, as expected, adducts like **4**[1] and **5**[3] are formed; cluster building blocks in **2** can, however, be exchanged for $Fe(CO)_5$, with formation of the species **6**.[4] Seemingly unusual to us however, is the access to the spirocluster **7** with the Wittig reagent **8**.[5]



Adducts comparable with **4** and **5** are known, e.g., in the case of $AsCo_3$ clusters;[6] this also applies in the case of the hydrido clusters **6**,[7] in which, as confirmed inter alia by an X-ray structure analysis, two $CpMo(CO)_2$ moieties are substituted by an $Fe(H)(CO)_3$ moiety and an $Fe(CO)_3$ moiety. The As atom in **6** functions as a 5-electron donor towards its neighbors. In the comparable cluster **9**,[7] the same situation exists for phosphorus.

The reaction of **2** with the phosphorus ylide **8** is surprising. Instead of a conceivable 1,2-addition to an As–Mo or a Mo–Mo bond or a transfer of the CH_2 group with formation of a μ-methylene complex,[8] the cluster is opened with cleavage of a hydrogen atom and formation of an arsenic-carbon-molybdenum three-membered ring. The chiral spirocluster **7** is unequivocally characterized by an elemental analysis, spectroscopic data,[5] and by an X-ray structure analysis (Fig. 1);[9] **7** crystallizes as a racemate.

In **7**, the arsenic is coordinated in a distorted tetrahedral fashion, all five valence electrons of the arsenic participate in bonding. The formal positive charges on the four-bonded arsenic and phosphorus are compensated by negative charges on two $Mo(CO)_2(C_5H_5)$ units. The latter must also be accounted for on the basis of the 18-electron rule, since no signals occur in the Mo–H and Mo–H–Mo regions of the ^{1}H-NMR spectrum. In the room temperature ^{1}H-NMR spectrum, three signals are observed for the C_5H_5 rings. This suggests that the molecule has the same configuration in the solid state and in solution.

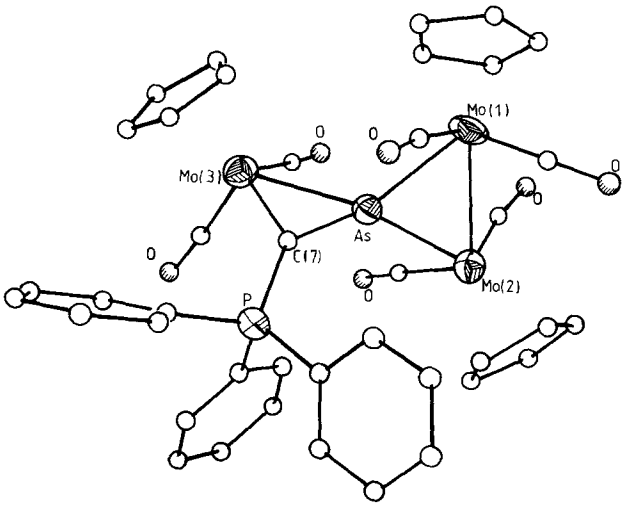


Fig. 1. Crystal structure of **7**: $P2_1$, $Z=4$, $a=965.8(5)$, $b=1805.0(9)$, $c=2331.6(7)$ pm, $\beta=95.30(3)°$, $V=4047.22\cdot10^6$ pm^3, $R_{aniso}=0.078$, $R_w=0.062$. Selected bond lengths [pm] and angles [°]: Mo(1)–Mo(2) 333.2(3), Mo(1)–As 254.4(4), Mo(2)–As 254.2(4), Mo(3)–As 257.3(4), As–C(7) 197(2), Mo(3)–C(7) 229(3), P–C(7) 175(3), Mo–C(=O) 192(3) (mean value), Mo–C(Cp) 236(2) (mean value); Mo(1)–As–Mo(2) 81.9(1), Mo(1)–As–Mo(3) 123.3(2), Mo(2)–As–Mo(3) 144.0(2), Mo(1)–As–C(7) 122.9(7), Mo(2)–As–C(7) 132.7(7), Mo(3)–As–C(7) 58.7(7), Mo(3)–C(7)–As 73.8(7), As–Mo(3)–C(7) 47.5(6), Mo(3)–C(7)–P 127(1), As–C(7)–P 132(1) [9].

In contrast to $(\mu_3,\eta^2$-methylenegermandiyl)tris[dicarbonyl-$(\eta^5$-cyclopentadienyl)manganese]*(Mn–Mn)* **10**,[10] the complex **7** described here exhibits no dynamic properties up to +100 °C (^{1}H-NMR). Between 60 and 100 °C one of the Cp signals broadens reversibly. This is explained in terms of a rotation of the phenyl rings of the $(C_6H_5)_3P$ ligand about the P–C axis. Hence, only the Cp ring on Mo(2) is affected (Fig. 1).

7 can be regarded as a μ_3,η^2-methylenearsanediyl complex, i.e. as a rare example in which a main group element and a transition element are bridged by an alkylidene group $[CHP(C_6H_5)_3]$.[11]

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CAS Registry numbers:
2, 93923-00-3; **4**, 97403-36-6; **5** (M = Cr), 97403-37-7; **5** (M = Mo), 97403-38-8; **5** (M = W), 97415-89-9; **6**, 97403-39-9; **7**, 97403-40-2; $(C_6H_5)_3P=CH_2$, 3487-44-3; $[(\eta^5\text{-}C_5H_5)Mn(CO)_2THF]$, 12093-26-4; $[Cr(CO)_5THF]$, 15038-41-2; $[Mo(CO)_5THF]$, 53248-43-4; $[W(CO)_5THF]$, 36477-75-5; $Fe(CO)_5$, 13463-40-6.

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[**] This work was supported by the Fonds der Chemischen Industrie and the Deutsche Forschungsgemeinschaft.

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[2] **3** is known: a) P. J. Sullivan, A. L. Reingold, *Organometallics 1* (1982) 1547; b) I. Bernal, H. Brunner, W. Meier, H. Pfisterer, J. Wachter, M. L. Ziegler, *Angew. Chem. 96* (1984) 428; *Angew. Chem. Int. Ed. Engl. 23* (1984) 438; c) G. Huttner, B. Sigwarth, O. Scheidsteger, L. Zsolnai, O. Orama, *Organometallics 4* (1985) 326.

[3] **4** and **5** were characterized by an accurate elemental analysis and by their ^{1}H-NMR, IR, and mass spectra.

[4] Spectroscopic data of **6**: IR (ν(CO) [cm^{-1}], KBr): 2044 (s), 2015 (vs), 1965 (vs), 1943 (vs), 1922 (vs), 1905 (s), 1893 (s); FD-MS (toluene): *m/z* 817 (M^+); ^{1}H-NMR [90 MHz, $CDCl_3$, 25 °C, tetramethylsilane (TMS)]: δ = 5.87 (s, 5H, C_5H_5), 5.14 (s, 5H, C_5H_5), −21.78 (s, 1H); m.p. 169 °C. An X-ray structure analysis has been carried out on **6** [9].

[5] A salt-free solution of **8** [obtained from $(C_6H_5)_3PCH_3Br$ (3 g, 8.40 mmol) and an excess of NaH (80% suspension in white oil)] was treated with 1.5 g (2.06 mmol) of **2** and the mixtured boiled under reflux for 14 h. After subsequent treatment with silica gel (10 g) the solvent was removed by evaporation. The solid residue was extracted with 100 mL of ether and the extract, after filtration, was concentrated by evaporation and chromatographed on silica gel (0.05–0.2, 40 × 2.5 cm, hexane). A small amount of **2** was first eluted with toluene, and then the red colored **7** was eluted with toluene/ether (1:1). Yield 40% referred to **2**, m.p. 163°C, red crystals. Spectroscopic data of **7**: IR (ν(CO) [cm^{-1}], KBr): 1946 (s), 1902 (s), 1857 (sh), 1836 (vs), 1817 (s); FD-MS (toluene) *m/z* 1001 (M^+); ^{1}H-NMR (300 MHz, $CDCl_3$, 25°C, TMS): δ = 7.91–7.49 (m, 15H, Ph_3). 5.21 (s, 5H, C_5H_5), 4.91 (s, 5H, C_5H_5), 4.60 (s, 5H, C_5H_5), 2.31 (d, 1H, ^2J = 3.52 Hz); correct total analysis; m.p. 163°C.

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[9] Further details of the crystal structure investigations of **6** and **7** are available on request from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2, on quoting the depository number CSD 51271, the names of the authors, and the full citation of the journal.

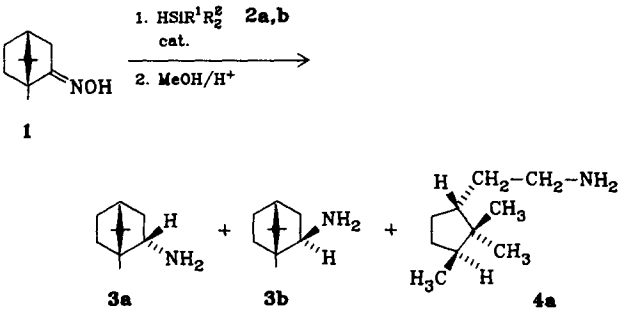
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[11] M. Luksza, S. Himmel, W. Malisch, *Angew. Chem. 95* (1983) 418; *Angew. Chem. Int. Ed. Engl. 22* (1983) 416.

Cleavage of a C–C Bond in the Catalytic Hydrosilylation of Camphor Oxime**

By *Henri Brunner** and *Richard Becker*

Rhodium-catalyzed hydrosilylation of ketoximes and subsequent hydrolysis leads to formation of primary amines, e.g. in the case of acetophenone oxime to the enantiomers of 1-phenylethylamine.[1a] Thirteen other alkylaryl- and alkylbenzyl ketoximes gave exclusively the corresponding amines[1b] in the amine fraction. All the more surprising was the finding that, in the hydrosilylation of (−)-(1*R*,4*R*)-camphor oxime **1**, not only the expected bornylamines **3a** and **3b** were formed, but also, and as main product, optically pure (+)-(1*R*,3*S*)-1-(2-aminoethyl)-2,2,3-trimethylcyclopentane **4a**.



2a, R^1 = H, R^2 = Ph; **2b**, R^1 = Me, R^2 = Cl

The reaction of 1 mole equivalent of **1** with 3.3 mole equivalents of diphenylsilane **2a** in toluene is catalyzed by 1 mol-% [$RhCl(PPh_3)_3$] (Table 1).[2] Gas chromatographic analysis[3] of the distilled product revealed a mixture of three amines, which were identified by GC/MS. Besides the expected mass peaks of the trifluoroacetamide derivatives of *endo*- and *exo*-bornylamine, **3a** and **3b**, respectively, the main product, two mass units higher, indicated cleavage of a C–C bond in the camphor skeleton. That this cleavage was a hydrogenolytic cleavage between the bridgehead carbon atom and the oxime carbon atom, with formation of **4a**, followed from the ^{1}H-NMR spectrum (two methyl singlets, one methyl doublet[4]) and the ^{13}C-NMR spectrum.[5]

In the reaction of **1** to give **4a**, the (*R*)-configuration at C4 of the educt (C3 of the product) is preserved. That the configuration at C1 of **4a** is also retained was established as follows: α-campholenonitrile **5**[6] was hydrogenated with H_2/Raney nickel. The two diastereomers **4a** (1*R*,3*S*) and **4b** (1*R*,3*R*) were formed in the ratio 36:64; the base lines of their trifluoroacetamide derivatives are separated on gas chromatographic analysis.[3] Co-injections with the trifluoroacetamide derivative of **4a** obtained on hydrosilylation show that only one of the two diastereomers is formed. The retention behavior on a Chirasil-L-Val® column (shorter retention time for *R*-compounsds[7]) lends support for assignment of the (*S*)-configuration at C3 in **4a**, which is also consistent with the concept that cleavage of the C–C bond and addition of hydrogen to the two C atoms takes place at one metal center.

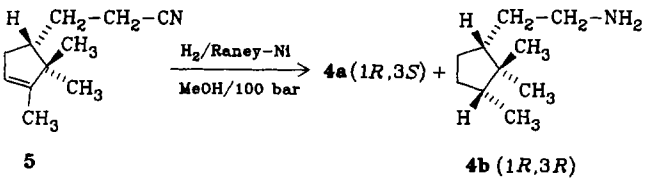
Table 1. Hydrosilylation of 2.7 g of (D)-camphor oxime **1** with the silanes **2a**, **b** in 5 mL of toluene.

No.	Catalyst		Rh:**1** or Pt:**1**	**1**:**2a/b**	*t* [h]	*T* [°C]	Total yield [%] (**3a**+**3b**+**4a**)	Relative yield [%] **3b**	**3a**	**4a**
1	$[RhCl(PPh_3)_3]$	**2a**	1:200	1:3.3	408	−10→20	29	14	2	84
2	$[RhCl(PPh_3)_3]$	**2a**	1:100	1:3.3	90	−10→20	38	15	4	81
3	$[RhCl(PPh_3)_3]$	**2a**	1:100	1:3.3	24	−10→50	24	25	3	72
4	$[RhCl(PPh_3)_3]$	**2a**	1:100	1:3.3	46	+ 5	29	27	2	71
5	$[RhCl(PPh_3)_3]$	**2a**	1:100	1:3.3	192	0	12	27	2	71
6	$[RhCl(PPh_3)_3]$ [a]	**2a**	1:100	1:3.3	24	−10→20	18	33	2	65
7	$[RhCl(PPh_3)_3]$ [b]	**2a**	1:100	1:3.3	23	−10→20	18	28	2	70
8	$K[PtCl_3C_2H_4]$	**2b**	1:100	1:6	48	0→b.p.	20	18	16	66
9	$K[PtCl_3C_2H_4]$	**2b**	1:200	1:6	70	0→b.p.	24	9	9	82
10	$PtO_2 \cdot H_2O$	**2b**	1:100	1:6	70	0→b.p.	16	13	5	82

[a] Addition of 0.5 mL (4 mmol) of $BF_3 \cdot OEt_2$ to **1** and catalyst, stirred for 5 min at 20°C, then addition of silane at −10°C. [b] Addition of 0.5 mL (4 mmol) of $BF_3 \cdot OEt_2$ to the mixture **1**/**2a** at −10°C, then addition of catalyst.

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5 **4b** (1*R*,3*R*)

Hydrosilylation of **1** with diphenylsilane, **2a**, furnishes **4a** in 80–85% relative yield (total yield 30–40%; Table 1, entries 1 and 2). Increasing or lowering the reaction temperature reduces the selectivity with respect to **4a** in the same way as addition of $BF_3 \cdot OEt_2$, which should catalyze the Beckmann rearrangement (Entries 3–7). **4a** is also obtained with dichloromethylsilane, **2b**, on homogeneous catalysis with Zeise salt and on heterogeneous catalysis with $PtO_2 \cdot H_2O$ (Entries 8–10).

Hence, the enantiomerically pure primary amine (+)-**4a** which, hitherto, has only been described in the form of a **4a/4b** diastereomeric mixture[8] can be synthesized in one step by catalytic hydrosilylation of (D)-camphor oxime.

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[1] a) H. Brunner, R. Becker, *Angew. Chem.* 96 (1984) 221; *Angew. Chem. Int. Ed. Engl.* 23 (1984) 222; b) H. Brunner, R. Becker, S. Gauder, *Organometallics*, in press.

[2] Work-up with methanol/20% aqueous hydrochloric acid, addition of KOH in excess, extraction with ether, and purification by distillation (55°C/0.1 torr).

[3] A solution of the amine (100 mg) in 2 mL of tetrahydrofuran (THF) was treated with 0.2 mL of trifluoroacetic anhydride. After 10 min, the mixture was neutralized with 3 mL of a saturated $NaHCO_3$ solution. The amines were extracted with ether (1.5 mL). The ether phase was dried with Na_2CO_3. GC: silicon phase Chirasil-L-Val®; glass capillary 25m, 110°C; injector 230°C. Error ± 1%.

[4] **4a**·HCl (enriched by recrystallization from ethyl acetate to 97%): ^{1}H-NMR (250 MHz, $CDCl_3$, TMS): $\delta = 0.53$ (s, 3H), 0.83 (d, 3H), 0.89 (s, 3H), 1.09–1.23 (m, 2H), 1.47–1.56 (m, 3H), 1.71–1.95 (m, 3H), 2.86–3.09 (m, 2H).

[5] **4a**·HCl: ^{13}C-NMR (22.64 MHz, 20% solution in $CDCl_3$, TMS, broadband decoupled): $\delta = 13.7$ (q), 14.4 (q), 25.6 (q), 27.8 (t), 28.7 (t), 30.1 (t), 39.7 (t), 42.5 (s), 45.0 (d), 48.0 (d).

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Dinuclear Nickel Complexes with Bridging Allyl Ligands**

By *Rudolf Hanko**

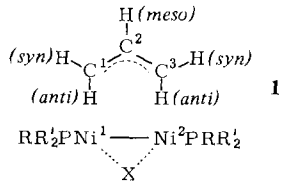
Dedicated to Professor Günther Wilke on the occasion of his 60th birthday

The great synthetic and catalytic potential of mononuclear η^3-allylnickel-X compounds **2** (X = halogen, allyl, H)[1] and the increasing importance of multinuclear transition metal complexes in homogeneous catalysis attracted interest in multinuclear Ni-complexes with bridging allyl ligands (type **1**). To my knowledge no such complexes have, as yet, been documented, although unsuccessful attempts at their synthesis have been reported.[2]

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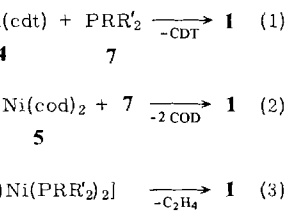
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[**] I wish to thank Professor *G. Wilke* for his participation in and support of this work.



1

In the following communication a simple and versatile entry to this special class of compounds is described: Reaction of a 1:1 mixture of a triorganophosphane **7** and a nickel(0)-complex **4** or **5** with an η^3-allylnickel halide complex **2** [Reactions (1) and (2), respectively (Scheme 1)] or of the bis(phosphane)ethylenenickel complex **6** with the complex **3** [Reaction (3)] leads, via displacement of the olefin ligands to formation of a crystallizable dinuclear nickel compound of the type **1** in high yields. The liberated olefin can be removed under vacuum or by recrystallization. Reaction (1) affords the best yields (ca. 80%)[3] (Table 1). With exception of the PMe_3-adduct **1a**, these wine-red, dinuclear complexes **1** are stable under argon at room temperature.[4]



Scheme 1. CDT = all-*trans*-1,5,9-cyclododecatriene; COD = *cis,cis*-1,5-cyclooctadiene.

Table 1.

Product	X	PRR'_2	Educts	Reaction	Yield [%]
1a	Br	PMe_3	**2a**, **4**, **7a**	(1)	82 [a]
1b	Cl	$P(i\text{Pr})_3$	**2b**, **4**, **7b**	(1)	63
1b	Cl	$P(i\text{Pr})_3$	**2b**, **5**, **7b**	(2)	54
1c	Cl	$P(c\text{-}C_6H_{11})_3$	**2c**, **4**, **7c**	(1)	80
1c	Cl	$P(c\text{-}C_6H_{11})_3$	**3c**, **6c**	(3)	41 [a]
1d	Br	$P(c\text{-}C_6H_{11})_3$	**2d**, **4**, **7d**	(1)	82
1e	Br	$P(t\text{Bu})(i\text{Pr})_2$	**2e**, **4**, **7e**	(1)	81
1f	C_3H_5	$P(i\text{Pr})_3$	**2f**, **4**, **7f**	(1)	84

[a] Determined by NMR spectroscopy.

The nuclear resonance spectra[5] are reconcilable with dinuclear structures. In each case, only one signal is to be seen in the ^{31}P-NMR spectrum. In the ^{13}C-NMR spectra[6,7] the signals of the carbon atoms bound to phosphorus can be interpreted as X-parts of ABX spin systems (A,B = ^{31}P; X = ^{13}C), from which a phosphorus-phosphorus coupling constant of ca. 25 Hz can be calculated for **1b** and **1d**. According to the ^{13}C- and ^{1}H-NMR spectra the allyl groups are symmetrically bound. Particularly striking is the upfield shift of the signal ($\delta = 32$–38) of the *meso*-carbon atom of the halogen-bridged compounds compared to that of the mononuclear analogues (e.g. $\delta = 31.8$ for **1e** compared to $\delta = 107.2$[8] for **2e**). In the case of the bis(allyl) compound **1f**, the upfield shifts of the allyl carbon atoms are less pronounced compared to those of the mononuclear starting complex ($\delta = 87.1$ (*meso*), 27.6 (terminal) for **1f** compared to $\delta = 112.2$ (*meso*), 52.6 (terminal) for **2f**[9]).

From the ^{13}C-NMR spectrum of **1f**, it follows that the allyl groups are *cis* oriented. A structure with more than two nickel atoms was ruled out in the case of **1f** by spectra simulation.[5]

The structure proposed for **1e** on the basis of NMR spectra was confirmed by an X-ray structure analysis,[10] according to which the nickel atoms are separated at a distance typical for Ni–Ni bonds and are almost symmetrically bridged by an allyl group and a halogen atom.

The catalytic properties of the new Ni complex of type **1** are presently being investigated.

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1a, 97416-01-8; **1b**, 97416-02-9; **1c**, 97416-03-0; **1d**, 97416-04-1; **1e**, 97416-05-2; **1f**, 97416-06-3; **2a**, 97416-07-4; **2b**, 97416-08-5; **2c**, 97416-09-6; **2d**, 47315-25-3; **2e**, 97416-10-9; **2f**, 97416-11-0; **3c**, 12145-00-5; **4**, 37246-55-2; **5**, 1295-35-8; **6c**, 41685-59-0; **7a**, 594-09-2; **7b**, 6476-36-4; **7c**, 2622-14-2; **7d**, 51567-05-6.

[1] P. W. Jolly, G. Wilke: *The Organic Chemistry of Nickel*, Academic Press, New York 1974.
[2] H. Werner, *Adv. Organomet. Chem.* 19 (1981) 155.
[3] Experimental: A solution of Ni(cdt) (362 mg, 1.64 mmol) in tetrahydrofuran (THF) (10 mL) was treated with 240 μL (289 mg, 1.64 mmol) of *tert*-butyldiisopropylphosphane at −78 °C under argon, and, after 10 min, further treated with a solution of **2e** (599 mg, 1.69 mmol) in THF (10 mL). The reaction mixture was then stirred for 15 h at −78 °C and, finally for 1 h at 0 °C. All volatile components were removed from the purplish wine-red solution at 0 °C by evaporation and the residue was then dried at 5×10^{-5} mbar and 20 °C for 24 h. The oily crude product was recrystallized from *n*-pentane/perfluorohexane. Yield: 760 mg (81%), correct elemental analysis. **1e**: ^{1}H-NMR (400 MHz, [D$_6$]benzene, 27 °C, ^{31}P-decoupled) $\delta = 2.18$ (m; 2H, *syn*-allyl, $^2J(2,3) = 3.1$, $^3J(2,1) = 7.8$ Hz), 2.12 and 2.08 (each m; $J = 7$ Hz, 4H, PC*H*), 1.38 (s), 1.15 and 1.10 (each d; $J = 7$ Hz, 24H, PCHC*H*$_3$), 1.24 (s; 18H, PCC*H*$_3$), 0.50 (dd; $^2J(3,2) = 3.1$, $^3J(3,1) = 12.3$ Hz, 2H, *anti*-allyl). The signal for *meso*-allyl is superposed.
[4] The elemental analyses are consistent with the empirical formula.
[5] NMR data collection, Max-Planck-Institut für Kohlenforschung, Kaiser-Wilhelm-Platz 1, D-4330 Mülheim a. d. Ruhr.
[6] I wish to thank Dr. *R. Mynott* and his co-workers for recording and interpreting the ^{13}C-NMR spectra, and for valuable help and discussions in elucidating the structure of **1**.
[7] Typical ^{13}C-NMR data: **1b** (75 MHz, [D$_8$]toluene, −20 °C): $\delta = 34.8$ (allyl-*C*H, J(PC) = 5.9 Hz), 24.8 (PCH, ^1J(PC) = 15.8, J(P′*C*) = 2.0 Hz), 21.9 (allyl-*C*H$_2$, J(P*C*) + J(P′*C*) = 10.2 Hz), 20.5 and 20.0 (each *C*H$_3$), J(PP) = 25.3 Hz, from analysis of the ABX spin system for PCH (A,B = ^{31}P), δ(P) = 51.3.
[8] R. Mynott, R. Hanko, unpublished.
[9] B. Henc, P. W. Jolly, R. Salz, G. Wilke, R. Benn, E. G. Hoffmann, R. Mynott, G. Schroth, K. Seevogel, J. C. Sekutowski, C. Krüger, *J. Organomet. Chem.* 191 (1980) 425.
[10] C. Krüger, K. Angermund, R. Hanko, unpublished. Selected distances [Å]: Ni1–Ni2 2.471(1), Ni1–P1 2.167(2), Ni1–C1 1.928(8), Ni1–C2 2.179(8), Ni1–Br 2.324(1), Ni2–P2 2.172(2), Ni2–C3 1.926(8), Ni2–C2 2.197(8), Ni2–Br 2.333(1), C1–C2 1.40(1), C2–C3 1.43(1).

Selective ^{1}H,^{13}C-NOE Difference Spectroscopy for the Elucidation of Structures

By *Peter Bigler** and *Matthias Kamber*

Development of the modern technique of nuclear resonance spectroscopy has been so rapid in recent years that the spectroscopist now has a wide 'spectrum' of informative methods at his disposal. We report here on a method that has proven very useful in the solution of problems regarding structural configurations and conformations. Used in combination with other NMR methods it enables unequivocal interpretation of the mutual positions of molecular fragments. The nuclear Overhauser enhancement (NOE) effect[1] resorted to in our method has been exploited ever since the advent of ^{13}C-NMR spectroscopy. It is responsible for the enhanced intensity of the ^{13}C-NMR signals in ^{1}H broad-band decoupling. In the case of quaternary carbon atoms the total observed nuclear Overhauser effect is made up of the individual contributions of the protons in the immediate vicinity. The contributions of the individual protons differs according to their relative distances from the C-atom under observation. Selective ^{1}H-irradiation, i.e. irradiation with the resonance frequency of these protons, allows these contributions to be measured and, consequently, also the relationships to be established that are important for structure elucidation. If usually well separated ^{1}H-NMR signals have been selected for the irradiation, which severely limits the scope of the method, then the technique proposed here[2–4] can, similarly to modern homonuclear methods (Fig. 1), be used even when large signal overlapping occurs in the ^{1}H-NMR spectrum.

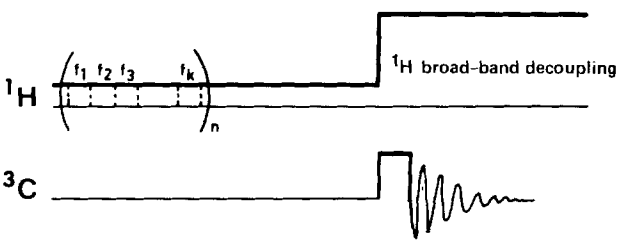


Fig. 1. Pulse scheme for the hetero-NOE experiment: During the NOE generation, the selected ^{1}H-NMR frequencies f_1 to f_k are rapidly irradiated one after the other.

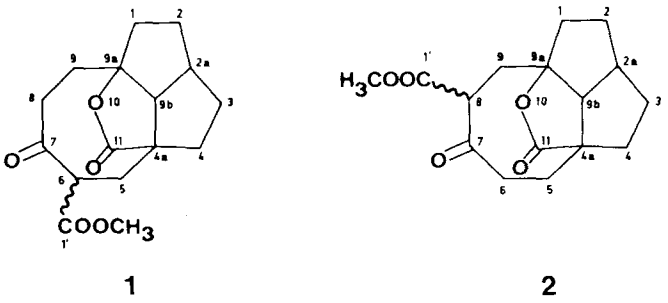
The high selectivity required for this, is achieved through the selected ^{1}H-NMR signals—more precisely associated ^{13}C satellites—being irradiated one after the other in rapid succession during the phase of the NOE generation with very small decoupler power. This also guaranties high efficiency, in that the signals of several protons, e.g. of a methylene group, with different chemical shifts, can be concomitantly saturated and the sum of several NOE contributions detected. The sensitivity of the method can be further increased by ^{1}H broad-band decoupling during the detection phase and representation of the effects in the form of difference spectra.

The NOE method has certain advantages over other methods which enable the environment of quaternary carbon atoms to be explored, e.g. the recently reported CH-shift correlation on the basis of long-range couplings:[5] As a 1D experiment, the method is favored by a relatively short measuring time. A knowledge of the coupling constants—in the case of geminal and vicinal C,H-couplings there are often uncertainties—is not required.

We have used the method for investigating the isomeric β-keto esters **1** and **2** (Fig. 2), which were formed during the synthesis of a tetraquinacane derivative.[6] An NMR spectroscopic investigation of the main components was expected to allow differentiation of the two isomers and to permit elucidation of the stereochemistry in the eight-membered ring (Fig. 3).

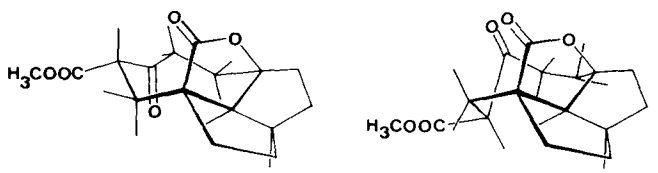
On the basis of signals which, due to their chemical shift and their multiplet structure, must be assigned to the H atoms on C6 and C8, the strongly overlapping signals of the other eight-membered ring protons on C5 and C9 could be located by decoupling experiments. In a prelimi-

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1 2

Fig. 2. β-Keto esters **1** and **2**.



1a 1b

Fig. 3. Stereoisomers of **1**. The bonds to the H-atoms on C2a, C5, C6, C8, and C9 are shown.

nary measurement of the hetero NOE effect, the multiplet lines of the C5 protons and then of the C9 protons were, as described above, successively irradiated several times; the two spectra were (in each case at the stage of the free induction decay) subtracted from each other. The ^{13}C-NMR difference spectrum (Fig. 4a) shows a positive signal for C4a and, thus, close proximity to the protons on C5, and a negative signal for C9a, and thus, a close proximity to the protons on C9. Since the quaternary C-atoms C4a and C9a can be identified from their chemical shifts, the position of the lactone bridge relative to the methine group C6 is established and, thus, also the structure of the main component **1**.

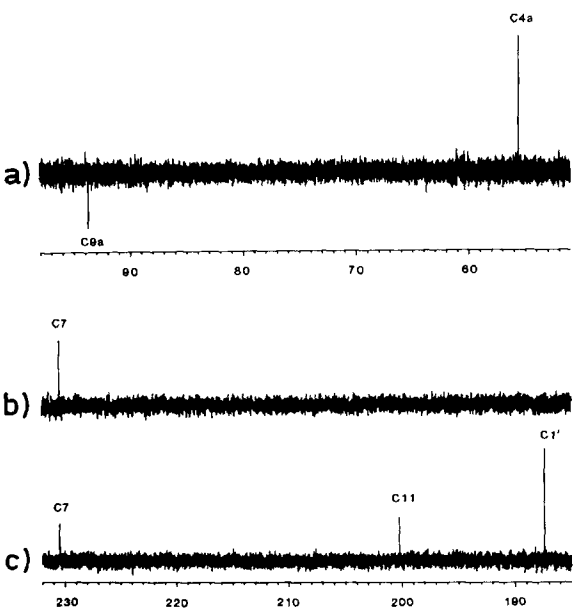


Fig. 4. Hetero-NOE difference spectra (δ values). a) Difference of the ^{13}C-NMR spectra in the region of C4a and C9a after irradiation of the protons on C5 and C9; b), c) difference of the ^{13}C-NMR spectra in the carbonyl region after irradiation of the proton on C8 (b) and of the proton on C6 (c).

For clarification of the stereochemistry in the eight-membered ring, the methine proton on C6 and one of the methylene protons on C8 were irradiated separately in a second hetero-NOE experiment. On the basis of the ^{1}H-coupling constants for their coupling with the neighboring methylene protons it could be assumed that they were the protons which lie relatively close to the lactone bridge in the case of **1a** but not so in the case of **1b** (Fig. 3).

Hence, in the presence of **1a** an NOE effect on C11 had to be expected from at least one of these protons. Indeed, the difference spectrum (Fig. 4c) shows, in the case of the irradiation of the proton on C6, a signal of C11 as well as the expected signals of C7 and C1′ (ester carbonyl-C). In the second difference spectrum (Fig. 4b), after irradiation of the one proton of the methylene group C8, only the expected signal of C7 appears. This confirms the finding of the preliminary NOE experiment and, due to the spatial proximity of the proton of the methine group C6 to C11 (lactone carbonyl-C), proves the presence of structure **1a**.

Thus, as a result of increased selectivity, the hetero-NOE experiment can be successfully employed even when strongly overlapping proton spectra are obtained.

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[6] R. Kesse, A. Pfenninger, A. Roesle, *Helv. Chim. Acta 62* (1979) 326.

Novel Cobalt- and Nickel-Clusters with S and PPh_3 as Ligands; Crystal Structures of $[Co_7S_6(PPh_3)_5Cl_2]$, $[Co_6S_8(PPh_3)_6]^+[CoCl_3(THF)]^-$, $[Ni_8S_6Cl_2(PPh_3)_6]$, and $[Ni_8S_5(PPh_3)_7]$**

By *Dieter Fenske,* Johannes Hachgenei,* and *Johannes Ohmer*

We recently described a simple method for the preparation of PPh-bridged clusters of Co and Ni. Reaction of MCl_2 (M = Co, Ni) with $PhP(SiMe_3)_2$ in the presence of Ph_3P leads to the formation of $SiMe_3Cl$ and $[Co_4(\mu_3\text{-}PPh)_4(PPh_3)_4]$ or **1**.[1,2] **1** contains four coordinatively unsaturated Ni atoms which are shielded in a crown-like fashion by Ph groups of the PPh- and PPh_3-ligands. As a result the cluster contains a channel of about 400–500 pm in diameter, and only small molecules, e.g. CO, can bind to the four Ni atoms with coordination vacancies.

In attempts to prepare clusters with greater coordination gaps we allowed $S(SiMe_3)_2$[3] to react with $[MCl_2(PPh_3)_2]$ (**1a**, M = Co; **1b**, M = Ni). Reactions of transition metal halides with $S(SiMe_3)_2$ have already been reported. Normally, metal sulfides are formed; only in one case could

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the formation of a binuclear complex be observed.[4] Reaction of **1a** with $S(SiMe_3)_2$, on the other hand, leads to formation of clusters. With tetrahydrofuran as solvent, a crystalline black precipitate consisting of **2** and **3**, separates out within a few minutes.[5]

$$[CoCl_2(PPh_3)_2] \xrightarrow[THF]{S(SiMe_3)_2} \underset{\textbf{1a}}{} [Co_6S_8(PPh_3)_6][CoCl_3(THF)] + [Co_7S_6(PPh_3)_5Cl_2]$$
$$\textbf{2} \qquad\qquad \textbf{3}$$

Reaction of the complex **2** with $[NBu_4]PF_6$ furnishes $[Co_6S_8(PPh_3)_6]PF_6$.

2 and $[Co_6S_8(PPh_3)_6]PF_6$ are paramagnetic, and, at 300 K, have magnetic moments of 4.55 and 2.49 μ_B, respectively. This manifests itself, e.g., in the ^{1}H-NMR spectrum of **2** by various isotropic shifts for the phenyl protons ($\delta = 6.60$–7.50).

The structures of **2** and **3** were determined by X-ray crystallography.[6] **2** contains isolated $[Co_6(\mu_3\text{-}S)_8(PPh_3)_6]^+$ (Fig. 1) and $[CoCl_3(THF)]^-$ ions.[7] The cluster cation consists of an almost regular Co_6-octahedron ($\bar{1}$ symmetry), whose Co_3-faces are each bridged by a μ_3-S ligand.[8, 9] In addition, each Co atom is bound to the P-atom of a PPh_3 ligand. The Co_6-cluster contains 97 valence electrons, i.e. 13 electrons more than expected according to the 18-electron rule.[10, 11] The Co–Co bond lengths (280–282 pm) correspond to those found in $[Co_6S_8(PEt_3)_8]^+$,[12] but are distinctly longer than those in $[Co_6(CO)_{15}]^{2-}$ and $[Co_6(CO)_{14}]^{4-}$ (246–254 pm).[13, 14]

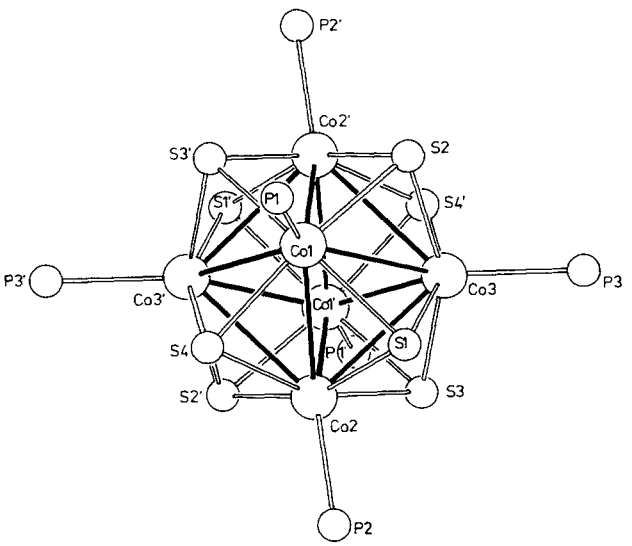


Fig. 1. Structure of the $[(Co_6(\mu_3\text{-}S)_8(PPh_3)_6]^+$ ion in the crystal of **2** (without phenyl groups) [6]. P1–P3 are the atoms of the PPh_3 ligands. (The dashed atomic positions are generated by the inversion center.) Important bond lengths [pm] (±0.2 pm) and bond angles [°] (±0.1°): Co–Co 279.8–282.8, Co–(μ_3-S) 220–223, Co–P 217.8–218.1; Co–Co–Co 59.4–60.5, 89.3–90.7, P–Co–(μ_3-S) 91–111, S1–Co1–S2 86.9, S2–Co1–S3′ 88.1, S3′–Co1–S4 87.7, S4–Co1–S1 87.8, S1–Co1–S3′ 156.8, S2–Co1–S4 156.5.

A complex containing seven Co atoms is present in **3** (Fig. 2). Formally, the Co_7-cluster can be derived from a cube from which one corner has been removed. The cluster distorts, and forms a polyhedron of three Co_4-faces and four Co_3-faces. The polyhedron faces (Co1, Co2, Co3, Co5; Co2, Co3, Co6, Co7; Co2, Co4, Co5, Co7) are not planar; the Co atoms lie 16 pm above or below the medium plane. The μ_4-S–Co ligand distances are 217–225 pm. Three of the Co_3 faces (Co1, Co3, Co6; Co1, Co4, Co5; Co4, Co6, Co7) are bound to μ_3-S ligands (Co–S 213.6–222.8 pm). The Co atoms in **3** are coordinated to a distorted tetrahedral array of three S atoms and the P atom of the PPh_3 ligand (Co1, Co2, Co4, Co6, Co7) or three S atoms and a Cl ligand (Co3, Co5). The Co–Co distances in the cluster are 257.4–263.7 pm. These values are comparable with the Co–Co bond lengths in $[Co_8S_6(SPh)_8]^{4-}$ (263–266 pm).[15] Three bonds (Co1–Co4, Co1–Co6, Co4–Co6), however, are markedly longer (286.1–289.7 pm). Presumably, this is the reason for **3** (99 valence electrons) already reacting with CO at room temperature to give $[Co_7(CO)_3Cl_2S_6(PPh_3)_5]$ (ν(CO) = 1960, 1940 cm^{-1}, 105 valence electrons).

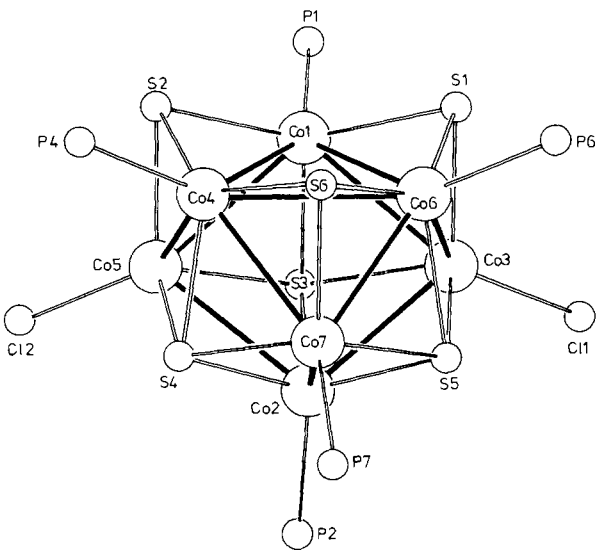


Fig. 2. Crystal structure of the cluster **3** (without phenyl groups) [6]. P1, P2, P4, P6 and P7 are the P atoms of the PPh_3 ligands. Important bond lengths [pm] and bond angles [°] (±0.1°): Co1–Co3 259.3(2), Co1–Co4 286.1(2), Co1–Co5 260.2(2), Co1–Co6 289.6(2), Co2–Co3 263.7(2), Co2–Co5 265.2(2), Co2–Co7 260.4(2), Co3–Co6 258.7(2), Co4–Co5 257.4(2), Co4–Co6 289.7(2), Co4–Co7 260.5(2), Co6–Co7 257.7(2), Co–P 220.9–227.5(4), Co–Cl 220.8–222.8(4), Co1–S 214.0–218.1(3), Co2–S 217.0–220.0(4), Co3–S 221.0–225.2(3), Co4–S 215.8–223.3(3), Co5–S 222.5–224.8(3), Co6–S 214.0–217.1(3), Co7–S 217.6–220.8(3); Co–Con–Co: Con = Co1 55.9–101.7, Co2 95.2–95.8, Co3 68.0–81.8, Co4 55.6–102.1, Co5 67.1–81.9, Co6 56.1–100.9, Co7 68.0–82.6; Co–(μ_3-S)–Co 71.8–85.3, Co–(μ_4-S)–Co 70.1–121.9, P–Co–S 94–119.4, Cl–Co–S 109.8–116.3.

The reaction of PR_3 complexes of the transition metal halides with $S(SiMe_3)_2$ also leads in other cases to S-bridged clusters. For example, reaction of $[NiCl_2(PPh_3)_2]$ with $S(SiMe_3)_2$ furnishes a mixture of **4** and a substance whose structure is so far unknwon.[16] According to analysis it is the complex **5**, which is readily soluble in THF and acetone and can be separated from the sparingly soluble **4**.

$$[Ni_8S_6Cl_2(PPh_3)_6] \qquad [NiS(PPh_3)Cl]_n \qquad [Ni_8S_5(PPh_3)_7]$$
$$\textbf{4} \qquad\qquad \textbf{5} \qquad\qquad \textbf{6}$$

A crystal structure analysis of **4** (Fig. 3) showed that a slightly distorted Ni_8 cube ($\bar{1}$ symmetry) is present which bears a μ_4-S ligand on each face.[17] In addition, the Ni atoms are bound to the P atom of the PPh_3 ligand (Ni1, Ni2, Ni4, Ni1′, Ni2′, Ni4′) or to Cl^- (Ni3, Ni3′). Consequently, the Ni is coordinated in a distorted tetrahedral fashion. **4** contains 118 valence electrons, and the Ni–Ni distances (266–270 pm) compare with those found in other Ni_8 clusters.[1, 2, 18]

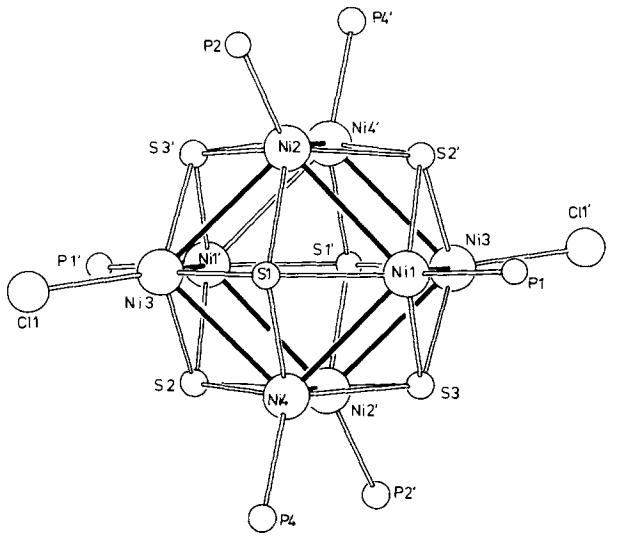


Fig. 3. Crystal structure of the cluster **4** (without phenyl groups). P1, P2, and P4 correspond to the P atoms of the PPh_3 ligands [17]. Important bond lengths [pm] (±0.1 pm) and bond angles [°] (±0.1°): Ni–Ni 265.8–271.0, Ni–(μ_4-S) 217.9–223.8, Ni–P 224.5–226.3, Ni–Cl 220.3; Ni–Ni–Ni 88.2–92.6, P–Ni–(μ_4-S) 107.9–125.8, Cl–Ni–(μ_4-S) 109.8–121.7, Ni–(μ_4-S)–Ni 74.2–76.9 (*cis*), 116.0–119.6 (*trans*).

Reduction of **4** with sodium amalgam in THF in the presence of CO affords $[Ni_8(CO)_2S_6(PPh_3)_6]$. Intercalation of metal atoms, as occurs during the reduction of $[Ni_8Cl_4(\mu_4\text{-}PPh)_6(PPh_3)_4]$, was, however, not observed.[2]

Reaction of **5** with Zn (in THF) leads to formation of **6** in 60% yield.[16]

6[19] (Fig. 4) is a Ni_8 cluster (114 valence electrons) consisting of two edge-to-edge coupled trigonal bipyramids. Owing to the large spatial requirement of the PPh_3 ligand attached to Ni1, Ni2, Ni3, Ni4, Ni5, Ni6, and Ni8, not all polyhedral faces can be occupied by S-ligands. Ni1, Ni4, and Ni6 and Ni3, Ni5, and Ni8 are bound to μ_3-S ligands. The Ni–S bond lengths (211–217 pm) and Ni–S–Ni bond angles (76.7–81.5°) are comparable with those in other complexes that contain μ_3-S ligands.[20] S3, S4, and S5 can also be regarded as μ_3-ligands (Ni–S 213–219 pm). However, the Ni–S–Ni bond angles (72.4–137.4°) are considerably larger. In addition there is still weak interaction between Ni7 and S3 (258.6 pm) and between Ni7 and S4 (268.8 pm).

The Ni–Ni distances can be classified into three groups: 1) 240–252 pm, from Ni7 to the Ni atoms bound thereto; 2) 263–268 pm; 3) 275–297 pm (Ni2–Ni6, Ni4–Ni6, Ni2–Ni5, Ni2–Ni3, Ni5–Ni8, Ni4–Ni6). Comparable bond lengths have also been observed in other Ni clusters.[20, 21]

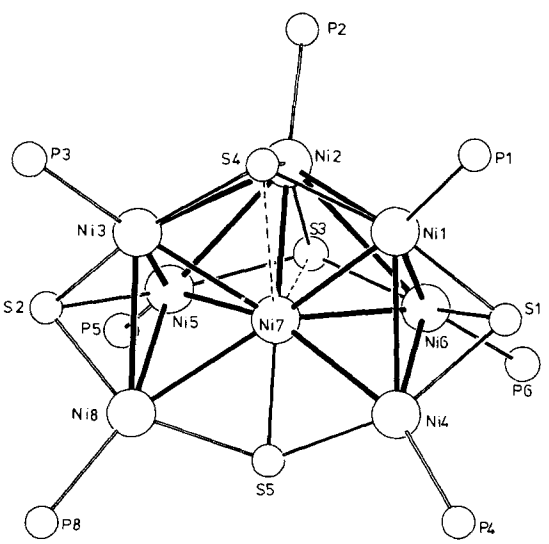


Fig. 4. Crystal structure of the cluster **6** (without phenyl groups). P1–P6 and P8 correspond to the P atoms of the PPh_3 ligands [19]. Important bond lengths [pm] (±0.3 pm) and bond angles [°] (±0.1°): Ni1–Ni2 268.0, Ni1–Ni4 268.8, Ni1–Ni6 263.0, Ni2–Ni3 276.7, Ni2–Ni5 276.6, Ni2–Ni6 295.7, Ni2–Ni7 239.5, Ni3–Ni5 267.2, Ni3–Ni7 247.2, Ni3–Ni8 267.2, Ni4–Ni6 275.5, Ni4–Ni7 250.9, Ni5–Ni7 241.6, Ni5–Ni8 282.2, Ni6–Ni7 243.9, Ni7–Ni8 252.7, Ni–P 214.8–218.5, Ni–(μ_3-S) 210.4–221.0, S3–Ni7 258.6, S4–Ni7 268.8; Ni–Nin–Ni: Nin = Ni1 55.2–110.5, Ni2 53.0–113.0, Ni3 54.1–108.6, Ni4 55.0–57.8, Ni5 54.6–61.1, Ni6 51.6–101.1, Ni7 64.6–144.7, Ni8 53.4–58.1; Ni–S1–Ni 76.2–80.1, Ni–S2–Ni 76.2–81.5, Ni–S3–Ni 78.9–118.4, Ni–S4–Ni 75.8–119.5, Ni–S5–Ni 72.4–137.4.

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2, 97415-85-5; **3**, 97403-25-3; **4**, 97415-86-6; **5**, 97403-27-5; **6**, 97403-28-6; $[CoCl_2(PPh_3)_2]$, 14126-40-0; $[CoS_8(PPh_3)_6]PF_6$, 97403-30-0; $[NiCl_2(PPh_3)_2]$, 14264-16-5; $[Ni_8(CO)_2S_6(PPh_3)_6]$, 97403-31-1.

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[5] Procedure: A solution of **1a** (16 g, 0.0245 mol) in THF (100 mL) was prepared under nitrogen and treated dropwise with 4.5 g (0.0252 mol) of $S(SiMe_3)_2$. The solution immediately changed color from blue to brown, and a mixture of **2** and **3** precipitated (yield 6.6–7.0 g). After addition of 100 mL of toluene and filtration, the residue was treated with toluene/$C_2H_4Cl_2$. About 4.1 g of **3** went into solution. (On covering the solution with pentane, **3** was obtained as long, black crystals. Crystals of the very sparingly soluble compound **2** were obtained by dissolution of the residue of crystallization in THF/$C_2H_4Cl_2$. After covering the solution with pentane, **2** separated out in the form of black crystals.
[6] **2** crystallizes with four molecules of THF per formula unit. Space group $P\bar{1}$, Lattice constants (180 K): $a = 1482.9(5)$, $b = 1603.6(5)$, $c = 2631.2(8)$ pm; $\alpha = 88.42(3)$, $\beta = 84.23(2)$, $\gamma = 76.31(3)°$, $Z = 2$, $\mu(Mo_{K\alpha}) = 11.5$ cm^{-1}. Syntex R3, $2\theta \leq 49°$, 19960 reflections, 13200 with $I > 2\sigma(I)$. Patterson methods, Co, P, S, Cl anisotropic, Ph refined as rigid group (C–C 139.5 pm). $R_1 = 0.078$, $R_2 = 0.069$.—**3**: crystals from toluene/C_2H_4Cl/pentane. **3** crystallizes with 1 mole of toluene per formula unit. Space group $P2_12_12_1$. Lattice constants (180 K): $a = 1813.7(7)$, $b = 1883.5(7)$, $c = 2896.2(10)$ pm; $Z = 4$, $\mu(Mo_{K\alpha}) = 13.5$ cm^{-1}. Syntex R3, $2\theta \leq 50°$, 10716 reflections, 8629 reflections with $I > 2\sigma(I)$. Patterson methods, Co, P, S, Cl, anisotropic, C atoms of the Ph groups isotropic (H calculated). $R_1 = 0.063$, $R_2 = 0.059$. Further details of the crystal structure investigations are available on request from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2, on quoting the depository number CSD 51402, the names of the authors, and the full citation of the journal.
[7] Important bond lengths [pm]: Co–Cl 222–223(0.2), Co–O1 206.2(10), O1–LC1 144(2), O1–LC4 145(2), LC1–LC2 155(2), LC2–LC3 151(3), LC3–LC4 151(3), (LCm and O1: C atoms and O atom of the THF ligand). Bond angles [°] (±0.2°): Cl1–Co7–Cl2 115.0, Cl1–Co7–Cl3 114.2, Cl1–Co7–O1 101.0, Cl2–Co7–Cl3 118.1, Cl2–Co7–O1 104.7, Cl3–Co7–O1 100.3.
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[15] G. Christou, K. S. Hagen, R. H. Holm, *J. Am. Chem. Soc. 104* (1982) 1744.
[16] Procedure: **1b** (16.3 g, 0.025 mol) was dissolved in THF (100 mL) under N_2 and treated with 13.4 g (0.075 mol) of $S(SiMe_3)_2$. The solution rapidly turned brown, and a fine crystalline precipitate separated out. After addition of 100 mL of toluene and filtration, 6.2 g of the reaction mixture were obtained, 1.6 g of which went into solution on treatment with THF (100 mL). The residue consisted of pure **4** (66% yield based on $[NiCl_2(PPh_3)_2]$). The THF solution was treated with 2 g of zinc powder and heated to about 60°C for 2 h. After filtration the solution was covered with heptane. **6** crystallized out at the phase boundary as black, flaky crystals. Crystals of **4** were obtained on recrystallization from toluene/$C_2H_4Cl_2$.
[17] **4** crystallizes with 1 mole of $C_2H_4Cl_2$ per formula unit. Space group: $P2_1/n$, lattice constants (180 K): $a = 1683.5(5)$, $b = 1553.8(3)$, $c = 2116.4(8)$ pm; $\beta = 95.21°$, $Z = 4$, $\mu(Mo_{K\alpha}) = 16.7$ cm^{-1}. Syntex R3, $2\theta \leq 55°$, 13716 reflections, 10889 with $I > 2\sigma(I)$, empirical absorption correction. Patterson methods, all atoms (except H) refined anisotropically, $R_1 = 0.053$, $R_2 = 0.054$ [6].
[18] L. D. Lower, L. F. Dahl, *J. Am. Chem. Soc. 97* (1975) 6917.
[19] Crystals of **6** from THF/pentane. **6** crystallizes with 2 moles of THF (disordered) and 1 mole of pentane. Space group: $P2_1/n$, lattice constants (180 K): $a = 1656.8(4)$, $b = 1664.3(4)$, $c = 4917.2(11)$ pm; $\beta = 94.40(2)°$, $\mu(Mo_{K\alpha}) = 13.3$ cm^{-1}, $Z = 4$. Syntex R3, $2\theta \leq 45°$, 19189 reflections, 13528 with $I > 2\sigma(I)$, empirical absorption correction. Patterson methods, Ni, P, S anisotropic, Ph refined as rigid group (C–C 139.5 pm). $R_1 = 0.078$, $R_2 = 0.079$ [6].
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Crinipellins, the First Natural Products with a Tetraquinane Skeleton**

By *Timm Anke, Jutta Heim, Falk Knoch, Ursula Mocek, Bert Steffan,* and *Wolfgang Steglich**

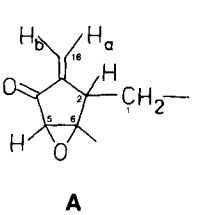
Dedicated to Professor Hans Musso on the occasion of his 60th birthday

Several years ago, we described an antibiotic that is produced by cultures of the basidiomycete *Crinipellis stipitaria* (Agaricales).[1] An investigation of several strains of this fungus has now led to the isolation of several related compounds, crinipellin A, crinipellin B, and *O*-acetylcrinipellin A, the latter of which is identical with the "crinipellin" we described earlier. In addition to these antibiotically active compounds, two inactive accompanying substances were found, dihydrocrinipellin B and tetrahydrocrinipellin A.

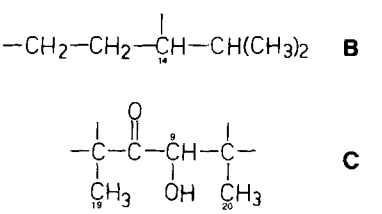
According to its NMR spectra (Table 1),[2] crinipellin A possesses a cyclopentane ring that contains an α-methylene ketone group and an epoxide function in an analogous arrangement to the hirsutane derivatives complicatic acid[3] and hypnophilin **4**.[4] This is shown by, among other things, the characteristic long-range coupling $^5J = 1.1$ Hz between the 5-H and the 18-H_a *trans* to the carbonyl group.[4,5] In contrast, 18-H_b exhibits a ^4J coupling of 1.4 Hz to the angular 2-H, which, along with the methylene protons on C-1, forms an ABX system. The partial structure **A** is thus obtained. From the ^{1}H,^{1}H-correlated 2D NMR spectrum, the proton sequence **B** can be derived starting from the isopropyl group, and, by selective decoupling, the acyloin moiety **C** can be recognized in the ^{13}C-NMR spectrum. Since the signal of the 20-methyl group in the ^{13}C-NMR spectrum exhibits two ^3J couplings to 9-H and 14-H, the partial structures **B** and **C** can be joined. By selective decoupling of the 19-methyl group, the multiplet of C-6 simplifies, allowing a relationship between the partial structures **A** and **C** to be obtained. Taking into consideration the presence of four carbon rings in crinipellin and the remaining quaternary C atom ($\delta = 62.3$) gives the structure **1a** for crinipellin A. The relative stereochemistry can be determined by NOE difference measurements. Acetylation of **1a** with acetic anhydride/4-(dimethylamino)pyridine affords *O*-acetylcrinipellin A **1b**, which was shown to be identical with the natural product described earlier.[1]

Table 1. ^{1}H- and ^{13}C-NMR data for crinipellin A **1a** (400 and 100.62 MHz, respectively, δ values, solvent $CDCl_3$ as internal standard). The NOE relationships are indicated. All ^{1}H- and ^{13}C-NMR assignments were confirmed by 2D NMR data.

1-H_a	1.41 (dd)	14.2/13.2	C-1	37.8	Tm	133
1-H_b	2.53 (dd)	14.2/7.5				
2-H	3.10 (ddddd)	13.2/7.5/1.4/0.8/0.5	C-2	42.0	Dm	136
			C-3	145.6	m	
			C-4	196.0	m	
5-H	3.48 (dd)	1.1/0.8	C-5	58.5	Dd	196/4
			C-6	77.8	m	
			C-7	50.0	ddd	9/4/2
			C-8	214.5	dq	8/4
9-H	4.42 (d)	2.5	C-9	84.7	Ddq	138/8.5/4.5
			C-10	53.9	m	
			C-11	62.3	m	
12-H_a	1.89 (ddd)	8.7/8.7/5.4	C-12	32.7	Tdd	129/8/4
12-H_b	1.61 (m)					
13-H_a	1.61 (m)		C-13	23.2	Tm	129
13-H_b	1.61 (m)					
14-H	1.33 (doub.)		C-14	51.8	Dm	120
15-H	2.11 (dsep)	7.0/2.5	C-15	28.2	Dm	129
16-CH_3	0.85 (d)	7.0	C-16	19.6	Qm	125
17-CH_3	0.82 (d)	7.0	C-17	24.8	Qm	125
18-H_a	5.49 (ddd)	1.1/0.5/0.5	C-18	123.5	Td	161/3
18-H_b	6.15 (dd)	1.4/0.5				
19-CH_3	1.04 (s)		C-19	15.1	Q	130
20-CH_3	1.33 (s)		C-20	16.2	Qdd	127/6/5
9-OH	2.88 (d)	2.5				



A



B

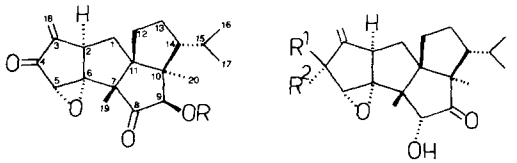
C

Similarly, the constitution **2a** can be derived for crinipellin B,[2] and was confirmed by an X-ray structure determination[6] (Fig. 1).

The structures **2b** and **3b** are obtained for dihydrocrinipellin B[2] and tetrahydrocrinipellin A,[2] respectively. The absence of the α-methylene ketone moiety explains the loss of biological activity.[7]

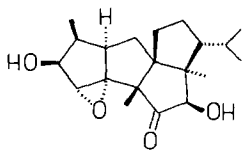
[*] Prof. Dr. W. Steglich, Dr. B. Steffan, Dipl.-Chem. U. Mocek
Institut für Organische Chemie und Biochemie der Universität
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Dr. F. Knoch
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Paul-Ehrlich-Strasse 22, D-6570 Kaiserslautern (FRG)

[**] Antibiotics from Basidiomycetes, Part 21. This work was supported by the Deutsche Forschungsgemeinschaft and the Bundesministerium für Forschung und Technologie. We thank Prof. *R. Appel* for help in the crystal structure determination.—Part 20: G. Schramm, B. Schwalge, B. Steffan, W. Steglich, *Liebigs Ann. Chem. 1984*, 1616.

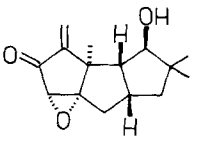


1a, R = H
1b, R = $COCH_3$

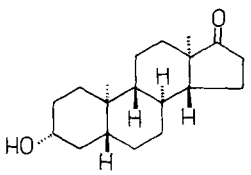
2a, $R^1 = R^2 = O$
2b, $R^1 = OH$, $R^2 = H$



3



4



5

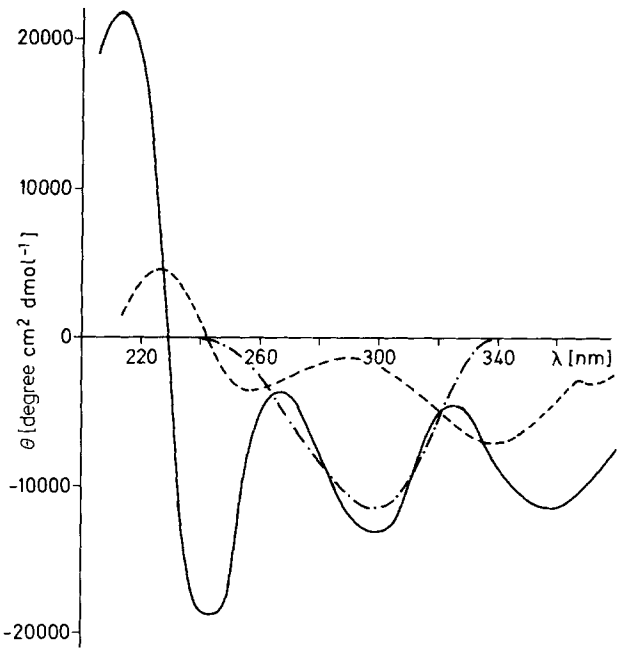


Fig. 2. CD curves of crinipellin B **2a** (—), hypnophilin **4** (------), and *ent*-3β-hydroxy-5α-androstan-17-one **5** (-·-·-). $[\theta] = 3300$ ($\varepsilon_l - \varepsilon_R$).

The crinipellins contain two isolated chromophores in asymmetric environments. We therefore attempted to derive their absolute configurations by comparison of their

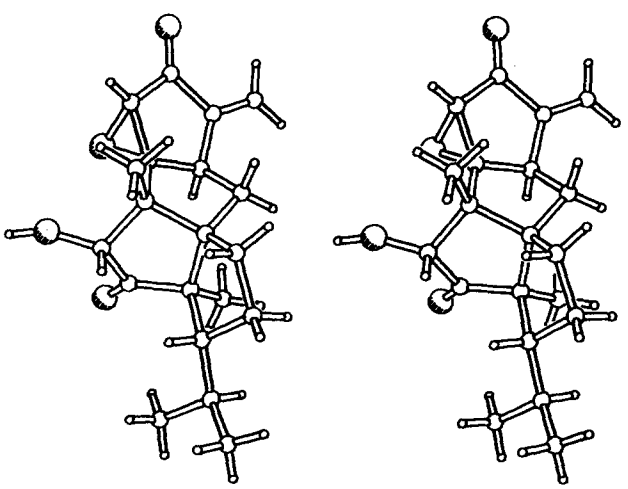


Fig. 1. Crystal structure of crinipellin B **2a**; stereograph.

CD curves with those of reference materials (Fig. 2). The CD curve of crinipellin B exhibits a negative Cotton effect at 290 nm, in accord with the CD spectrum of *ent*-3β-hydroxy-5α-androstan-17-one **5**.[8] If it is assumed that the shape of the CD curves is determined to a first approximation by the immediate environment of the CO groups, the configuration shown in Formula **2a** is obtained for crinipellin B. It is supported by comparison with the CD spectrum of hypnophilin **4**,[9] the shape of whose curve is in qualitative agreement with that of **2a**.

In recent years, sesquiterpenoids having a triquinane skeleton have especially attracted the attention of synthetic chemists since many of these compounds are biologically active natural products.[13] The discovery of the crinipellins, the first tetraquinanes of the diterpenoid type, demonstrates that the variety of possible cyclopentanoid natural products has not yet been fully explored.

Biochemically, the crinipellins undergo the same type of cyclization as the dolabellanes isolated from a moss[10] and from marine organisms.[11] Moreover, for the crinipellins, a methyl group migration subsequently takes place;[12] the carbocation formed is stabilized by formation of the tetraquinane system.

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CAS Registry numbers:
1a, 97294-60-5; **1b**, 97315-00-9; **2a**, 97294-61-6; **2b**, 97294-62-7; **3**, 97294-63-8.

[1] J. Kupka, T. Anke, F. Oberwinkler, G. Schramm, W. Steglich, *J. Antibiot.* *32* (1979) 130.

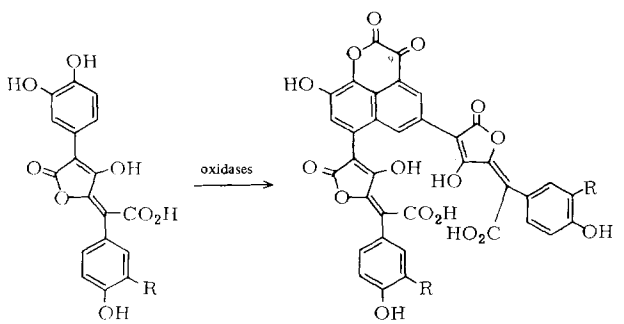
[2] Crinipellin A **1a**: mp = 148°C. $[\alpha]_D$ −168 ($c = 0.35$, $CHCl_3$). CD (MeOH): $[\theta]_{375}$ −6450, $[\theta]_{367}$ −8240, $[\theta]_{304}$ −24720, $[\theta]_{263}$ 0, $[\theta]_{255}$ +1430, $[\theta]_{222}$ +11700. UV (MeOH): $\lambda_{max}(\lg\varepsilon) = 235$ nm (3.74). IR (KBr): 3560, 3465, 1740, 1730 (sh), 1640 cm^{-1}. MS (direct inlet, 180°C, 70 eV): *m/z* 330.1834 (M^+, 34.3%, calcd. for $C_{20}H_{26}O_4$ 330.1831), 302 (13.9), 259 (24.3), 241 (6.7), 189 (100).— **1b**: mp = 107°C. $[\alpha]_D$ −136 ($c = 0.66$, ethyl acetate).—Crinipellin B **2a**: mp = 150—151°C. $[\alpha]_D$ −118.5 ($c = 0.27$, $CHCl_3$). $[\theta]_{357}$ −11530, $[\theta]_{325}$ −4400, $[\theta]_{299}$ −13190, $[\theta]_{267}$ −3640, $[\theta]_{243}$ −18650, $[\theta]_{229}$ 0, $[\theta]_{213}$ +21840. ^{1}H-NMR ($CDCl_3$, selected): $\delta = 1.08$ (s, 20-CH_3), 1.31 (s, 19-CH_3), 4.73 (s, 8-H). ^{13}C-NMR ($CDCl_3$, selected): $\delta = 10.31$ (Qd, $J = 127/5$ Hz, C-20), 21.37 (Qd, 129/5 Hz, C-19), 79.80 (Dq, 143.5/4 Hz, C-8), 217.44 (dq, 8/3.5 Hz, C-9).— **2b**: oil. $[\alpha]_D$ −63.9 ($c = 1.86$, MeOH). ^{1}H-NMR (CD_3OD, selected): $\delta = 1.35$ (s, 19-CH_3), 2.37 (ddddd, $J = 12.8/7.2/2.2/1.2/0.8$ Hz, 2-H), 3.26 (ddd, 0.8/0.8/0.5 Hz, 5-H), 4.30 (s, 4-H), 4.80 (s, 8-H), 5.13 (dddd, $J = 2.2/1.2/0.8/0.6$ Hz, 18-H_a), 5.22 (ddd, 1.2/1.2/0.6 Hz, 18-H_b). ^{13}C-NMR (CD_3OD, selected): $\delta = 21.15$ (Qd, $J = 128/6$ Hz, C-19), 44.32 (m, C-7), 47.10 (Dm, 135 Hz, C-2), 60.19 (Ddd, 186/5.5/3 Hz, C-5), 74.15 (Dm, 150 Hz, C-4), 80.34 (m, C-6), 81.21 (Dq, 142/5.5 Hz, C-8), 115.80 (Tdd, 157/3/2.5 Hz, C-18), 155.46 (m, C-3), 220.46 (dq, 8/4 Hz, C-9). MS: *m/z* 332.1979 (M^+, 27.9%, calcd. for $C_{20}H_{28}O_4$ 332.1988).— **3**: mp = 182°C. $[\alpha]_D$ −84.3° ($c = 1.06$, MeOH). ^{1}H-NMR ([D_6]DMSO/CD_3OD, selected): $\delta = 0.95$ (d, $J = 7.5$ Hz, 18-CH_3), 1.90 (m, 3-H), 2.16 (ddd, 13.5/7.0/7.0 Hz, 2-H), 3.28 (br. s, 5-H), 3.92 (d, 6 Hz, 4-H). ^{13}C-NMR ([D_6]DMSO/CD_3OD, selected): $\delta = 9.73$ (Qd, $J = 126/5$ Hz, C-18), 39.03 (Dm, 148 Hz, C-4), 80.04 (m, C-6). MS: *m/z* 334.2151 (M^+, 37.1%, calcd. for $C_{20}H_{30}O_4$ 334.2144).

[3] G. Mellows, P. G. Mantle, T. C. Feline, *Phytochemistry 13* (1973) 2717.
[4] W. Steglich, *Pure Appl. Chem. 53* (1981) 1233; B. M. Giannetti, W. Steglich, J. Heim, T. Anke, unpublished results.
[5] F. W. Commer, F. McCapra, I. H. Qureshi, J. Trotter, A. I. Scott, *Tetrahedron 23* (1967) 4761.
[6] **2a**: $P2_1$, $a = 756.3(1)$, $b = 766.6(1)$, $c = 1482.2(2)$ pm, $\beta = 92.06(1)°$, $V = 858.8 \cdot 10^6$ pm^3, $\sigma_{calcd} = 1.28$ g/cm^3, $Z = 2$. Direct methods (SHELXTL), 2160 reflections, $R = 0.048$, $R_w = 0.039$. Further details of the crystal structure investigation are available on request from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2, by quoting the depository number CSD 51231, the names of the authors, and the journal citation.
[7] E. Fujita, Y. Nagao, *Bioorg. Chem. 6* (1977) 287; see also T. Anke, W. H. Watson, B. M. Giannetti, W. Steglich, *J. Antibiot. 34* (1981) 1271.
[8] The CD spectrum of **5** in Figure 2 was drawn using the CD spectrum of 3β-hydroxy-5α-androstan-17-one; see P. Crabbé: *Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry*, Holden-Day, San Francisco 1965, p. 21.
[9] The CD spectrum of **4** agrees well with that of complicatic acid [3], whose absolute configuration is confirmed by correlation with that or hirsutic acid [5].
[10] A. Matsuo, K. Uohama, S. Hayashi, J. D. Conolly, *Chem. Lett. 1984*, 599.
[11] Review: D. J. Faulkner, *Nat. Prod. Rep. 1* (1984) 251.
[12] Diterpenoids with this skeletal modification are known. B. F. Bowden, J. C. Braekman, J. C. Coll, S. J. Mitchell, *Aust. J. Chem. 33* (1980) 927; M. Kobayashi, B. W. Son, T. Fujiwara, Y. Kyogoku, I. Kitagawa, *Tetrahedron Lett. 25* (1984) 5543.
[13] Cf. L. P. Paquette, *Top. Curr. Chem. 119* (1984) 1.

A Simple Approach to the Naphtho[1,8-*bc*]pyrandione System**

By *Wolfgang Steglich,* Hans-Theo Huppertz,* and *Bert Steffan*

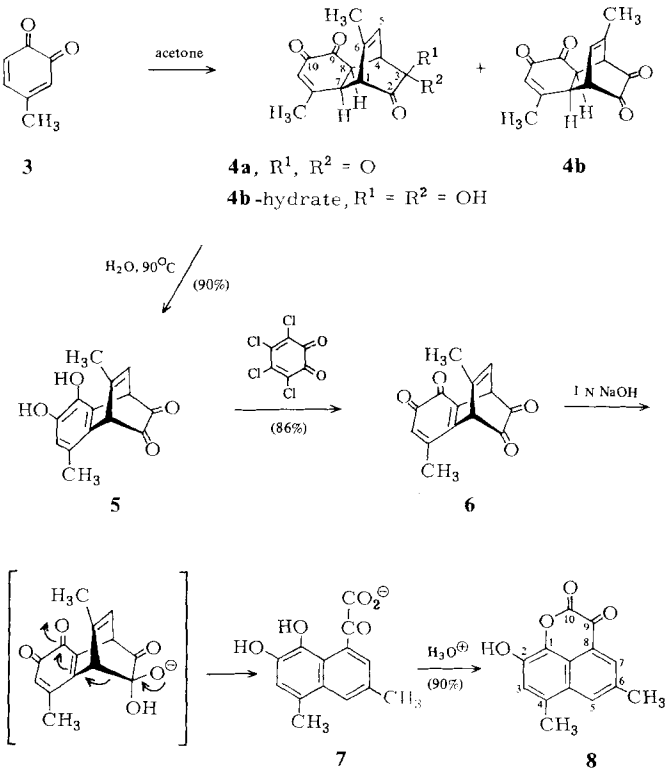
The bolete pigments badione A and B, **2a** and **2b**, respectively, have a naphtho[1,8-*bc*]pyrandione partial structure,[1] which may be formed in the fungus by oxidative dimerization of the pulvinic acids **1a** and **1b**, respectively. A biosynthetic pathway involving the Diels-Alder dimerization of a 1,2-benzoquinone intermediate is conceivable.



1a, R = H
1b, R = OH

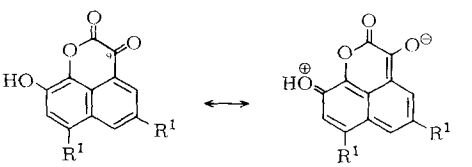
2a, R = H
2b, R = OH

In order to test this idea experimentally, we have studied the base-induced fragmentation of the model compound **6**, which is accessible from 4-methyl-1,2-benzoquinone **3** according to the procedure of *Horner* and *Dürckheimer*.[2] Thus, we have found that the dimerization of **3**[2,3] in acetone produces a 7:3 mixture of the regioisomers **4a** and **4b**, the former of which can be separated as a stable hydrate[4,5] in 36% yield by crystallization from acetone/ether. Isomerization to the diol **5**[2,5] and subsequent oxidation with tetrachloro-1,2-benzoquinone[6] gave the single tetraketone **6**.[5] When **6** is suspended in 1 N NaOH, it goes into solution within a few minutes with formation of the anion **7**. After acidification, the dark red naphtho[1,8-*bc*]pyrandione **8** is obtained in 90% yield. The formation of the naphthalene system can be rationalized according to the fragmentation shown.



3 **4a**, R^1, R^2 = O **4b**
4b-hydrate, R^1 = R^2 = OH
5 **6** **7** **8**

The spectroscopic data for **8**[5] are in good accord with those for the badione **2**.[1] The unusually high-field shift of the NMR signal ([D$_6$]DMSO) of C-9 in badione A ($\delta = 173.03$) and in **8** (172.76) may be a consequence of the importance of the dipolar resonance structure **9** in representing the ground state. **8** dissolves as the monoanion in aqueous base, turning the solution blue. After a short period of time, ring opening to **7** occurs and the solution turns green.



2, 8 **9**

The transformation of **3** into **8** can be viewed as a model for the biosynthesis of the badiones. It opens up a simple approach to the preparation of the naphtho[1,8-*bc*]pyrandiones, which have not yet been studied in detail.[7]

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Gerhard-Domagk-Strasse 1, D-5300 Bonn 1 (FRG)

[**] Fungal Pigments, Part 47. This work was supported by the Deutsche Forschungsgemeinschaft.—Part 46: B. Fugmann, B. Steffan, W. Steglich, *Tetrahedron Lett. 25* (1984) 3575.

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German version: *Angew. Chem. 97* (1985) 716

CAS Registry numbers:
2a, 90295-66-2; **2b**, 97486-15-2; **3**, 3131-54-2; **4a**, 97486-08-3; **4a** (hydrate), 97486-09-4; **4b**, 97486-10-7; **5**, 97486-11-8; **6**, 97486-12-9; **7**, 97486-13-0; **8**, 97486-14-1.

[1] B. Steffan, W. Steglich, *Angew. Chem. 96* (1984) 435; *Angew. Chem. Int. Ed. Engl. 23* (1984) 445. For the isolation of another natural product containing this partial structure, see W. A. Ayer, Y. Hoyano, I. van Altena, Y. Hiratsuka, *Rev. Latinoam. Quim. 1982*, 84.

[2] L. Horner, W. Dürckheimer, *Z. Naturforsch. B 14* (1959) 742. No further details are given on the regioselectivity of the dimerization of **3**.

[3] R. Willstätter, F. Müller, *Ber. Dtsch. Chem. Ges. 44* (1911) 2171.

[4] The structure of **4a**-hydrate was confirmed by X-ray structure determination: W. H. Watson, private communication. The formation of the hydrate is probably due to the presence of traces of water in the solvent. For *endo-cis* ring junction of the 1,2-benzoquinone dimers, see L. Horner, W. Dürckheimer, *Chem. Ber. 95* (1962) 1219.

[5] **4a**-Hydrate: light yellow needles, m.p. 128–130°C; ^{1}H-NMR ($CDCl_3$, 400 MHz): $\delta = 1.91$ (d, $J = 1.8$ Hz, 6-CH_3), 2.28 (br. s, 12-CH_3), 3.49 (dd, $J = 8.8$, 2.8 Hz, 8-H), 3.58 (br. d, $J = 8.8$ Hz, 7-H), 3.71 (dd, $J = 1.8$, 1.8 Hz, 1-H), 3.98 (dd, $J = 6.4$, 2.8 Hz, 4-H), 6.16 (ddq, $J = 6.4$, 1.8, 1.8 Hz, 5-H), 6.57 (dq, $J = 1$, 1 Hz, 11-H).—**5**, gold-yellow resin.—**6**, dark red needles, m.p. above 225°C (decomp.); ^{1}H-NMR ([D_6]DMSO): $\delta = 2.10$ (d, $J = 1.8$ Hz, 6-CH_3), 2.20 (d, $J = 1.0$ Hz, 12-CH_3), 4.42 (d, $J = 1.8$ Hz, 1-H), 4.54 (d, $J = 6.4$ Hz, 4-H), 6.30 (q, $J = 1.0$ Hz, 11-H), 6.45 (ddq, $J = 6.4$, 1.8, 1.8 Hz, 5-H).—**8**, dark red microcrystals, m.p. = 244–248°C; UV/VIS (MeOH): $\lambda_{max} = 275$, 360, 458 nm; ^{1}H-NMR ([D_6]DMSO): $\delta = 2.54$ (br. s, 6-CH_3), 2.59 (d, $J = 0.8$ Hz, 4-CH_3), 7.14 (q, $J = 0.8$ Hz, 3-H), 8.10 (br. d, $J = 1.5$ Hz, 5-H), 8.18 (br. s, $J = 1.5$ Hz, 7-H), 10.62 (br., OH); ^{13}C-NMR ([D_6]DMSO): $\delta = 18.00$ (Qd, $J = 127.4$, 5.3 Hz, 4-CH_3), 20.84 (Qt, $J = 127.4$, 4.5 Hz, 6-CH_3), 120.51 (t, $J = 6.6$ Hz, C-8a), 120.99 (Dq, $J = 158.4$, 5 Hz, C-3), 125.57 (s, C-8), 126.54 (m, C-6), 129.51 (Ddq, $J = 164$, 7.2, 4 Hz, C-7), 129.64 (d, $J = 7.0$ Hz, C-1), 132.52 (dq, $J = 5$, 4 Hz, C-4), 132.61 (Ddq, $J = 164$, 6.9, 4 Hz, C-5), 133.69 (m, C-4a), 142.33 (br. s, C-2), 154.37 (s, C-10), 172.76 (d, $J = 4.4$ Hz, C-9); MS: $m/z = 242.0575$ (10%, M^+, calcd. for $C_{14}H_{10}O_4$ 242.0579), 214 (100), 186 (6), 158 (49), 130 (14), 115 (29).

[6] L. Horner, W. Dürckheimer, *Z. Naturforsch. B 14* (1959) 741.

[7] A. B. Neill, E. D. Amstutz, *J. Am. Chem. Soc. 73* (1951) 3687, obtained traces of a substance that was assigned a naphtho[1,8-*bc*]pyrandione structure on reaction of 1,5-naphthalenediol with ethyl cyanoformate.

Monomeric, Mononuclear Enediolate Complexes of Zirconium: Molecular Geometry and Electronic Structure of the Products of Reductive CO Coupling on the Metal**

By *Peter Hofmann,* Martin Frede, Peter Stauffert, Wiltraud Lasser,* and *Ulf Thewalt*

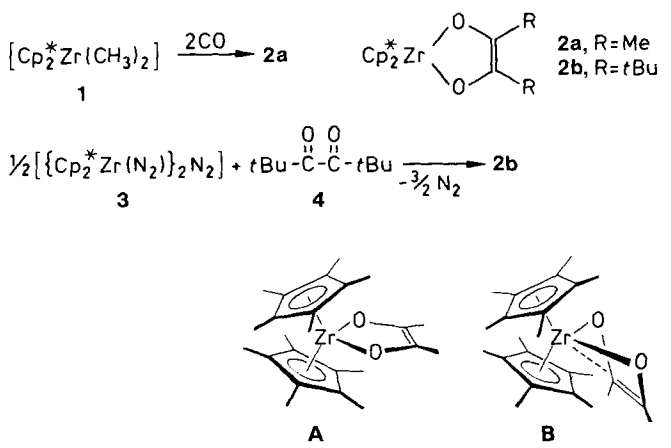
Dedicated to Professor Helmut Behrens on the occasion of his 70th birthday

Insertion reactions of CO into transition-metal–carbon bonds are of great interest.[1] Carbonylation of dialkylbis(cyclopentadienyl) complexes of early transition metals [Cp_2MR_2] and [$Cp^*_2MR_2$] ($Cp = \eta^5$-C_5H_5, $Cp^* = \eta^5$-C_5Me_5; M = Ti, Zr, Hf) in some cases results in direct reductive coupling of two CO building blocks to yield mononuclear enediolate complexes (e.g. **1** → **2a**)[4]; the initially formed η^2-acyl complexes and their chemistry have been intensely studied both experimentally[2] and theoretically.[3]

The mechanism of this remarkable synthetic reaction is not yet known with certainty.[5] In order to elucidate it, among other things, a knowledge of the ground state geometry and electronic structure of complexes **2** is important. We report here relevant results for **2a** and **2b** that confirm the predictions of MO calculations.

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2a was synthesized by the method of *Bercaw* et al.[4a] by carbonylation of **1**. The X-ray structure analysis[6] confirms the monomeric structure of the compound (Fig. 1, left). The ZrO_2C_2 chelate ring of **2a** in the crystal is not planar, but rather folded around the O–O axis so that the ZrO_2 and the O_2C_2 planes form an angle of 16.8° (Fig. 1, bottom left).

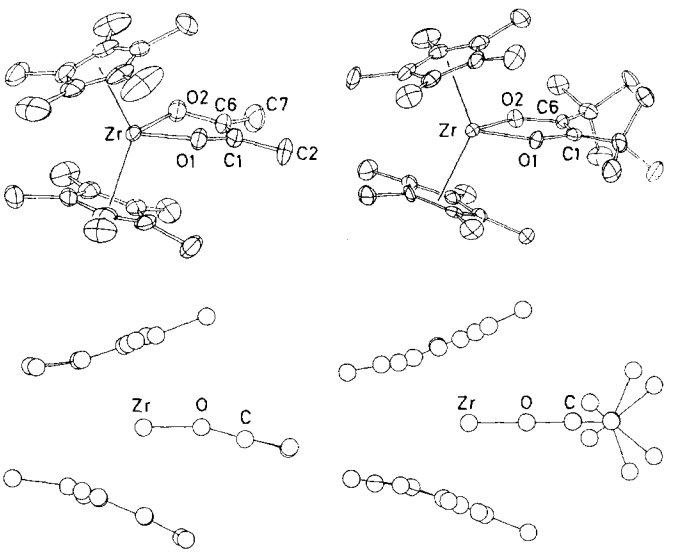


Fig. 1. Left: Structure of **2a** in the crystal; above, top view; below, side view. Selected bond lengths [Å] and angles [°]: Zr–O1 2.031(4), Zr–O2 2.048(6), O1–C1 1.371(10), O2–C6 1.367(9), C1–C6 1.315(13), Zr–C(C_5Me_5) 2.519–2.570, C–C (C_5 rings) 1.357–1.435; O1–Zr–O2 79.2(2), Zr–O1–C1 111.2(5), Zr–O2–C6 110.0(6), O1–C1–C6 117.3(7), O2–C6–C1 118.7(8), Z1–Zr–Z2 137.0(3) (Z1, Z2: centers of the C_5 rings). Right: Structure of **2b** in the crystal; above, top view; below, side view. Selected bond lengths [Å] and angles [°]: Zr–O1 2.022(6), Zr–O2 2.011(6), O1–C1 1.372(11), O2–C6 1.400(11), C1–C6 1.357(13), Zr–C(C_5Me_5) 2.525–2.616, C–C (C_5 rings) 1.372–1.458; O1–Zr–O2 75.9(2), Zr–O1–C1 118.4(5), Zr–O2–C6 118.0(5), O1–C1–C6 114.2(9), O2–C6–C1 113.5(8), Z1–Zr–Z2 136.1(4) (Z1, Z2: centers of the C_5 rings).

Thus, **2a** exhibits a geometry that deviates clearly from **A** and a σ^2 structure toward B and a σ^2,π bonding mode, in analogy to enedithiolate complexes[7] or *s-cis*-diene complexes of Cp_2Zr fragments.[8] We conclude from this finding for Cp^*_2Zr, which is a weaker Lewis acid and makes the ring folding sterically more difficult, that the nonplanar geometry is a general structural feature[10] of monomeric d°-Cp_2M enediolate complexes.[9] MO model calculations[11] for **2a**, with a planar geometry corresponding to

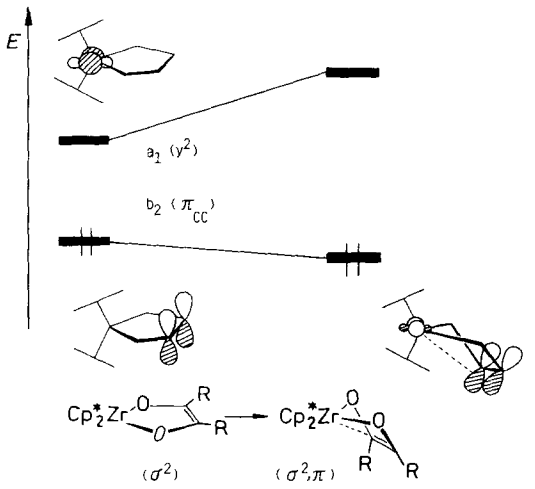


Fig. 2. Frontier orbital energies for σ^2 and σ^2,π geometries (only main contributions to the wave functions of the C=C part and on Zr shown).

Figure 2, give the π orbital of the C=C bond as the HOMO (b_2) and an MO with y^2 character (a_1) on the metal as the LUMO.

Only the folding of the ring[12] allows the π and y^2 orbitals to interact, thus causing an increase of the frontier orbital gap; the decrease in π back-bonding of the oxygen lone pairs to the metal with increasing folding of the chelate ring opposes the frontier-orbital-based trend toward a σ^2,π geometry. The deep violet color of solutions of **2a** (λ_{max}(pentane) = 495 nm, ε = 299, band extending far into the visible), which is unusual for d° systems (Zr^{IV}), may be ascribed to an electronic transition from the HOMO(π) to the LUMO (y^2) and, according to Figure 2, should be more shifted to longer wavelengths the less the ZrO_2C_2 ring is folded. In order to test this, and because explicit calculations for **2a** only gave energy differences of a few kcal between **A** and (even strongly folded) **B**, we have attempted to prepare a model system with a planar chelate ring and pure σ^2 bonding of the enediolate ligand. Accordingly, **2b** was prepared from the nitrogen complex **3**[2a] and the diketone **4**. The complex **2b** crystallizes in the form of intensely blue crystals;[13] its electronic spectrum exhibits a long-wavelength maximum with a considerable bathochromic shift (λ_{max}(pentane) = 570, ε = 120) as compared to **2a**, and its X-ray structure analysis[14] (Fig. 1, right) shows a sterically constrained, completely planar metallacycle in the crystal. The distances between the C atoms of the double bond and Zr are 0.11 Å longer than in nonplanar **2a**. It is thus shown experimentally that σ^2,π structures on d°-Cp_2M or Cp^*_2M fragments are electronically preferred also for enediolate ligands, but that the extent to which this bonding mode is found is easily influenced. The preference for such nonplanar ground-state geometries may be of significance for both stereochemistry and the mechanism of CO coupling on the metal.

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[1] a) F. Calderazzo, *Angew. Chem. 89* (1977) 305; *Angew. Chem. Int. Ed. Engl. 16* (1977) 299; b) J. P. Collman, L. S. Hegedus: *Principles and Applications of Organotransition Metal Chemistry*, University Science Books, Mill Valley, CA 1980, p. 259ff.

[2] a) P. T. Wolczanski, J. E. Bercaw, *Acc. Chem. Res. 13* (1980) 21; b) G. Erker, *ibid. 17* (1984) 103, and references cited therein.

[3] a) P. Hofmann, P. Stauffert, K. Tatsumi, A. Nakamura, R. Hoffmann, *Organometallics 4* (1985) 404; b) K. Tatsumi, A. Nakamura, P. Hofmann, P. Stauffert, R. Hoffmann, *J. Am. Chem. Soc. 107* (1985) 4440.

[4] a) J. M. Manriquez, D. R. McAlister, R. D. Sanner, J. E. Bercaw, *J. Am. Chem. Soc. 100* (1978) 2716; b) the reaction proceeds similarly for Cp in place of Cp*: G. Erker, private communication; c) for R = CH_2SiMe_3 and Th, U: J. M. Manriquez, P. J. Fagan, T. J. Marks, C. S. Day, V. W. Day, *J. Am. Chem. Soc. 100* (1978) 7112; d) the hydridochloride $(Cp_2ZrHCl)_n$ can also be carbonylated to an (albeit dimeric) enediolate complex of type **2** (R = H, Cp instead of Cp*): S. Gambarotta, C. Floriani, A. Chiesi-Villa, C. Guastini, *J. Am. Chem. Soc. 105* (1983) 1690.

[5] Crossover experiments with $[Cp^*_2Zr(CH_3)_2]$ and $[Cp^*_2Zr(CD_3)_2]$ confirm the clean intramolecular course of the reaction **1a** → **2a**: P. Hofmann, P. Stauffert, unpublished results.

[6] $P\bar{1}$, a = 13.732(4), b = 10.375(2), c = 9.760(2) Å, α = 114.12(2), β = 104.46(2), γ = 98.89(3)°, Z = 2; R = 0.068, $R_w(F)$ = 0.075 for 2906 reflections (Philips PW-1100 single-crystal diffractometer, $Mo_{K\alpha}$ radiation; $F_0 \geq 2\sigma(F_0)$, $\theta \leq 23°$). We thank *J. Riede* for technical assistance. Further details of the crystal structure investigation are available on request from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2, by quoting the depository number CSD 51296, the names of the authors, and the journal citation.

[7] A. Kutoglu, *Acta Crystallogr. Sect. B 29* (1973) 2891.

[8] a) C. Krüger, G. Müller, G. Erker, U. Dorf, K. Engel, *Organometallics 4* (1985) 215 and references cited therein; b) K. Tatsumi, H. Yasuda, A. Nakamura, *Isr. J. Chem. 23* (1983) 145.

[9] Dimerization may be possible (as described in [4d]) for Cp derivatives analogous to **2a**; this would eliminate the tendency toward σ^2,π coordination as well as remove the origin of the deep color of the systems.

[10] The σ^2,π-type coordination should therefore also be exhibited by enediamide and eneamidolate complexes of this type: cf. A. K. McMullen, I. P. Rothwell, J. C. Huffman, *J. Am. Chem. Soc. 107* (1975) 1072.

[11] Of the extended Hückel type. For parameters see [3a].

[12] J. W. Lauher, R. Hoffmann, *J. Am. Chem. Soc. 98* (1976) 1729.

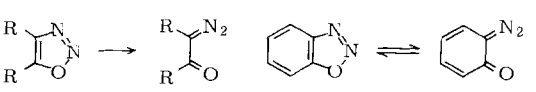
[13] Experimental procedure: **4** (0.75 g), dissolved in 20 mL of toluene, was added to **3** (1.8 g) in 40 mL of toluene at −60°C. Upon warming the mixture to room temperature, N_2 started to evolve and the solution turned from violet to dark blue. The crude product, which crystallized out upon concentration of the solution to 10 mL at −80°C, was recrystallized from pentane or sublimed. (120–130°C, 10^{-4} torr). Yield 1.7 g (76%); m.p. = 150°C (decomp.); correct C,H analysis; ^{1}H-NMR (60 MHz, C_6H_6): δ = 1.4 (s, 18H), 1.9 (s, 30H); IR (Nujol): ν = 1700 cm^{-1} (C=C).

[14] $P2_1/n$, a = 15.288(2), b = 18.937(3), c = 9.980(1) Å, β = 96.96(1)°, Z = 4; R = 0.072, $R_w(F)$ = 0.073 for 2477 reflections, ($F_0 \geq \sigma(F_0)$; $\theta \leq 23°$); see also [6].

Can 1,2,3-Oxadiazole be Stable?**

By *Minh Tho Nguyen, Anthony F. Hegarty,** and *José Elguero*

Although 1,2,3-oxadiazoles **1** were first postulated as intermediates in the 1,3-dipolar cycloaddition of dinitrogen oxide (N_2O) to alkynes almost thirty-five years ago,[1] this class of heterocycles was unknown until recently. The weakness of the NO σ-bond, which provides a thermodynamic driving force for ring opening to form the more stable acyldiazomethanes **2** was considered as the main reason for the nonexistence of stable 1,2,3-oxadiazoles.[2]



1 **2** **3** **4**

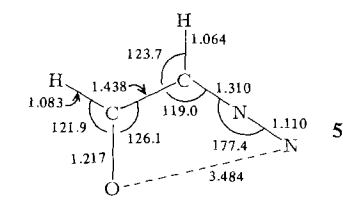
In 1979, *Schulz* and *Schweig* reported spectroscopic evidence for the existence of the 1,2,3-benzoxadiazole **3** in the gas phase (by PE spectroscopy);[5] more recently, they

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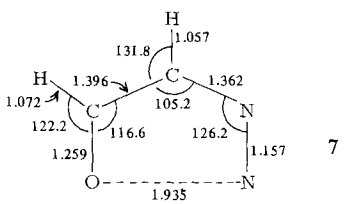
[**] *M. T. N.* and *A. F. H.* thank the Department of Education (Irish Government) for financial support.

demonstrated its existence in an argon matrix as well as in solution (by IR and UV/VIS spectroscopy).[4] Both studies indicated that there is an equilibrium between **3** and the 6-diazo-2,4-cyclohexadienone **4**. In all reaction media considered, 80—90% **3** and 10—20% **4** were present as deduced from intensities of absorption bands. If an equilibrium is established between open and cyclic forms, the existence of the thermodynamically less stable isomer will be crucially dependent upon the energy difference between them. In an attempt to quantitatively assess the relative stabilities of the isomers, we have performed ab initio calculations on the interconversion pathway between the two simplest model species **5** (**2** with R=H) and **6** (**1** with R=H) via a 1,5-dipolar cyclization. Calculations have been carried out using modified Gaussian-80 programs[5] on an AMDAHL 470 computer.

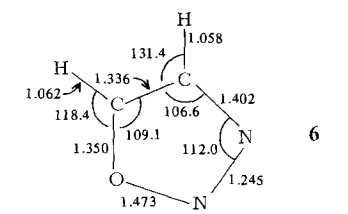
The geometrical parameters of the formyldiazomethane **5**, the 1,2,3-oxadiazole **6**, and the transition state **7** connecting them were determined using the force-field method with analytical gradients and the 3-21G basis set[6] (Fig. 1).



5



7



6

Fig. 1. HF/3-21G-optimized geometries of formyldiazomethane **5**, 1,2,3-oxadiazole **6**, and the transition state **7**. Bond lengths in Å, bond angles in degrees. For **7**, the eigenvalue of the Hessian matrix and the imaginary frequency are -0.409 and $398i$ cm^{-1}, respectively.

The calculated CO, CC, CN, and NO bond lengths in **5** are close to the values determined by X-ray analysis for 5-diazouracil and 5-diazocyclouridine compounds.[7] Of particular interest is the NO distance in three stationary points; this distance has been used as the principal reaction coordinate for the cyclization of a number of 1,5-dipoles containing an azido group.[8] At the transition state **7**, the NO distance of 1.935 Å is found to be closer to that of 1.473 Å in **6** than of 3.484 Å in **5**. In addition, the value of 1.473 Å in the cyclic form **6** is significantly larger than that of 1.438 Å determined for H—N=N—OH at the same HF/3-21G level. The former is rather similar to the typical NO single bond (1.469 Å, HF/3-21G) in hydroxylamine, H_2NOH. This clearly indicates the particular weakness of the NO bond in 1,2,3-oxadiazole.

Figure 1 also shows that the diazo group in **5** deviates by 2.6° from linearity, adopting a slightly *cis*-bent conformation. As the NO distance compresses along the reaction pathway, the CNN bond angle becomes notably bent (50° smaller).

In order to obtain improved relative energies, we have carried out single point calculations on three stationary structures employing the HF/3-21G-optimized geometries at the Hartree-Fock level with the 6-31G and 6-31G** basis sets (including polarization functions on all atoms) as well as at the level of Møller-Plesset perturbation theory to second-, third-, and fourth-order[9] (denoted MP2, MP3, and MP4SDQ); the HF/6-31G wave functions were used as references (Table 1). The MP4SDQ/6-31G** values given in Table 1, taking into consideration both the polarization and correlation effects, are obtained from the following additivity relationship:[10]

$$\Delta E(\text{MP4SDQ/6-31G**}) = \Delta E(\text{MP4SDQ/6-31G}) + \Delta E(\text{HF/6-31G**}) - \Delta E(\text{HF/6-31G})$$

These relative values together with the correction for zero-point vibrational energies (ZPVE, Table 1) thus provide our best relative energies. The ZPVE values were computed from HF/3-21G and multiplied by a factor of 0.9.[11]

Table 1. Calculated total energies [a.u.], relative energies ([kcal/mol] values in parentheses), and zero-point vibrational energies (ZPVE, [kcal/mol]) of stationary points considered at different levels.

Method [a]	**5**	**7**	**6**	ΔE^{+}(6-7) [e]
HF/3-21G	−259.09381 (0.0)	−259.06673 (17.0)	−259.08029 (8.5)	9.0
HF/6-31G	−250.44415 (0.0)	−260.40767 (22.9)	−260.41290 (19.6)	3.3
HF/6-31G**	−260.58507 (0.0)	−260.54737 (23.6)	−260.56177 (14.6)	9.0
MP2/3-21G	−259.63288 (0.0)	−259.62148 (7.2)	−259.62457 (5.2)	2.0
MP2/6-31G	−260.97697 (0.0)	−260.95724 (12.4)	−260.95456 (10.7)	1.6
MP3/6-31G	−260.95761 (0.0)	−260.93037 (17.1)	−260.94049 (10.7)	6.4
MP4SDQ/6-31G	−260.98245 (0.0)	−260.96282 (12.3)	−260.96225 (12.7)	−0.4
MP4SDQ/6-31G** [b]	(0.0)	(13.0)	(7.7)	5.3
ZPVE [c]	26.3	26.0	27.5	(3.8)
Estimated [d]	(0.0)	(12.7)	(8.9)	

[a] Using HF/3-21G optimized geometries given in Fig. 1. [b] Estimated values from MP4SDQ/6-31G, see text. [c] Zero-point vibrational energies calculated at HF/3-21G and reduced by a factor of 0.9. [d] Estimated values including MP4SDQ/6-31G** relative energies and ZPVE. [e] Energy barrier for the ring opening **6** → **7** → **5**.

One sees that at all levels of theory, the 1,2,3-oxadiazole **6** is calculated to be of higher energy than the formyldiazomethane **5**. Both polarization and correlation effects tend, however, to reduce the energy difference between them. For the transition state **7**, polarization and correlation effects cancel each other (as seen in ΔE^{+}, Table 1). According to the best values obtained in the present work, the heterocycle **6** lies 8.9 kcal/mol above its open chain

isomer **5** and undergoes ring opening with an energy barrier of 3.8 kc l/mol. These values obviously suggest that the unsubstitu ed 1,2,3-oxadiazole can not be stable in the gas phase or even in an inert matrix at low temperature.

Although the geometrical parameters were not optimized at higher levels of accuracy, we note that at the MP4SDQ/6-31G//HF/3-21G level (Table 1), **6** becomes even higher in energy than the transition-state structure **7**. Thus, the energy difference between both structures is probably very small (within a few kcal/mol) after a complete optimization of geometry at this level. In addition, recent studies of the Wolff rearrangement of some perfluorodiazoketones[12] in argon matrices do not provide any spectroscopic indication for the formation of 1,2,3-oxadiazoles, even though strong electron-withdrawing substituents such as perfluoroalkyl groups (e.g., CF_3, C_2F_5) could enhance the ring stability.

In their recent work, *Schultz* and *Schweig*[4] also reported some semiempirical MNDO results which predicted, among other things, that the cyclic 1,2,3-benzoxadiazole **3** lies about 11 kcal/mol below the open-chain form **4**. A separate MNDO calculation on the structures **5**, **6**, and **7** yields the following heats of formation [kcal/mol]: **5**: 26.6; **6**: 24.2; **7**: 69.1. It is well known that the MNDO method[13] usually overestimates the stability of rings compared with their open-chain isomers. Nevertheless, these MNDO data show that the cyclic isomer becomes significantly stabilized (by 8.6 kcal/mol) by attachment to a benzene ring.

The present ab initio study therefore suggests that the unsubstituted 1,2,3-oxadiazole **6** cannot be isolated as a discrete species even in an inert matrix at low temperature.

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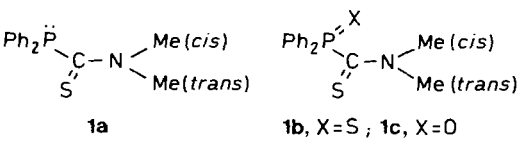
Phosphorus-Substituted Thioformamides and Thioformimidates: Molecular Structure and Solid State ^{13}C-NMR Spectra**

By *Klaus Albert, Andreas Bruns, Hans Förster, Wolfgang Hiller,* and *Udo Kunze**

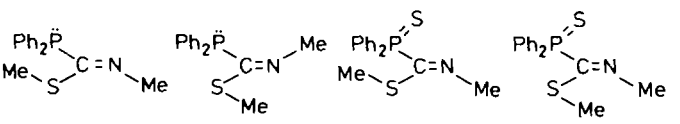
In the past few years, solid-state NMR spectroscopy (CP-MAS NMR spectroscopy) has found increasing application in structural elucidation, e.g. for detecting differences in molecular conformation in the solid and dissolved state.[1,2] The results are especially valuable if the crystal structure of the molecule under investigation is already known. In the CP-MAS-^{13}C-NMR spectrum of nitrogen compounds (amino acids, peptides, nitro compounds, nitriles), an asymmetric signal splitting of the C-atoms bound to the nitrogen by quadrupole interaction is often observed which is not detectable in solution. Since the electrical quadrupole splitting of the ^{14}N isotope ($I = 1$) is of the same order of magnitude as the magnetic interaction, the Zeeman eigenstates experience a perturbation, so that an unsymmetrical three-line signal instead of the expected triplet appears in the ^{13}C-NMR spectrum of single crystals.[3] *In normal, polycrystalline material two lines* usually coincide and a field dependent, asymmetric "doublet" is formed whose splitting increases with the s-share of the carbon hybrid orbital.[4,5]

To our knowledge, no solid-state ^{13}C-NMR spectra of *simple P,N,S compounds* have, as yet, been published. We report now on some phosphorus-substituted thioformamides and the linkage-isomeric thioformimidates whose crystal structures are, in part, known[6,7] (see Table 1).

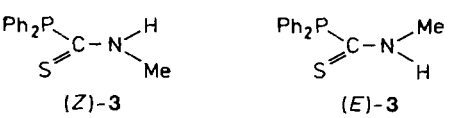
The tertiary thioformamides **1a–c** show an asymmetric doublet splitting of the *cis*- and *trans*-*N*-methyl signals at a spectrometer frequency of 75.5 MHz. At 50.3 MHz the two central lines in the spectrum of **1b** coincide, since the qua-



1a **1b**, X = S ; **1c**, X = O



$(Z)_{sp}$-**2a** $(E)_{ap}$-**2a** $(Z)_{sp}$-**2b** $(E)_{ap}$-**2b**



(*Z*)-**3** (*E*)-**3**

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Table 1. CP-MAS-^{13}C- and CP-MAS-^{31}P-NMR data of the compounds **1a–c**, **2a**, **b**, and **3** [9]; in brackets, corresponding values in solution ($CDCl_3$ of THF) [6, 7].

	1a	**1b**	**1c**	**2a**	**2b**	**3**
^{13}C-NMR [a]						
NCS	207 [b] (208.9, d, $J=33$)	194, d, $J=75$, $\Delta\approx50$ [c] (194.6, d, $J=70$)	196, d, $J=94$, $\Delta\approx45$ (196.0, d, $J=91$)	169, d, $J=45$ (170.0, d, $J=47$)	164, d, $J=116$ (164.4, d, $J=110$)	210 [b] (206.7, d, $J=34$)
Ph	137–128 (136.9–124.3)	135–128 (135.6–125.1)	136–127 (133.5–124.6)	137–128 (134.1–127.7)	134–129 (137.3–127.9)	137–129 (135.2–128.5)
NMe(*c*) [d]	46.2 [b], $\Delta\approx35$ (44.8, s)	47.7, $\Delta=35$ (45.8, d)	46.3, $\Delta=37$ (44.7, d)			
NMe(*t*) [d]	43.0 [b] (43.6, d)	46.7, $\Delta=35$ (44.9, d)	42.9, $\Delta=37$ (43.3, d)	42.5, $\Delta=35$ (42.3, d)	40.0, s (42.6, d (*Z*))	37.5, $\Delta=45$ 35.0, $\Delta=45$ (33.8, s)
SMe				14.0, s (14.5, s)	16.5, s (15.9, s (*Z*))	
^{31}P-NMR [e]	21 (17.6)	47 (48.1)	31 (27.9)	[f]	[f]	12 (15.9)

[a] Spectrometer frequency 75.46 MHz; δ rel. TMS, $|^1J(PC)|$ [Hz], ^{14}N-quadrupole splitting Δ [Hz]. [b] Splitting only indicated. [c] Pseudo-triplet (50.33 MHz). [d] *c* = *cis*, *t* = *trans* to phosphorus. [e] Spectrometer frequency 121.46 MHz; δ rel. H_3PO_4. [f] Not measured.

drupole splitting is inversely proportional to the field strength.[4–6] The band shape (downfield line with lower intensity) indicates a quadrupole moment of positive sign; the amount of splitting corresponds to the literature values for amino acids.[4] In the CP-MAS-^{13}C-NMR spectrum of the thioimidate **2a** a splitting with reversed intensity ratio is observed for the *N*-methyl group ($Q<0$), whereas the *P*-sulfide **2b** shows only a singlet (cf. trimethylimidazole[4]). As has been confirmed by an X-ray structure determination,[7] **2b** is present only in the $(Z)_{sp}$ conformation in the crystalline state; in solution, an equilibrium is established between *Z*- and *E*-isomers.

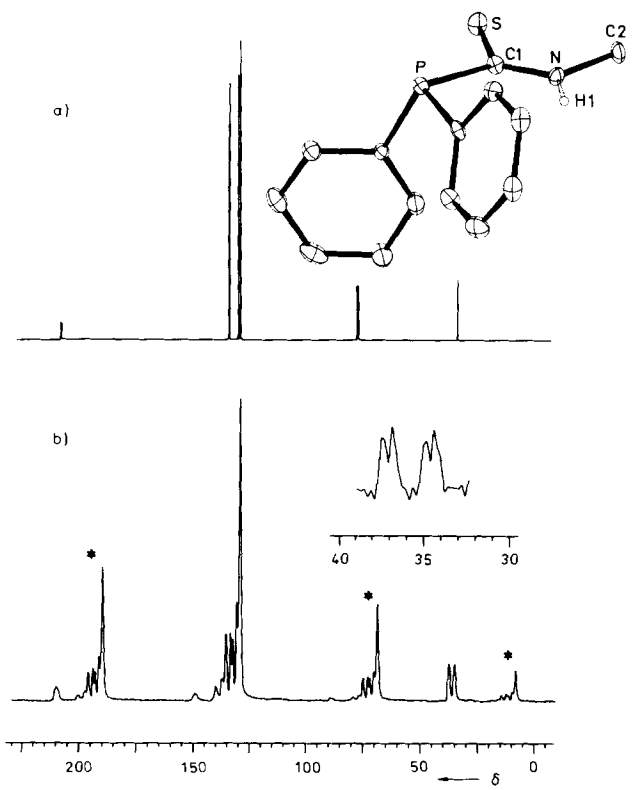


Fig. 1. (a) Crystal structure (molecule 1) [10] and ^{13}C{^{1}H}-NMR spectrum ($CDCl_3$), (b) CP-MAS-^{13}C-NMR spectrum (δ rel. TMS; * spin side bands) of **3**. Important bond lengths: S1–C1 165.6(5), P1–C1 184.8(5), N1–C1 131.5(6), N1–C2 144.7(6) pm.

Due to superposition of direct phosphorus coupling and quadrupole splitting, the NCS signal of **1b**, **c** appears as a "doublet of doublets", which, in the case of **1b**, degenerates to a pseudo-triplet at lower spectrometer frequency (50.3 MHz). The spectra of the thioimidates **2a**, **b**, on the other hand, show only the normal P–C coupling.

Surprisingly, the ^{13}C-NMR spectrum of the solid, secondary thioamide **3**[8] shows two signals in the *N*-methyl region, with $\Delta\delta=2.5$ ppm and a quadrupole splitting of 45 Hz (spectrometer frequency 75.5 MHz), whereas only a singlet appears in solution (Fig. 1). This unexpected signal doubling, however, is not to be ascribed to alternating *E*/*Z* arrangement in the crystal, but to the existence of two symmetry-independent molecules with the same *Z*-configuration, which differ only in the conformation of the phenyl rings. The situation is similar to that in crystalline *tert*-butoxycarbonylphenylalanine (Boc-Phe-OH),[2] whose unit cell likewise contains two conformers which lead to a splitting of all ^{13}C-resonance signals. An unusual finding, however, is that in **3** only a slight difference in conformation effects a relatively large signal splitting.

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[9] Recording conditions: Apparatus C × P 300, field 7 T, decoupling field strength 0.0015–0.0020 *T*, spin rate 3.5–5 kHz, contact time 1 ms, repeat rate 4 s, number of scans 500–1000.
[10] X-ray structure analysis of **3**: $P2_1/n$, $a=1688.2(2)$, $b=978.6(2)$, $c=1712.8(2)$ pm, $\beta=107.66(2)°$, $V=2696.3\times10^6$ pm^3, $Z=8$; $R_1=0.065$, $R_2=0.078$ for 2426 observed reflections with $I>3\sigma(I)$ (20°C, $3\leq2\theta\leq52°$, CAD4, $Cu_{K\alpha}$ radiation). Further details of the crystal structure investigation are available on request from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2, on quoting the depository number CSD 51263, the names of the authors, and the full citation of the journal.

Polymers. Properties and Applications. Vol. 7: Introduction to Polymer Spectroscopy. By *W. Klöpffer*. Springer-Verlag, Berlin 1984. xii, 184 pp., bound, DM 98.00.—ISBN 3-540-12850-6

This book is a valuable addition to polymer literature. The range and organization make it possible to grasp the aim of the author very rapidly. This book is intended as a cohesive synopsis of the most important physical and chemical aspects of polymer spectroscopy written in the style of a second-semester lecture. An up-to-date presentation of the various modern methods is aimed at. In this sense this book is a review of and introduction to the spectroscopic methods of polymer physics and chemistry, which can be recommended to the first degree student and to the "research novice". The literature reviewed at the end of each chapter enables the interested reader to deepen his knowledge.

Electronic, vibrational and magnetic conditions are dealt with at a similar level and supplement the numerous books on polymer spectroscopy. This is revealed by the main chapters entitled "Electronic Spectroscopy", "Vibrational Spectroscopy" and "Spin-Resonance Spectroscopy" which are of almost equal length. The work is rounded off with an introduction to the definition of polymer spectroscopy, to the information contained in the spectra and the field of spectra and with rather too short a conclusion. As is to be expected from the subtitle, this book only skims the surface all the way through. The various topics in the three main chapters are only dealt with very fleetingly. On the one hand, this has the advantage that the reader can very quickly review the many spectroscopic possibilities. On the other hand, it is not possible for him to enhance his knowledge; there is no room even for explanations, which are of such great importance to the student. A deeper understanding is only possible with a lecture or by studying the literature which is cited.

There is no theoretical explanation of the material presented. The quantitative description is kept very basic and too short. Although the book is intended for teaching most of the formulae are assumed to be known and are described in too cursory a manner as are the figures.

Unfortunately this book has its weak points. The following may be quoted as examples:

—P. 73, Fig. 6.9 has three arrows but four laser lines with the wavelengths given in nanometers which the reader has to recalculate for himself in wave numbers along the axes, in order to obtain an assignment. The direction of the polymer axis is incorrectly marked.

—P. 79 "Using polychromatic radiation ... the resulting interferogram has the form of a damped oscillation." A damped oscillation is obtained with a Lorentz line.

—P. 116 "The relaxation processes deactivating the energetically higher ("excited") state ... are T_1 (spin-lattice relaxation) and T_2 (spin-spin relaxation)" and later on p. 159 "... roughly analogous to luminescence decay." T_1 and T_2 are coherence-destroying processes whereby only T_1 is to be correlated with decay of the excitation and not T_2 which describes the loss of phase.

—P. 120 (ESR Experimental) "The sample has to be introduced into the region of highest magnetic field strength." This does not refer to the static magnetic field but to the magnetic field component of the oscillating microwave field. Further: "The frequency can be precisely kept constant by modifying the tension of the reflector (AFC)". "Tension" is an error in translation, what is meant is voltage or potential. The abbreviation in brackets AFC = automatic frequency control is not explained. This circuit is not intended to keep the frequency constant but to drive the frequency of the clystrons in frequency variations especially in resonance transition.

—P. 132, Fig. 9.15. Instead of 2E only E appears in the energy level scheme, axis $\parallel B$ should be $B \parallel y$, the Zeeman splitting has an incorrect starting point. Too much importance should certainly not be attached to this list compared with the merits enumerated and the overall good impression made by this book. However the student will surely ask himself whether or not he ought perhaps to expect more of an English language book costing almost 100 DM, even if only from the point of view of scope. At this price it is not to be expected that the book will be widely sold.

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Hemoglobin: Structure, Function, Evolution and Pathology. By *R. E. Dickerson* and *I. Geis*. Benjamin/Cummings Publishing Co., Menlo Park, CA 1983. 176 pp., bound, $ 40.50.—ISBN 0-8053-2411-9

The authors are known internationally amongst other achievements for their excellent book "Structure and Function of Proteins" published in 1969. Their new book is based on this in that the first chapter "The Rules of the Game" has only been changed slightly. The second chapter "Hemoglobin Structure and Function" contains sections of the previous book but also presents many details of new research results. The third chapter "Evolution of Oxygen Carriers" which reflects the authors' interests in general questions of natural history is a pleasure to read. The last chapter deals with "Abnormal Human Hemoglobins" and elegantly bridges the gaps between medicine, molecular biology and physical methods of structural analysis. The title "Hemoglobin" is too narrow judging by the contents of the book; this is particularly evident in chapters I and II.

The outstanding indefatigable life work of *Max Perutz* as well as the efforts of other scientists have led to a wealth of information on hemoglobins. As important biological and chemical concepts of protein research are based on a mosaic of experimental details, the authors of a monograph face a difficult problem. Either older results can be presented as simple and approved concepts, or new data can be offered, fresh and hence scarcely filtered. *Dickerson* and *Geis* have decided on the second alternative. Readers who are unable to review the literature on hemoglobin strewn throughout the world will find a lucid, comprehensive and exact presentation together with the original references.

In conclusion, this book is to be most warmly recommended to all scientists and physicians who are interested in the relationship between structure and function of macromolecules. Throughout the book there are general principles exemplified by hemoglobin which will fascinate

even lay persons. In addition, the book presents amazing details. The challenge cannot be ignored: All knowledge in the chemistry of natural substances, in biology but particularly in medicine, should be measured by the level of understanding which has been achieved in the case of hemoglobin.

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New Books

The following books have been received by the editor. All the publications listed are available through W & P Buchversand für Wissenschaft und Praxis, Boschstrasse 12, D-6940 Weinheim (Federal Republic of Germany). Tel. (06201) 606-0, Telex 465516 vchwh d, Telefax (06201) 602328.

Advances in Carbohydrate Chemistry and Biochemistry. Vol. 42. Edited by *R. S. Tipson* and *D. Horton*. Academic Press, New York 1984. xii, 444 pp., bound, $ 65.00.—ISBN 0-12-007242-4

Advances in Heterocyclic Chemistry. Vol. 36. Edited by *A. R. Katritzky*. Academic Press, New York 1984. ix, 416 pp., bound, $ 95.00.—ISBN 0-12-020636-6

Oligonucleotide Synthesis. A Practical Approach. Edited by *M. J. Gait*. IRL Press, Oxford 1984. 232 pp., paperback, £ 11.00.—ISBN 0-904147-74-6

Asymmetric Synthesis. Vol. 4. The Chiral Carbon Pool and Chiral Sulfur, Nitrogen, Phosphorus, and Silicon Centers. Edited by *J. D. Morrison* and *J. W. Scott*. Academic Press, New York 1984. xii, 380 pp., bound, $ 85.00.—ISBN 0-12-507704-1

Coulomb Liquids. By *N. H. March* and *M. P. Tosi*. Academic Press, New York 1984. ix, 351 pp., bound, $ 59.00.—ISBN 0-12-470520-0

Gas Phase Ion Chemistry. Vol. 3: Ions and Light. Edited by *M. T. Bowers*. Academic Press, New York 1984. xiv, 453 pp., bound, $ 75.00.—ISBN 0-12-120803-6

Heidelberger Taschenbücher, Vol. 230: Analytische Chemie. Chemie—Basiswissen III. By *H. P. Latscha* and *H. A. Klein*. Springer-Verlag, Berlin 1984. xii, 538 pp., stitched, DM 48.00.—ISBN 3-540-12844-1

Specialist Periodical Reports. Amino Acids Peptids and Proteins. Vol. 15. A Review of the Literature Published during 1982. Edited by *J. H. Jones*. The Royal Society of Chemistry, London 1984. xiii, 464 pp., bound, £ 78.00.—ISBN 0-85186-134-2

Elementare Quantenchemie. By *H. Primas* and *U. Müller-Herold*. B. G. Teubner, Stuttgart 1984. 398 pp., paperback, DM 39.00.—ISBN 3-519-03500-6

Advances in Electrochemistry and Electrochemical Engineering. By *H. Gerischer* and *C. W. Tobias*. John Wiley, Chichester 1984. xi, 360 pp., bound, £ 52.00.—ISBN 0-471-87881-2

Rückstände und Verunreinigungen in Frauenmilch. Mitteilung XII der Kommission zur Prüfung von Rückständen in Lebensmitteln. A publication of the Deutsche Forschungsgemeinschaft. Verlag Chemie, Weinheim 1984. vi, 99 pp., paperback, DM 28.00.—ISBN 3-527-27333-6

Freiberger Forschungshefte. A 687. Herstellung und Eigenschaften von Kohlenstoffwerkstoffen. Teil II: Herstellung und Eigenschaften von Elektrodenkoks sowie Bewertung von Graphit- und Sonderkohlenstoffwerkstoffen. Vorträge zum Berg- und Hüttenmännischen Tag 1982 in Freiberg. Edited by the Rektor der Bergakademie Freiberg. VEB Deutscher Verlag für Grundstoffindustrie, Leipzig 1984. 200 pp., stitched, DM 60.00.—Requisition No. 544-145-9

Normalwerte. Untersuchungsergebnisse beim gesunden Menschen unter besonderer Berücksichtigung des Kindesalters. 6th completely revised and supplemented edition. By *W. Plenert* and *W. Heine*. S. Karger, Basel 1984. 518 pp., bound, SFr. 41.00.—ISBN 3-8055-3896-0

Lehrbuch der Organischen Chemie. 20th revised and supplemented edition. By *W. Walter*. Founded by *H. Beyer*. S. Hirzel Verlag, Stuttgart 1984. xvi, 954 pp., bound, DM 68.00.—ISBN 3-7776-0406-2

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Applications of Synthetic Peptides

By Rudolf Moser, Stephan Klauser, Thomas Leist, Hanno Langen, Thomas Epprecht, and Bernd Gutte*

Peptide chemists are increasingly concerned with the synthesis of polypeptides of biological and medical interest. This article describes several important applications of synthetic peptides in biochemistry, molecular biology, immunology, and medicine. Synthetic peptides may be useful in structure-function studies of polypeptides, as peptide hormones and hormone analogues, in the preparation of cross-reacting antibodies, and in the design of novel enzymes. Peptide chemists can actively contribute to progress in these fields if they are aware of the current problems in the life sciences.

1. Introduction—Methods of Peptide Synthesis

The goal of *peptide* synthesis is the formation of peptide bonds between amino acids (Fig. 1). Although entire *proteins* may be prepared chemically, such efforts are not very economic, since genetic engineering of bacteria is at present far superior to chemical synthesis.

Peptides can be chemically synthesized in solution or on solid supports. A comprehensive account of the former has been given by *Wünsch* et al.[1] The solid-phase method was introduced by *Merrifield*[2,3] in 1963. Although RNase A (ribonuclease A), which consists of 124 amino acid residues, has been synthesized by both methods with high specific activity[4,5] (the synthetic RNase A of *Yajima* and *Fujii*[5] was even crystallized), peptide chemists usually confine themselves to the synthesis of polypeptides not larger than about 50 residues in order to avoid misinterpretation of results obtained with inhomogeneous synthetic products. Polypeptides of high purity prepared recently by the solid-phase method include crystalline glucagon (*Mojsov* and *Merrifield*[6]) and an artificial 24-residue DDT-binding peptide that, after a single purification step, could be crys-

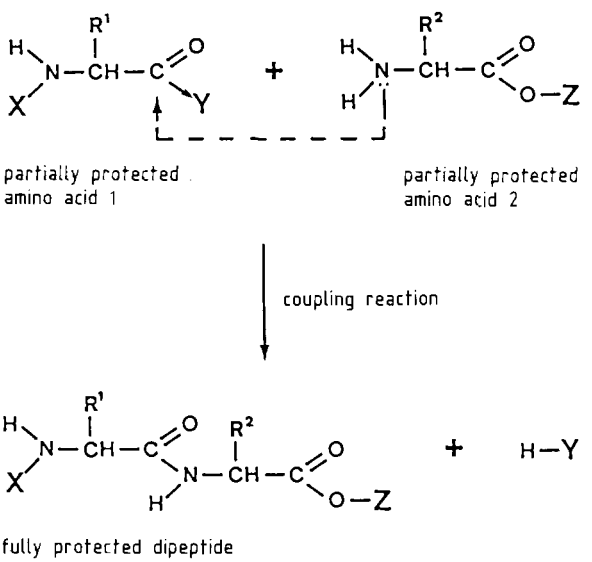


Fig. 1. Synthesis of a peptide bond. X, amino protecting group (a frequently used group is the acid-labile *tert*-butyloxycarbonyl group). CO-Y, carboxyl group activated for the coupling reaction (Y = N_3; azide method, Y = OC_6H_4-*p*-NO_2; *p*-nitrophenyl ester method, Y = O-C(-NH-C_6H_{11})=N-C_6H_{11}; dicyclohexylcarbodiimide method). Z, carboxyl protecting group. In solid-phase peptide synthesis, Z is an insoluble resin (frequently a 1% cross-linked polystyrene) to which the COOH-terminal amino acid residue is linked by an ester bond throughout the synthesis of the target peptide. The synthesis proceeds from the COOH-terminal to the NH_2-terminal end of the chain. The last step is the removal of the synthetic product from the resin by specific hydrolysis of the ester bond.

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tallized and had the expected amino acid sequence based on Edman degradation (*Moser* et al.[7,8]).

2. Structure-Function Studies Using Synthetic Peptides and Proteins

2.1. Peptide Hormones, Releasing Factors, Opioid Peptides

Modification, exchange, and deletion of amino acid residues are valuable tools in studies of the conformation and mechanism of action of biologically active polypeptides. Short peptide hormones, releasing factors, and opioid peptides are particularly well suited for these studies because they can be synthesized with a high degree of purity. In fact, numerous analogues of these compounds have been described. An example of particular interest is the highly active cyclic hexapeptide analogue of the 14-residue peptide hormone somatostatin prepared by *Veber* et al.[9] in which nine residues of the somatostatin sequence were replaced by a single proline residue (Fig. 2). The resulting conformational constraint and reduced susceptibility to proteolytic digestion were most likely responsible for the high activity and the long-acting effect of this analogue.

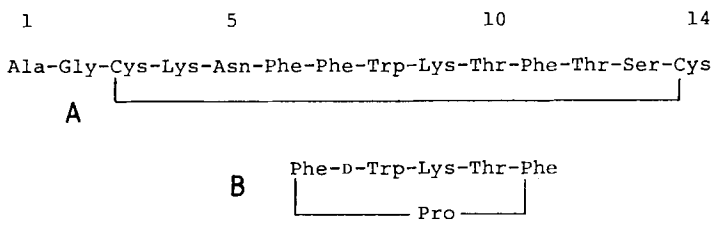


Fig. 2. Sequence of somatostatin **A** [36] and of the active cyclic hexapeptide somatostatin analogue **B** [9].

2.2. Proteins

2.2.1. Chemical Synthesis of Protein Analogues

The number of proteins that, upon chemical or enzymatic cleavage, yield biologically active complexes of the constituent fragments is increasing. In many cases fragments are formed that are small enough for chemical synthesis. Great progress has been made in recent years in the structural elucidation of both native proteins and their active complexes. This has facilitated the structure-function studies of proteins.

A classical example is RNase S, a fully active complex of two fragments (RNase 1-20 and RNase 21-124), which is obtained by subtilisin cleavage of RNase A.[10] The effects of modification, substitution, or deletion of amino acid residues in the synthetic NH_2-terminal fragment (RNase 1-20) on formation and activity of the complex with natural RNase 21-124 have been studied extensively.[11] More recent work has shown that His12, which is believed to be essential for the mechanism of action of RNase A,[11] can be replaced by β-(4-pyridyl)-L-alanine with retention of approximately 30% of the enzymatic activity of RNase A using RNA as substrate.[12] Moreover, a 63-residue analogue of RNase A comprising mainly the hydrophobic substrate binding site and lacking several surface regions of the parent protein, including residues 1 to 25, had approximately 10% activity in the transphosphorylation step of the cleavage reaction catalyzed by RNase A using poly(C) and poly(U) as substrates.[13] Recently, we synthesized RNase 1-14 and des-His-12-RNase 1-14 for further investigation of the effect of His12 on structure and function.[14] It is known that a mixture of RNase 1-14 and RNase 21-124 has full enzymatic activity.[15] When RNase 1-14 was replaced by des-His-12-RNase 1-14, the mixture showed only residual activity. There is strong evidence that des-His-12-RNase 1-14 has lost the helix-forming potential of RNase 1-14 and therefore cannot bind to RNase 21-124.[14] This seems to support the hypothesis[16] that a salt bridge between the side chains of Glu 9 and His 12 stabilizes the α-helix that extends from residue 3 to residue 13 of RNase 1-20[17] (or RNase 1-14). In des-His-12-RNase 1-14 this salt bridge does not exist. Perhaps His 12 is more important for the structural integrity of the substrate binding site than for catalysis. The properties of des-His-12-RNase 1-14 are a striking example of the dramatic consequences that deletion of a single amino acid residue may have for the structure and function of a protein.

The importance of individual residues at the COOH-terminal end of RNase A has been investigated using mixtures of natural RNase 1-118 with synthetic analogues of RNase 111-124.[18-20] The overlapping residues are essential for the formation of complexes between the two fragments.

Limited tryptic digestion of staphylococcal nuclease in the presence of thymidine 3',5'-diphosphate and Ca^{2+} yields a partially active complex called nuclease-T consisting of fragment 6-48 and fragment 49-149 or 50-149. In solution, the separated fragments do not adopt a stable structure, but a nearly native conformation is regenerated upon reconstitution of the complexes.[21,22] Furthermore, the X-ray diffraction patterns of single crystals of liganded native nuclease[23] and liganded nuclease-T complex (fragment 6-48 plus fragment 49-149)[24] are very similar, and the crystals are isomorphous. A second active complex is formed from the overlapping fragments 1-126 and 99-149 or 111-149.[25] Synthetic analogues of fragment 6-48 and fragment 99-149 have been prepared[26-28] to study the effects of truncated fragments and replacement of individual amino acid residues on formation, three-dimensional structure, and activity of the complexes.

More recently, *Juillerat* et al.[29] described a biologically active three-component complex formed from fragments of horse heart cytochrome c. The three components comprised residues 1-25 (containing the covalently bound heme), 28-38, and 56-104. With respect to their size, all three would be suitable for studies of structure-function relationships in horse heart cytochrome c using synthetic peptides.

2.2.2. Site-Directed Mutagenesis

Site-directed mutagenesis is a combined chemical-molecular biological approach to introduce specific mutations

in genes.[30-33] A circular single-stranded DNA template containing the wild-type gene is hybridized with a synthetic oligodeoxynucleotide primer that is noncomplementary to the template at the position that is to undergo mutation. The primer is then elongated and the ends spliced to form the circular complementary strand using DNA polymerase and DNA ligase. The heteroduplex formed is cloned in *E. coli*. Some of the clones contain the gene of the wild type, others that of the mutant. If the cloned genes are expressed, the gene products can be isolated and compared. Site-directed mutagenesis has already become a widely used method in structure-function studies of proteins.

3. Synthesis of Peptide Hormones

3.1. Chemical Syntheses

Numerous human polypeptide hormones are needed for therapeutic purposes. The shorter ones, like oxytocin, are easily accessible by chemical synthesis. But even larger ones such as human adrenocorticotropic hormone (ACTH, 39 residues) have been prepared in pharmaceutically pure form by conventional methods[34] as well as by the solid-phase procedure.[35] In the case of ACTH the task of the peptide chemist is made easier by the fact that the first 24 residues of the ACTH sequence are responsible for the biological activity of the hormone.

Somatostatin (14 residues, Fig. 2) is an inhibitor of the secretion of various hormones such as growth hormone, glucagon, and insulin. Since its isolation in 1973,[36] numerous syntheses have been carried out (see, for example, ref. [37] and [38]). The possible application of somatostatin analogues in the treatment of diabetes has stimulated great interest in this polypeptide hormone. Analogues that only inhibit glucagon release would be ideal.[39] Chemical peptide synthesis is the most practical way to prepare somatostatin analogues for biological assays. This approach also allows the incorporation of D-amino acids, which cause conformational changes that might increase the lifetime and the biological activity of the peptide hormone analogues.[9] In ribosomal protein biosynthesis, only L-amino acids are incorporated.

The use of synthetic peptides as drugs and for diagnostic purposes was reviewed recently by *Geiger*.[40]

3.2. Synthesis of Human Polypeptide Hormones in Bacteria

Synthetic genes for somatostatin[41] and for the A- and B-chains of human insulin[42] have been expressed in *E. coli* following transformation of the bacteria by the corresponding hybrid plasmids. Although human insulin obtained by combination[43] of bacterially produced A- and B-chains is available on the market, the interest of pharmaceutical companies in chemically synthesized somatostatin has remained strong.

4. Raising of Antibodies against Synthetic Peptides

There is great interest in antibodies that are raised against a synthetic segment of a protein chain and that cross-react with the intact native protein. Such antibodies are formed if the synthetic peptide used as immunogen corresponds to a surface region of the parent protein and adopts the native conformation at least part of the time. Figure 3 illustrates the formation of cross-reacting antibodies. Synthetic peptides shorter than about twenty residues are usually good immunogens when coupled to carrier proteins such as serum albumin. Longer peptides do not need a carrier for immunization. Often synthetic peptides corresponding to surface regions of a protein are stronger immunogens than the corresponding structures on the native protein.

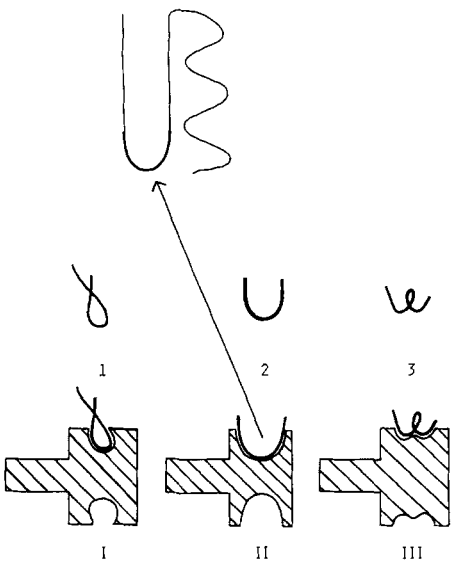


Fig. 3. Raising of antibodies against a surface segment of a native protein. Top: Assumed folding of the hypothetical protein; the segment shown in bold face is synthesized chemically. Middle: Three out of many possible interconvertible structures of the synthetic peptide in solution. Bottom: Antibody-antigen complex. If conformers 1, 2, and 3 of the synthetic peptide stimulate the production of antibodies, antibodies I and III will bind the peptide only; antibody II will also recognize the native protein because of close structural similarity of the antigenic determinants of peptide conformer 2 and the native protein (see arrow).

4.1. Antibodies for Immunoaffinity Chromatography

Affinity chromatography allows rapid and specific purification of a polypeptide from a complex mixture of products. Immunoaffinity chromatography can be used to isolate an antigen or, when pure antigen is available, to fractionate polyclonal and monoclonal antibodies. Here, we give two examples from our laboratory.

First, we synthesized the fragment 111-166 of human interferon (IFN) α1,[46] which is a largely conserved region of the IFN-α and IFN-β family.[44,45] However, the hope that this fragment might have antiviral activity was not fulfilled.[46] On the other hand, a monoclonal antibody prepared against the synthetic fragment cross-reacted with human IFN α1, IFN α2,[46] and IFN αA[47] produced by *E. coli*. It was therefore coupled to CNBr-activated Sepharose 4B for affinity chromatographic purification of human IFN α2 from *E. coli*. Purified interferon with a specific activity of approximately 10^8 units per mg of protein was obtained.[46] Further studies showed that the antigenic determinant recognized by the monoclonal antibody is lo-

cated between residues 151 and 166 of the IFN-α1 sequence.[48]

Second, we coupled the purified, artificial 24-residue DDT-binding polypeptide[7] to Affi-Gel 10 in order to resolve the IgG (immunoglobulin G) fraction of the antiserum raised against the polypeptide in rabbits. Only about 5% of the IgG isolated was bound by the immobilized peptide.[49] The remaining 95% did not recognize the antigen, which was linked to the insoluble carrier by its NH_2-terminal amino group. The specifically binding antibodies can be used to test the expression in *E. coli* of the cloned synthetic gene for the artificial DDT-binding polypeptide.[50]

4.2. Synthetic Peptides as Potential Vaccines

Recently, synthetic peptides corresponding to surface sequences of viral coat proteins or toxins have been used successfully for immunization. If the antibodies so elicited protect against viruses or toxins, the process is called active immunization. There is hope that active immunization using synthetic peptides will become generally applicable in medicine.

In 1965, *Anderer* and *Schlumberger*[51] showed that rabbit antisera to artificial antigens carrying synthetic hexa-, penta-, tetra-, or tripeptides homologous to the COOH-terminal amino acid sequence of the coat protein of tobacco mosaic virus (TMV, strain *vulgare*) readily precipitated and neutralized the intact virus. The neutralizing capacity of the antiserum toward the hexapeptide antigen was comparable to that of anti-TMV antiserum. Although TMV is a plant virus and plants do not produce antibodies, this work pointed the way to active immunization using synthetic peptides.

The sequences of these synthetic peptides have been selected in various ways. *Lerner* et al.[52] chose peptides corresponding to the amino acid sequence of the NH_2- or COOH-terminal end and to the sequences of hydrophilic segments and possible surface turns of the polypeptide chain of the hepatitis-B surface antigen (HBsAg), the major surface antigen of the 42-nm Dane particles of hepatitis-B virus. The amino acid sequences were deduced from the nucleotide sequence of the HBsAg gene. Antisera from rabbits against several peptides longer than ten residues reacted with native HBsAg and specifically precipitated the 23000- and 28000-dalton forms of the antigen from Dane particles. The peptides that elicited the formation of these antisera are potential synthetic vaccines.

Arnon et al.[53,54] and *Audibert* et al.[55] used a disulfide "loop" peptide and a peptide subtended by a disulfide bridge to raise antibodies that cross-reacted with the respective native parent proteins. Antibodies from rabbits against the natural fragment 64–83[53] and antibodies from rabbits and goats against the synthetic fragment 64–82[54] of hen egg-white lysozyme also bound intact lysozyme (all three antigens contain a disulfide bridge formed by cysteines 64 and 80), whereas they did not interact with the oxidized open-chain fragments. *Audibert* et al.[55] raised antibodies in guinea pigs against the synthetic tetradecapeptide 188–201 of diphtheria toxin. The sequence of this peptide is contained in the loop that is formed by the disulfide bridge between cysteines 186 and 201 of the native toxin. The antibodies specifically bound and neutralized diphtheria toxin. This is the first example of successful active immunization against a lethal bacterial toxin using a synthetic peptide antigen.

Since long stretches of polar amino acid residues exist only on the surface of protein molecules, *Hopp* and *Woods*[56] concluded that sequences containing mainly polar residues may correspond to antigenic determinants. They showed that the points of highest local hydrophilicity, obtained by stepwise averaging of the hydrophilicity values[57] of six successive amino acid residues along the polypeptide chain, agreed closely with the location of antigenic determinants. Twelve proteins, for which extensive immunochemical studies had been carried out, were analyzed. To test their method of identifying antigenic determinants, they synthesized fragment 138–149 of HBsAg, which contains the hydrophilic hexapeptide sequence Lys(141)-Pro-Thr-Asp-Gly-Asn(146), by the solid-phase procedure, replacing cysteine residues 138, 139, 147, and 149 by α-aminobutyric acid residues. The deprotected peptide resin was found to bind ^{125}I-labeled anti-HBsAg antibodies. This confirmed experimentally that the synthetic fragment contained all or a large part of an antigenic determinant of HBsAg.

The following steps are necessary for the development of synthetic peptide vaccines:

- Prediction of protein antigenic sites by the methods of *Hopp* and *Woods*[56] or *Pfaff* et al.[58] (the latter is discussed below)
- Chemical synthesis of these sequences
- Raising of antibodies against the synthetic peptides
- Testing of the ability of these antibodies to bind to the antigenic determinants of the native protein and to neutralize its pathogenic properties

Those peptides that elicit the formation of neutralizing antibodies are potential synthetic vaccines. Antibodies are also likely to be formed that recognize the native parent protein, but that do not neutralize its biological activity.

An antigenic determinant formed by amino acid residues belonging to an α-helix on the surface of the protein cannot be clearly detected by the method of *Hopp* and *Woods*[56] because a surface α-helix has a hydrophobic side making contact with the interior of the protein molecule and a hydrophilic side interacting with water. Consequently, it does not have a continuous sequence of six or more hydrophilic residues but rather hydrophilic and hydrophobic residues alternating approximately pairwise according to the helical wheel representation[59] of the amino acid sequence of a surface helix. Therefore, *Pfaff* et al.[58] took the following approach in order to develop a synthetic peptide vaccine against foot and mouth disease virus (FMDV). Using secondary structure prediction and helical wheel representation and taking into account the results of a serological analysis of large viral protein 1 (VP1) fragments,[60] *Pfaff* et al.[58] localized a major immunogenic site of FMDV on a predicted surface helix of VP1 between amino acid residues 144 and 159. A synthetic hexadecapeptide corresponding to this sequence elicited the formation

in rabbits of high titers of antibodies that specifically recognized and neutralized the virus. The high quality of the immune response was ascribed to the conformational stability of the immunogenic synthetic 16-residue peptide, which most likely is α-helical.

Synthetic peptides have also been used successfully to raise antibodies against polio virus.[61] Synthetic peptide vaccines against influenza virus would be of particularly great medical interest.

4.3. Antibodies for Identification of Gene Products

The availability of rapid DNA sequencing techniques has led to an exponential increase in the number of DNA sequences known. The accumulation of data is so rapid that protein chemistry can hardly keep place. In many cases it is not known whether a DNA segment with an open reading frame (i.e., a long sequence of codons uninterrupted by a stop codon) encodes a protein or not. To identify a putative protein, synthetic peptides again can be very useful. First, the sequence of this protein is deduced from the DNA sequence. Then, a fragment of the predicted protein sequence (preferably a COOH-terminal peptide[62,63] or an internal hydrophilic peptide selected by the method of *Hopp* and *Woods*[56]) is synthesized chemically and antibodies are raised against the synthetic fragment. Finally, if the putative protein exists, it can be detected immunologically provided the antibodies produced against the synthetic peptide cross-react with the gene product.

This scheme was applied by *Sutcliffe* et al.[64] to detect a new retroviral gene product. Analyzing the nucleotide sequence of the 3'-end of the Moloney murine leukemia virus genome, they found an open reading frame that extended beyond the coding region of the known viral products. Antibodies raised against a synthetic pentadecapeptide sequence of the putative protein cross-reacted with material in infected cells. In the same way, *Chomyn* et al.[63] identified the polypeptides encoded in the ATPase 6 gene and in the open reading frames 1 and 3 of human mitochondrial DNA. The antibodies produced against synthetic COOH-terminal peptides (seven to eleven residues long) of the three putative gene products immunoprecipitated specifically components 17, 12, and 24 of the mitochondrial translation products of HeLa cells. An extensive review article on antibodies against synthetic peptides has been published by *Walter* and *Doolittle*.[65]

5. Design of Novel Polypeptides

The design of novel biologically active polypeptides is a new field in protein chemistry. At the outset, two questions need to be asked: 1) Do we need novel polypeptides or proteins? 2) Is the design of novel polypeptides feasible?

The answer to the first question is unequivocally "yes." Proteins with novel enzymatic activities, for example, could be useful for research, biotechnology, and medicine. They could also play an important role in environmental protection if they were capable of degrading long-lived toxins such as DDT (Fig. 4) or dioxin.

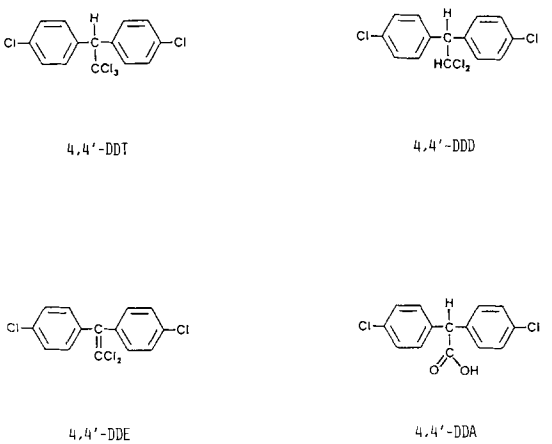


Fig. 4. 4,4'-DDT, 1,1,1-trichloro-2,2-bis(*p*-chlorophenyl)ethane; 4,4'-DDD, 1,1-dichloro-2,2-bis(*p*-chlorophenyl)ethane; 4,4'-DDE, 1,1-dichloro-2,2-bis(*p*-chlorophenyl)ethylene; 4,4'-DDA, bis(*p*-chlorophenyl)acetic acid. DDD, DDE, and DDA are metabolites of DDT.

The answer to the second question is not clear at present. If a microorganism could be easily adapted to using DDT as a substrate for growth, the biological approach to the development of new enzymes would be superior to theoretical-chemical approaches. In addition, our knowledge of the folding mechanism of proteins is still incomplete.[84] We can predict, with some confidence, the location of secondary structural elements (α-helices, β-strands, and turns) on a polypeptide chain of known amino acid sequence (see *Pfaff* et al.[58] and *Gutte* et al.[66]) but not the arrangement of these structural elements relative to each other in the three-dimensional biologically active structure of a protein. This means that, at present, it is possible to design an α-helix, a β-pleated sheet, or a turn but not to construct and synthesize a novel functional protein having a complex structure. Therefore, up to now, only small biologically active polypeptides have been constructed that adopt relatively simple "one-dimensional" or "two-dimensional" structures such as a single α-helix,[67] a β-pleated sheet,[7,68] or a combination of both.[69] Despite this restriction, the results obtained are very interesting and encouraging.

5.1. Ligand-Binding Polypeptides

The preparation of biologically active models of binding sites,[68,70] peptide hormones,[9] and protein inhibitors[71] is the first step towards the design of novel polypeptides. *Lee* and *Atassi*[70] introduced "surface simulation synthesis" to confirm the location and topology of an antigenic determinant of lysozyme. This antigenic determinant is formed by amino acid residues that are adjacent in the three-dimensional structure but partly separated from one another in the amino acid sequence. A linear decapeptide was synthesized in which the amino acid residues that are adjacent to each other at the antigenic site are linked either directly or via spacer amino acids. This peptide was indistinguishable in its immunological properties from the corresponding antigenic determinant of native lysozyme. *Kullmann*[68] constructed a 40-residue peptide that mimicked the binding properties of naturally occurring opioid receptors. The amino acid sequence of this artificial receptor was deter-

mined using rules for the prediction of secondary structure and knowledge of the structure of various enkephalin and morphine derivatives. The sequence and the folding of the binding site of natural opioid receptors are not yet known. The highly active cyclic hexapeptide model of the peptide hormone somatostatin prepared by *Veber* et al.[9] was discussed already in Section 2.1.

A 13-residue competitive trypsin inhibitor was constructed by *Kitchell* and *Dyckes*.[71] This model inhibitor comprised the trypsin-binding region (two antiparallel β-strands, residues 13 to 18 and 35 to 39) of basic pancreatic trypsin inhibitor[72] and the dipeptide D-Phe-Pro, which linked the two β-strands and allowed their antiparallel alignment.

Additional synthetic peptide models of binding sites have been discussed.[66]

5.2. Construction of Polypeptides Having Enzymatic Activity

Examples of designed synthetic enzymes solely consisting of polypeptide chains and, if necessary, prosthetic groups are scarce. *Chakravarty* et al.[67] employed the known mechanism of action of lysozyme[73] and secondary structure prediction rules[74] to design and synthesize an α-helical decapeptide (Fig. 5) that had considerable lysozyme-like activity using chitin and dextran as substrates. Most likely, the spatial arrangements of the essential side chain carboxyl groups[73] were very similar in this lysozyme model and the natural enzyme. Whether the activity of the synthetic decapeptide is sequence-specific[67] or whether analogues containing the same amino acid residues in random order are also enzymatically active is still unknown.

We constructed a 34-residue polypeptide (Fig. 5) that interacts with nucleic acids.[69] This peptide and its disulfide-bridged dimer preferentially bound cytidine phosphates and had weak ribonuclease activity (0.1% and 2.5%, respectively, of the activity of ribonuclease A using tRNA as substrate) with high preference for cleavage of polynucleotide chains at the 3′-end of 3′-cytidylic acid residues. As pleasing as these results were, they once more pointed to our fragmentary knowledge of the factors that determine the folding of proteins.[84] The 34-residue polypeptide had been designed to interact specifically with the trinucleotide GAA. However, the binding of C by the synthetic product was about 100 times stronger ($K_D = 5 \times 10^{-6}$ M) than that of GAA, and the enzymatic activity of the artificial polypeptide had not been anticipated. The proposed secondary structure of the 34-residue polypeptide[69] was partly confirmed by circular dichroism measurements.[75] A more rigorous proof of the suggested folding was not possible because the crystals of the synthetic nucleic-acid-binding peptide were not suitable for X-ray studies.

5.2.1. Construction of a DDT-Binding/Degrading Polypeptide—Present State of Knowledge and Future Prospects

Model building and the secondary structure prediction rules of *Chou* and *Fasman*[76] and *Levitt*[77] were also used

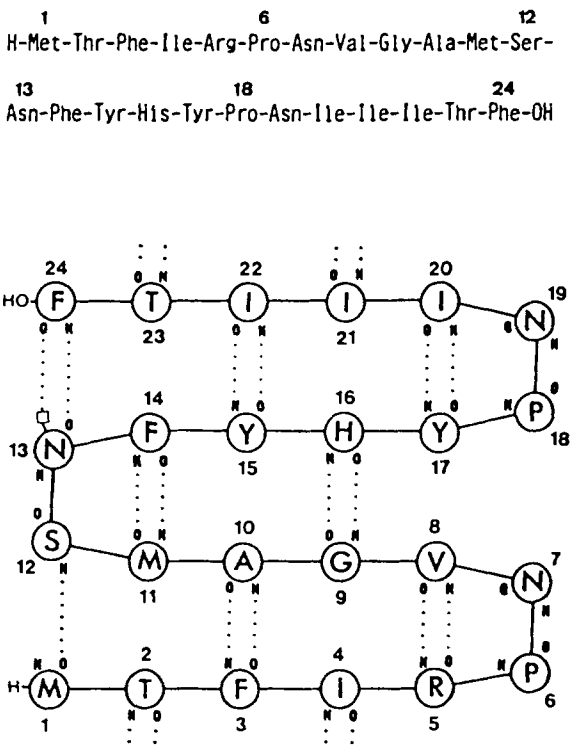


Fig. 6. Sequence and proposed secondary structure of an artificial DDT-binding 24-residue polypeptide. Dotted lines indicate hydrogen bonds between NH and CO groups of the backbone and side chains. Reprinted by permission from [7] (Copyright 1983, Federation of European Biochemical Societies).

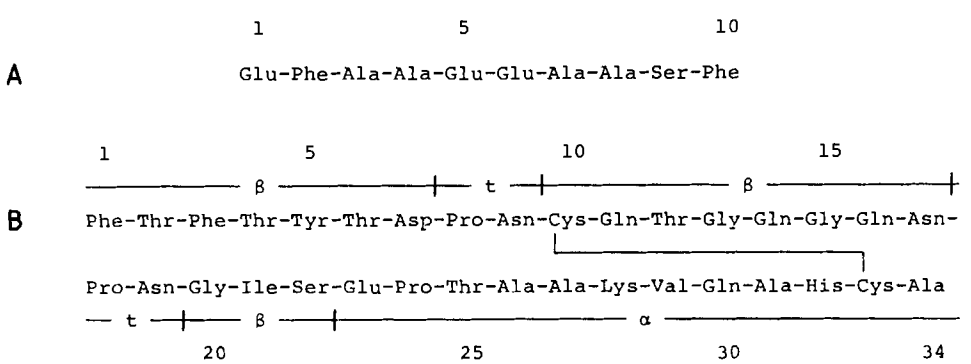


Fig. 5. Sequences of the designed α-helical decapeptide with lysozyme-like activity (**A**) [67] and of the artificial 34-residue ribonuclease (**B**) [69]. The latter is proposed to contain three β-strands (β), two β-turns (t), and one α-helical segment (α).

as the basic tools for the construction of a 24-residue DDT-binding peptide.[7] The amino acid sequence deduced seemed to be capable of producing a stable four-stranded antiparallel β-pleated sheet (Fig. 6) that could provide a DDT binding site of high complementarity involving the side chains of Phe 14, His 16, Ile 21, Met 11, and Ile 4. Since DDT is insoluble in water and, if taken up by an organism, accumulates in membranes, the artificial DDT-binding peptide had to be lipophilic as well.

The polypeptide was synthesized by the solid-phase method.[2,3] After a single gel-filtration step, the synthetic product had the expected amino acid composition, was homogeneous on thin layer chromatography, and could be crystallized.[7] Moreover, it gave a symmetrical peak on high performance liquid chromatography (HPLC) and had the correct amino acid sequence as determined by solid-phase Edman degradation.[8]

The synthetic peptide was found to bind DDT.[7] In ethanol/0.05 M NH_4HCO_3 (6 : 5, v/v), the dissociation constant K_D of the complex is about 2×10^{-5} M. Nucleotides such as 2′-CMP are not bound. The interaction of DDT with an analogue of the synthetic peptide, possessing the same amino acid residues in a random sequence, and with bovine serum albumin is much weaker ($K_D \approx 3 \times 10^{-3}$ M and 1×10^{-2} M, respectively).

It would be of theoretical and practical importance if the DDT-binding peptide could be converted into a DDT-degrading or modifying enzyme. In vivo, membrane-bound DDT is a poor substrate of cytochrome P-450 enzymes, the prosthetic group of which is a heme. Anaerobic and aerobic pathways of DDT degradation can be distinguished. An example of the former is the reductive dechlorination of DDT to DDD (Fig. 4),[78] an example of the latter the formation of DDA (Fig. 4) which is the principal urinary excretion product of DDT in mammals. Hydroxylation of the aromatic rings of DDT might also occur.

Several simple cytochrome P-450 models have been described. *Sakurai* et al.[79,80] used hemin-cysteine and hemin-glutathione complexes to carry out hydroxylations, dealkylations, and methyl migrations on aromatic substrates. We found that the hemin-cysteine complex also modified DDT. The products were more polar than DDT as shown by thin layer chromatography and HPLC of the reaction mixtures (Fig. 7A). The major products have been identified[81,82] and possible mechanisms of their formation are shown in Figure 8. In the presence of the DDT-binding peptide, the hemin-cysteine-mediated degradation of DDT was similar (Fig. 7B). Extending the 24-residue peptide to introduce a hemin binding site opposite the DDT binding site might result in a complex with increased DDT-degrading activity.

In order to study the in-vivo properties of the designed DDT-binding polypeptide, the gene for this artificial polypeptide was synthesized, inserted into a suitable plasmid, and cloned in *E. coli*. These experiments were performed in collaboration with *E.-L. Winnacker* et al.[83] If all rules of protein folding were known and all difficulties of expressing foreign DNA in bacteria or higher organisms could be overcome, designed proteins might be produced in highly pure form solely by genetic engineering methods, making their chemical synthesis superfluous.

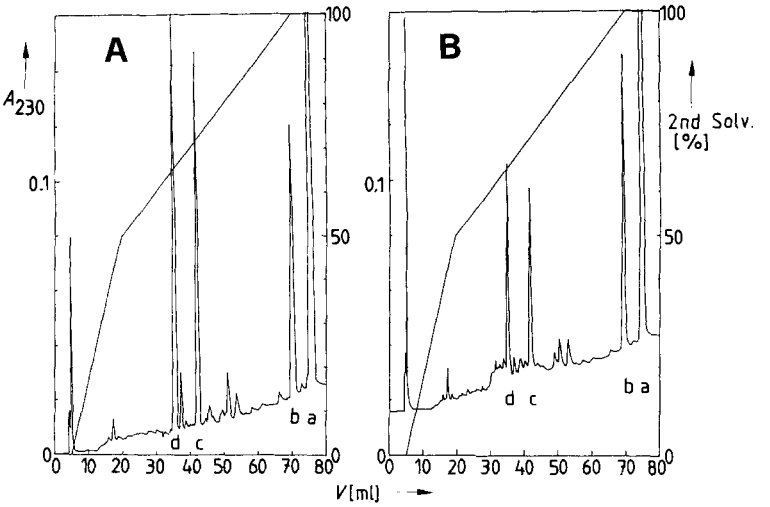


Fig. 7. HPLC separation of the DDT degradation products formed in the absence (**A**) and in the presence (**B**) of the designed 24-residue DDT-binding polypeptide. DDT, hemin, and cysteine were incubated in ethanol/0.05 M sodium acetate, pH 5.2 (6 : 5, v/v) at 37 °C for 48 h. Then the reaction mixtures were centrifuged and an aliquot of the supernatant was separated by HPLC [Aquapore RP-300 column (Brownlee), gradient elution (first solvent: 0.1% trifluoroacetic acid, second solvent: 60% acetonitrile in 0.1% trifluoroacetic acid)]. The following products have been identified: a, DDT; b, DDD; c, DDE-cysteine conjugate; d, DDA-cysteine conjugate. The millimolar extinction coefficients of DDT and DDD are $\varepsilon^{230}_{1\,cm} = 15.002$ and 19.125, respectively. A_{230}, absorption at 230 nm; 2nd solv., proportion of second solvent.

Elucidation of the structure of the artificial 24-residue DDT-binding polypeptide is essential for future work on protein design. It is important to know to what extent the folding found and that proposed agree. Furthermore, if the structure of the DDT binding site were known, the binding properties of the artificial polypeptide could be improved.

Work has begun on the raising of antibodies (preferably a monoclonal antibody) against DDT in order to compare

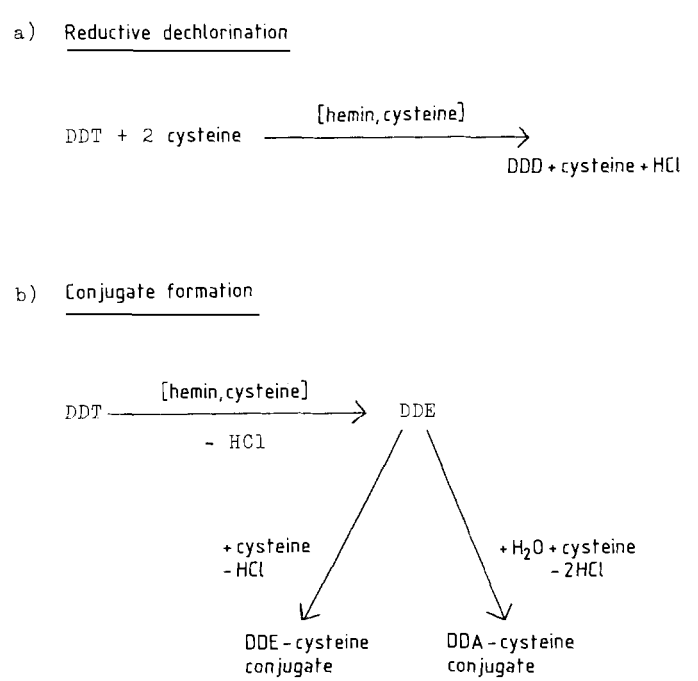


Fig. 8. Pathways of DDT degradation at pH 5.2 in the presence of the hemin-cysteine cytochrome P-450 model system.

natural and artificial DDT-binding polypeptides and to determine DDT in biological samples quantitatively.

Finally, inspection of the space-filling model of the designed peptide showed that dioxin may also fit the DDT binding site after minor adjustments of a few amino acid side chains. However, it will be difficult to test this possibility experimentally.

6. Outlook

The design of novel polypeptides still involves many unknowns, but once a workable system has been found it can be highly exciting. The future for peptide synthesis appears optimistic, especially if protein chemists collaborate with biologists. The protein chemist can play a very active role thereby if he is familiar with the modern experimental techniques of molecular biology and immunology. Moreover, the search for novel methods that allow rapid chemical synthesis of proteins in good yield and of high purity should remain a challenge for every protein chemist.

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Host/Guest Chemistry of Organic Onium Compounds—Clathrates, Crystalline Complexes, and Molecular Inclusion Compounds in Aqueous Solution

By Fritz Vögtle,* Hans-Gerd Löhr, Joachim Franke, and Detlev Worsch

The importance of organic onium compounds for host/guest interactions in biological processes has been long recognized. In contrast, the versatility of synthetic onium compounds as host molecules in abiotic chemistry has only been investigated in detail for the last few years. Due to their inclusion ability and selectivities, organic ammonium, pyridinium, and phosphonium salts and other organic salts with specific structural features are interesting as clathrate-forming molecules. The crystal structures of the clathrates afford insight into the conformational adaptability of onium clathrands with limited flexibility to the geometric requirements of the guest molecules. Optically active onium hosts can be used for enantiomeric enrichment. In crystalline tetracyanoquinodimethane(TCNQ) complexes and radical anion salts, the structure of the organic heterocation has a marked effect on the electrical conductivity. Macrocyclic onium compounds of the phane type with "exohydrophilic" and "endolipophilic" cavities are suitable as models of enzymes and biological receptors. They can also be used to transfer aromatic and aliphatic guest molecules selectively into aqueous solution. Catalytic activity (including H/D exchange) has already been obtained with synthetic compounds having large cavities. The further development of such host/guest systems may contribute to the understanding of biological systems and the improvement of technical processes (catalysis in molecular cavities).

1. Introduction

Onium compounds have important functions in biological processes; they contribute to the hydrophilization of the exterior surfaces of membranes and enzymes, they are involved in the transfer of one-carbon units, and they play a part in biochemical host/guest processes, for instance in the electrostatic binding of biologically active substances to receptors or of substrates to enzymes.[1]

Use of organic ammonium, phosphonium, and sulfonium salts in abiotic chemistry was for a long time limited to the fields of preparative intermediates,[2] herbicides, bactericides, and surfactants (e.g., invert soaps).[3] Only during the last few years has the versatility of onium compounds as clathrate- and complex-forming molecules and as models for enzymes and biological receptors been recognized.

This development was promoted by the introduction of new and improved solid-state research methods, such as solid-state NMR spectroscopy, X-ray crystallography, high-resolution electron microscopy, Fourier transform IR spectroscopy, and Raman difference spectroscopy, which facilitated the identification and characterization of inclusion phenomena.[4] The increasing number of scientific contributions and patents concerning inclusion compounds during the last few years documents the growing interest in such systems.

Host/guest compounds have a wide range of applications. For instance, host/guest interactions permit the separation of mixtures of substances according to molecular shape and size using reversible crystallization/solution processes,[5] chromatographic procedures,[6] or suspension methods (molecular sieves).[4e] Host/guest selectivities are sufficient to separate aromatic compounds from other compounds in multicomponent hydrocarbon mixtures,[5] to separate branched from normal hydrocarbons,[7] to fractionate isomers[8] and isotopomers,[9] and to resolve enantiomers (see Section 4). Of general interest is the use of in-

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clusion compounds to store and handle toxic, radioactive, or explosive substances,[10] to stabilize sensitive substances and unusual conformations of molecules,[11] as chemical reagents or specific catalysts,[12] to detoxify contaminated systems, to promote phase transfer of sparingly soluble hydrophobic or hydrophilic compounds (surfactants[13]), and as molecular templates for polymerization reactions.

Host/guest interactions also play a significant role in many medical and pharmacological processes. In the chemotherapeutic treatment of cancer, for example, the replication of DNA is inhibited in part by intercalative binding of drugs.[15]

A topological subdivision of host systems into *cavitands* having intramolecular cavities (i.e., within *one* molecule), and *clathrands* having extramolecular cavities (i.e., between different molecules) is useful[16] (Fig. 1).

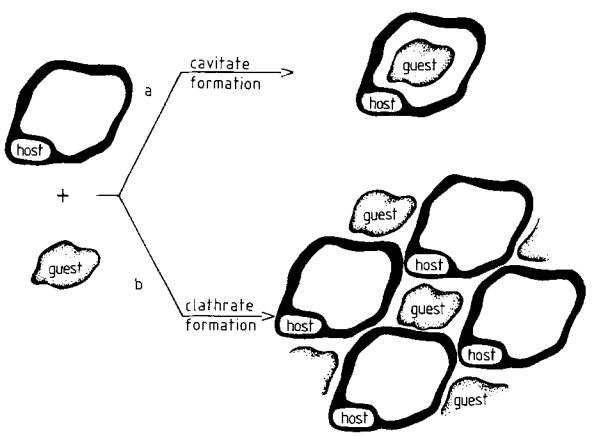


Fig. 1. Schematic differences between cavitates and clathrates: a) conversion of a cavitand into a cavitate by inclusion of the guest in the cavity of a host molecule; b) inclusion of guest molecules in cavities formed between the host molecules in the lattice; conversion of a clathrand into a clathrate.

Typical host compounds with *intra*molecular cavities are cyclodextrins, crown ethers, cryptands, calixarenes, and some cyclophanes. They form host/guest aggregates in the solid state and in solution and have been employed as models of enzymes and receptors (cf. Fig. 1a and Section 6).

Unlike cavitates, *clathrates* can form only in the crystalline state: guest molecules either are incorporated into *extra*molecular cavities already present in the lattice or, during crystallization, they induce host-lattice structures with guest-specific vacancies (Fig. 1b).

An essential feature of inclusion compounds is that the host and guest molecules are bound together by noncovalent forces. The type and strength of the bonding (ion–ion, ion–dipole, dipole–dipole, dipole–induced dipole, dispersion and electron donor-acceptor interactions, hydrogen bonding) between host and guest molecules necessitates another subdivision.[16] If predominantly electrostatic interactions between host and guest are decisive for adduct formation, the compounds are considered as complexes. If, on the other hand, aggregate formation occurs without specific bond forces between individual host and guest molecules, the term cavitate or clathrate is correct.

The driving force for the formation of crystalline clathrates and cavitates is first and foremost the thermodynamically favored, dense molecular packing (cf. ref. [4c]), which frequently is not observed when pure host lattices crystallize, owing to, for example, steric barriers or intramolecular cavities. The distinction between complexes and clathrates or cavitates is not always clear and the assignment of a host/guest compound to one or the other of these classes is left to the observer to a certain degree.[17]

Comparison of the structural formulas of known *clathrate*-forming molecules indicates that bulky molecular geometries occur frequently and that the number of possible stable conformations is limited. Replacement of single atoms or atomic groups leads frequently to further host compounds with similar or markedly changed cavity geometries and new guest selectivities, but often also to complete loss of inclusion ability.[18] Characteristics of many host compounds are the formation of intramolecular hollows as well as trigonal symmetry as in tri-*o*-thymotide (TOT) **3**,[19] cyclotriveratrylene (CTV) **4**,[20] triphenylmethane,[21] or perhydrotriphenylene.[22]

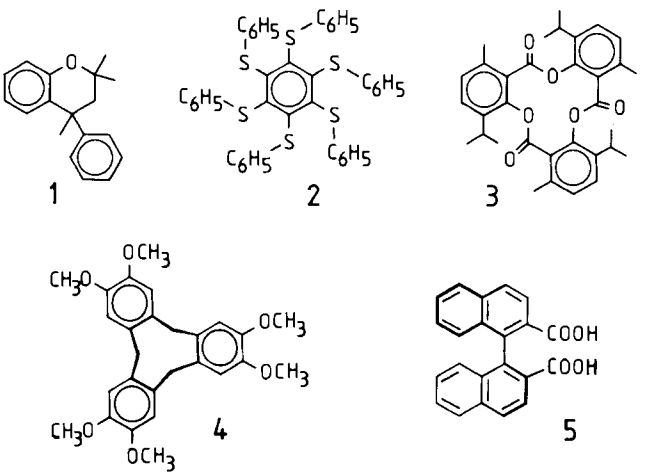


Fig. 2. Parent compounds of some "classical" clathrate-forming host systems; dianine **1** [4b, 18], hexakis(phenylthio)benzene **2** [23], tri-*o*-thymotide **3** [19], cyclotriveratrylene **4** [20], 1,1'-binaphthyl-2,2'-dicarboxylic acid **5** [26].

Predictions concerning the inclusion ability of new host compounds are still not possible or only in a limited way. Only by starting from known clathrate hosts and systematically varying their structures could clathrand families with considerable capacity and selectivity be developed. Such host systems include dianine **1** and its derivatives,[4b] the family of "hexahosts" derived from it, for example, **2**,[23] and the Schaeffer-[24] and Hofmann-type[25] inorganic transition-metal complexes.

The recently investigated hinge compounds, such as the binaphthyl derivative **5**,[26] are promising in view of the wide range of variation possible. This host system with bulky molecular structures is based on the combination of steric barriers with possible coordination via hydrogen bonds. Accordingly, polar guest molecules such as alcohols are incorporated preferentially in the sense of "coordinato clathrates."[17a]

The subject of this survey is organic onium compounds, a class of clathrate-, cavitate-, and complex-forming molecules with extensive inclusion ability, diverse selectivities, ready availability, and wide variability.

2. Clathrates of Organic Onium Salts: Properties and Guest Selectivities

As for many of the presently known clathrand systems, the discovery of the family of onium clathrate hosts was due to a chance observation. When the bisammonium compound **6** was prepared by reacting 1,3-bis(dimethylaminomethyl)azulene with excess iodomethane in ethanol, variable amounts of iodomethane and ethanol remained in the crystalline product.[27] The guest molecules could not be removed, even by "drying" in vacuum for several days. Attempts to recrystallize **6** revealed that it can incorporate a variety of solvent molecules, mostly in stoichiometric amounts. Systematic structural variations of the host compound **6** by replacement of the alkyl residues on the ammonium nitrogen, modification of the onium side arms, and exchange of the anchor group (azulene ring in **6**) and of the anions led to further clathrate-forming molecules (Fig. 3) with different guest selectivities.[28-30] Table 1 displays the clathrates of the onium compounds **6**–**22**. The "adducts" of organic onium compounds with alkyl halides that have been described in the older literature have partly been taken into consideration in Table 1.[31,32]

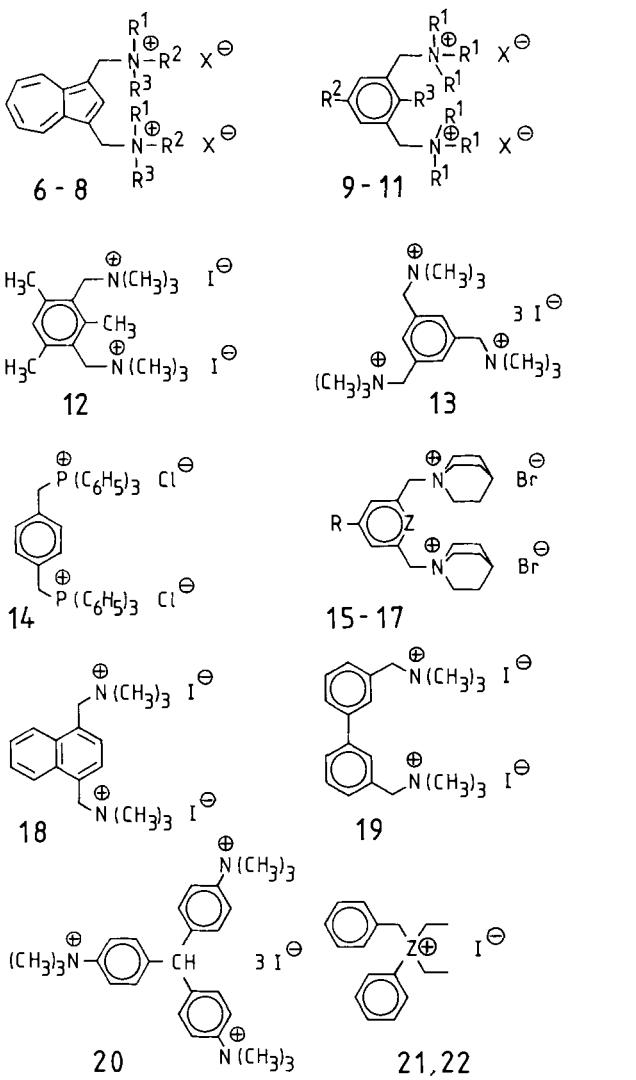


Fig. 3. Clathrate-forming onium compounds **6**–**22** [27–29, 31, 34].

	R^1	R^2	R^3	X		Z	R
6	CH_3	CH_3	CH_3	I	**15**	CH	H
7	CH_3	CH_3	CH_3	Br	**16**	CH	*t*Bu
8	CH_3	CH_3	C_2H_5	I	**17**	N	H
9	CH_3	H	H	I	**21**	N	—
10	CH_3	*t*Bu	H	I	**22**	As	—
11	C_2H_5	H	H	I			

The extensive inclusion ability of the bisammonium host **6** is clearly diminished when the anion $I^{\ominus}$ is replaced by $Br^{\ominus}$ (**7**). Whereas **6** hosts primary and secondary alcohols from methanol to pentanol, diols, and numerous halo- and nitroalkanes, the host **7** incorporates mainly smaller molecules with the exception of alcohols. In the series dichloro-, trichloro-, and tetrachloromethane, only dichloromethane is hosted selectively by bisbromide **7**. Here, the reduction in size of the anion obviously leads to smaller lattice cavities.

The naphthalene derivative **18** selectively forms clathrates with "BTX" aromatic compounds (*b*enzene, *t*o-

Table 1. Clathrates of the host compounds **6**–**22**. DMF = dimethylformamide.

Clathrand [a]	Molar ratio host : guest	Guest molecules	Ref.
6	1 : 1	ethanol, 1-propanol, 2-propanol, 1-butanol, 2-butanol, 1-pentanol, 1,2-ethanediol, 1,3-propanediol, 1,4-butanediol, 1,5-pentanediol, ethanethiol, pyridine, DMF, nitromethane, nitroethane, 1-nitropropane, 2-nitropropane, trichloromethane, tetrachloromethane, iodomethane, iodoethane, 1-iodopropane, 1-iodobutane, malononitrile, benzoquinone	[28]
	3 : 2	2-methyl-1-propanol, acetone, acetonitrile	
	2 : 1	1,3-butanediol	
	1 : 2	acetic acid	
	1 : 3	bromotrichloromethane	
	— [b]	H_2O, methanol, dichloromethane	
7	1 : 1	bromomethane, dichloromethane, nitromethane, nitroethane, 1-nitropropane, acetonitrile, acetic acid, acetone, DMF	[34]
8	ca. 1 : 2	ethanol	[27]
9	1 : 1	methanol, trichloromethane	[28]
	— [b]	acetonitrile, acetic acid, DMF	
10	1 : 1	ethanol, 2-propanol	[28]
	2 : 1	1-propanol	
11	1 : 1	dichloromethane, trichloromethane, acetic acid	[34]
	— [b]	acetonitrile	
12	1 : 1	methanol	[28]
	3 : 1	acetonitrile	
	— [b]	ethanol	
13	1 : 1	nitromethane	[28]
14	1 : 1	pyridine	[29]
15	1 : 1	methanol	[29]
	2 : 1	ethanol	
16	1 : 1	ethanol, 1-propanol, 2-propanol	[29]
17	ca. 2 : 1	ethanol	[29]
18	2 : 1	benzene, toluene, 1,2-xylene, 1,3-xylene, 1,4-xylene, 1-butanol	[29]
19	— [b]	DMF	[28]
20	1 : 1	DMF	[29]
	2 : 1	acetone	
21	1 : 1	trichloromethane, tribromomethane	[31]
22	1 : 1	tribromomethane	[31]

[a] Some of the clathrands and the clathrates contain stoichiometric amounts of H_2O. [b] Nonstoichiometric.

luene, xylene) and 1-butanol in a stoichiometry of 2 : 1. Inclusion complexes containing mesitylene, other hydrocarbons, alcohols, alkyl halides, or nitroalkanes have not been found.[29] The affinity of **6** for iodoalkanes, and of **7** for bromomethane as well as the specifity of **18** for nitromethane are considerable.

More than 30% of the onium compounds that have been synthesized to date and studied with respect to their inclusion ability have turned out to be clathrate-forming molecules. If one includes the iodoform adducts, which belong to the family of coordinato clathrates, the "hit rate" is more than 50%!

What are the causes of this remarkable variety of inclusion complexes? In addition to the general features of many clathrate hosts, such as bulkiness and limited conformational flexibility, the stability of the ionic host lattice is certainly of significance. The higher energies of ionic interactions are more important in forcing bulky molecules to crystallize than the interaction forces in molecular lattices.

Figure 4 shows some onium compounds for which, up to now, no inclusion compounds have been found. Extension or removal of the spacer unit (methylene bridge) between the anchor group (aromatic ring) and the onium group always led to a strong decrease or total loss of inclusion ability. If the "onium branches" on the benzene ring are in *o*- or *p*-positions (compare **9** with **29** and **30**) or if a small substituent is present on the anchor group (compare **10** with **24**–**28**), the effect is also negative. Apparently, these substituents fill the vacant spaces in the lattice.

What structural features are important in the design of potential onium clathrate hosts? Factors that have a favorable effect on the ability of molecules to form clathrates ("clathratogenic structural features," cf. Fig. 3) include a) a rigid molecular part such as benzene, naphthalene, azulene, or other aromatic compound as an anchor group, b) methylene bridges as spacer units, c) rigid, bulky, or voluminous substituents on the anchor group, and d) positioning of the "onium branches" on the anchor group in such a way that conformations with hollow-shaped spaces can form (for example, the 1,3-arrangement on benzene and azulene).

Molecular symmetry and flexibility play, as expected, a decisive part in determining the inclusion ability of a host compound. In the formation of crystal lattices containing cavities, a too high conformational mobility of the atomic groups counteracts the "bulkiness" of the molecules; conversely, a too low flexibility makes the adaptation of the host conformation to the requirements of the guest molecules more difficult.[28]

The stability of the onium clathrates is shown by the fact that they normally only decompose noticeably at temperatures far above the boiling points of the guest substances and that in vacuum no liberation of solvent molecules is usually observed. Predominantly cage-like lattice inclusions are presumably present. Subsequent saturation of guest-free host crystals requires channel- or layer-like cavities, and is only possible for host compound **6** (after recrystallization from methanol) with smaller guest molecules (CH_2Cl_2, CH_3OH, CH_3CN, H_2O).[28]

Owing to the ionic character of organic onium compounds, they are normally soluble to a significant extent only in polar solvents. Clathrates containing lipophilic guests can therefore only be prepared by recrystallization of the host substances from mixtures of solvents or by precipitation from alcoholic solution. In order to recover the guest substance (declathration), the clathrates are dissolved in water or methanol, and the guest is obtained by subsequent extraction from aqueous solution or vacuum distillation. By reducing the volume of the clathrand solution, the host compound can also be recovered; thus, the process is reversible (cf. ref. [5]).

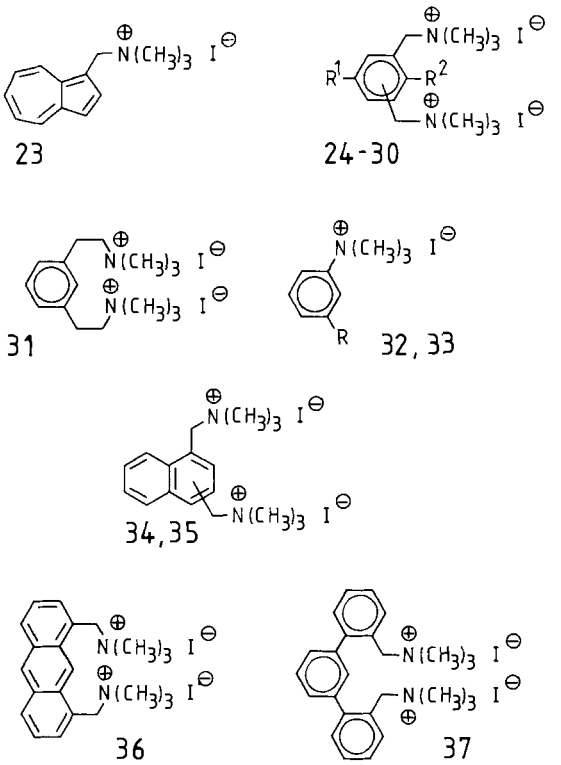


Fig. 4. Selected onium compounds **23**–**37** for which no clathrate formation has been observed.

	R^1	R^2	Position of the $CH_2\overset{\oplus}{N}(CH_3)_3$ groups
24	CH_3	H	1,3
25	NO_2	H	1,3
26	OCH_3	H	1,3
27	H	OCH_3	1,3
28	OCH_3	OCH_3	1,3
29	H	H	1,2
30	H	H	1,4

	R	Position of the $CH_2\overset{\oplus}{N}(CH_3)_3$ groups
32	H	—
33	$\overset{\oplus}{N}(CH_3)_3I^{\ominus}$	—
34	—	1,3
35	—	1,8

3. Clathrate Lattice Structures

X-ray structure determinations of host inclusions in organic onium compounds show that multimolecular crystal-lattice cavities are present. The guest molecules are sterically constrained by the ionic lattice of the host without exhibiting strong interactions between individual host and guest molecules, such as specific ion-dipole bonding.

Thus, these structures are definitely to be classified as clathrates (cf. ref. [16]).

Figures 5–7 display the crystal structures of three different clathrates of the same host compound **6**. The guest molecules iodomethane (Fig. 5), 1-butanol (Fig. 6), and 1,4-butanediol (Fig. 7) are each surrounded by several host molecules. In all three cases, the crystal lattices differ. The conformation of the host molecule **6** is significantly adapted to the structure of each guest molecule.

In the CH_3I clathrate of **6** (Fig. 5), the "onium branches" of the host molecule are aligned in a cisoid way (C_m symmetry) and embed the guest molecule partly in the hollow-shaped space. The remaining boundary surfaces of the CH_3I cage are formed by the bulky azulene rings and the voluminous trimethylammonium units.[27]

In the 1-butanol clathrate of **6**,[34] the "onium branches" are aligned in a transoid way on opposite sides of the plane formed by the azulene ring (C_2 symmetry, Fig. 6, left). The guest molecules are in tube-shaped cavities with an alternating series of expansions and contractions in the longitudinal direction ("tubulato clathrate"[16]). The top and bottom of the tubes are formed by the planes of azulene rings aligned in parallel layers, and the lateral sides are bounded by the ammonium groups that project between the layers (Fig. 6, left).

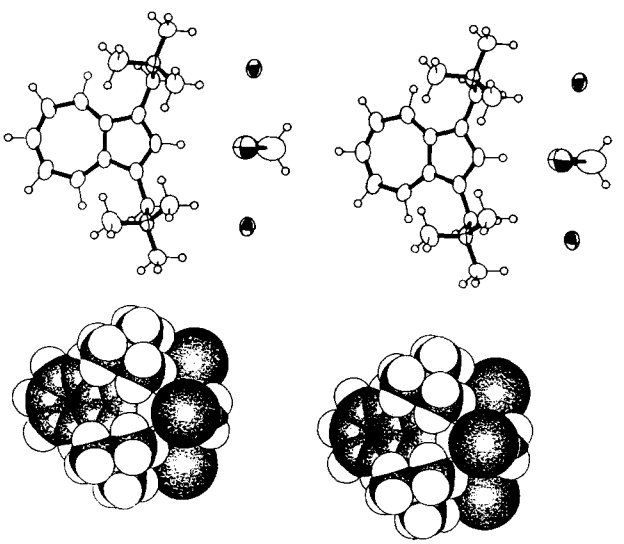


Fig. 5. Crystal structure of the CH_3I clathrate of **6** (stereoscopic pictures) [27]. Above: Molecular framework. Below: Space-filling model.

The butanol molecules are disordered in a characteristic way: although each of the CH_2 groups is located in a similar position, the OH group sometimes points in one, sometimes in the opposite direction along the tube. Thus, 1,4-butanediol appears to be present (Fig. 6, right).

Indeed, **6** forms clathrates with 1-butanol and 1,4-butanediol having the same stoichiometric ratio (1 : 1). However, the crystal lattices and the conformations of the host molecules differ clearly, even though there are no specific coordination interactions (e.g., hydrogen bonds) between host and guest or between guest molecules. In contrast to the tube-shaped 1-butanol inclusion, **6** forms a clathrate of cage type with 1,4-butanediol (Fig. 7).[35]

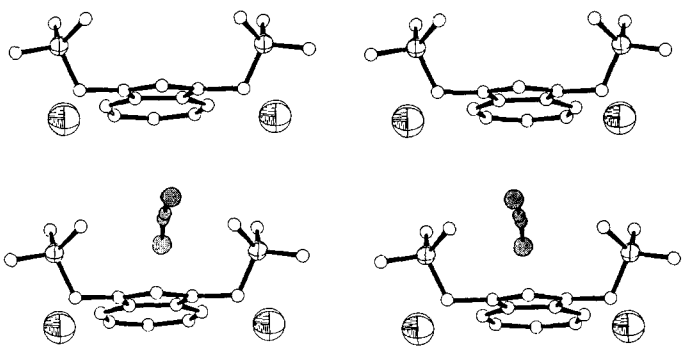


Fig. 7. Crystal structure of the 1,4-butanediol clathrate of **6** (stereoscopic picture). Butanediol shaded [35].

The shape and size of the hollows that are required by the guest molecules in the crystal lattice are similar to those of the 1-butanol inclusion. The planes formed by the azulene rings are again aligned in parallel layers and form the top and bottom of the cavity; the ammonium groups serve as lateral boundaries. The oval cavities are aligned in a longitudinal direction; as a result of the greater contraction, isolated cages rather than tubes are present.

Another difference between the butanol and butanediol inclusion is the position of the guest molecules. The plane formed by the C atoms (zigzag chain) of the butanol molecules is nearly parallel to the planes formed by the aromatic compounds; however, the middle layers of the C

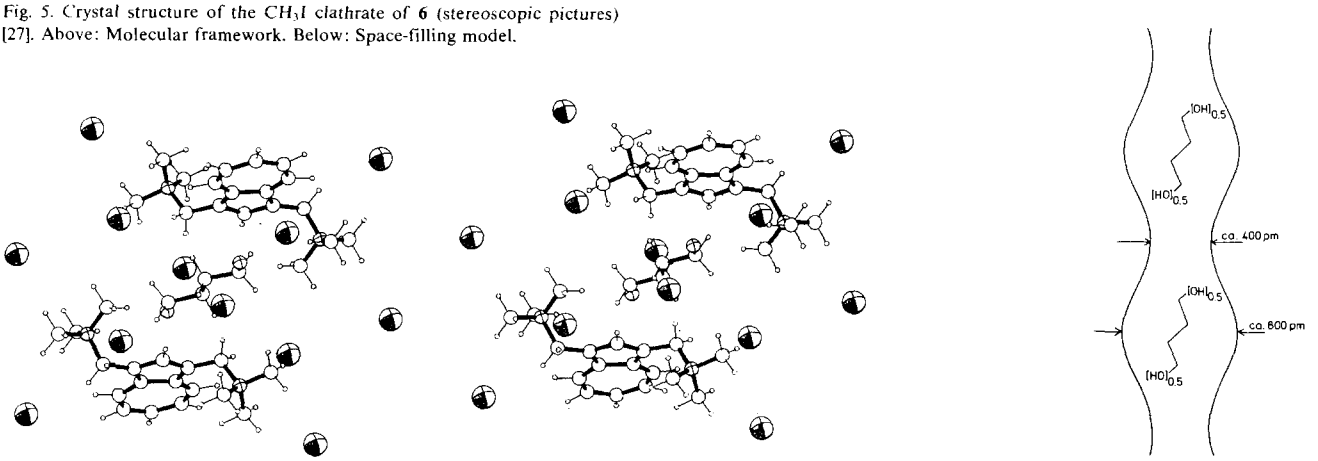


Fig. 6. Left: Crystal structure of the 1-butanol clathrate of **6**, observed in the direction of the $a-b$ diagonal (steroscopic picture) [34]. Right: Longitudinal section of the tube-shaped cavity (schematic drawing).

Table 2. Crystal data of some clathrates of the host compounds **6**, **10** and **16**.

Host	Guest molecule	Molar ratio host : guest	Space group	Crystal system	Z	Unit cell volume [nm^3]	Remarks [a]	Cavity type	Ref.
6	1-propanol	1 : 1	C2/c	monoclinic	4	2.556	isotypic to **6** · 1-butanol	channel	[35]
	1-butanol	1 : 1	C2/c	monoclinic	4	2.574	X-ray (Fig. 6)	channel	[35]
	2-butanol	1 : 1	C2/c	monoclinic	4	2.598	isotypic to **6** · 1-butanol	channel	[35]
	1,4-butanediol	1 : 1	$P2_1/m$	monoclinic	2	1.324	X-ray (Fig. 7)	cage	[35]
	iodomethane	1 : 1	Pnma	orthorhombic	4	2.485	X-ray (Fig. 5)	cage	[27]
	bromotrichloromethane	1 : 3	—	orthorhombic	8	5.550	—	—	[35]
	nitromethane	1 : 1	—	triclinic	4	2.566	—	—	[35]
10	ethanol	1 : 1	$P2_1/c$	monoclinic	4	2.618	X-ray (Fig. 8)	cage	[28]
16	1-propanol	1 : 1	Pnma	orthorhombic	4	3.028	X-ray (Fig. 9); contains 0.5 H_2O	cage	[29]

[a] X-ray = X-ray structure determination.

atoms of the 1,4-butanediol molecules form planes that are perpendicular to the plane formed by the azulene rings.

The cell data of these and several other clathrates of **6**, **10**, and **16** are shown in Table 2. The crystal lattices of the 1-butanol, 2-butanol, and 1-propanol clathrates of **6** are isotypic; they differ only slightly in cell parameters and should therefore have the same cavity dimensions.

Other lattice structures of **6** with changed cavity proportions—depending on the incorporated species—are formed upon inclusion of CH_3NO_2 and $BrCCl_3$; they demonstrate the extraordinary adaptability (induced fit) of the host compound **6** to the geometry of the guest molecules.

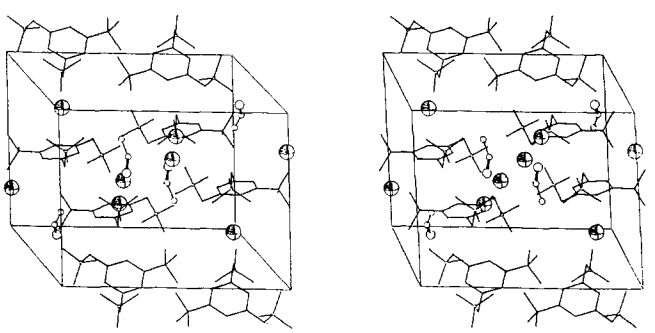


Fig. 8. Unit cell of the ethanol clathrate of **10** (stereoscopic picture) [28].

Figures 8 and 9 show the crystal structures of alcohol inclusions (ethanol, propanol) in host lattices of the compounds **10** and **16**, which have *tert*-butylbenzene as anchor group and *meta*-oriented ammonium groups. Along with the voluminous transoid-oriented trimethylammonium units, the *tert*-butyl groups also serve as cavity boundaries in the ethanol clathrate of **10**[28] (Fig. 8).

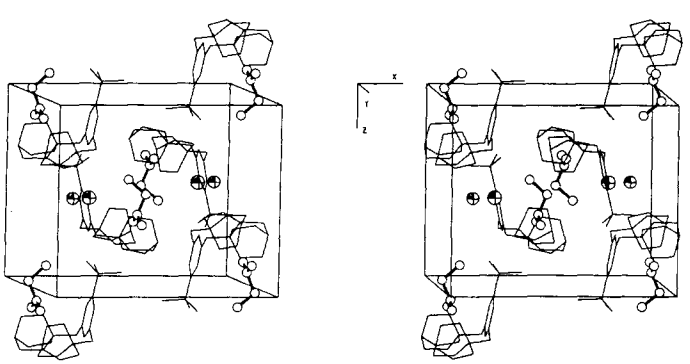


Fig. 9. Unit cell of the 1-propanol clathrate of **16** (stereoscopic picture) [29].

In the crystal of the 1-propanol clathrate,[29] the quinuclidinium branches of the host compound **16** are aligned on the same side of the *tert*-butyl anchor group (Fig. 9). In addition to the stoichiometric amounts of 1-propanol, one-half mole of water of crystallization per mole of clathrate is present in defined lattice positions. One terminal group (OH or CH_3) of propanol is disordered and is not in the plane formed by the other three C and O atoms.

X-ray analyses of the different clathrates of **16**[29] support the conceptual picture of the onium hosts: the molecular combination of voluminous onium groups with rigid, bulky anchor groups leads frequently to gaps in the crystal lattice. Only the inclusion of suitable guest molecules makes a dense molecular packing in the crystal possible—in addition, more beautifully shaped crystals are frequently produced.

The methylene bridges as spacer units permit a somewhat limited conformational flexibility which ensures a *dynamic adaptability of the conformation of the host molecules to the geometry of the guest molecules* during crystallization. A certain analogy to the induced adaptation of enzymes or receptors to substrate or ligand molecules (induced fit) is unmistakable.

A dependence of the structure of the host lattice on the incorporated species is known for only a few other synthetic clathrands. Tri-*o*-thymotide (TOT) **3**, for instance, forms trigonal cage clathrates with smaller guest molecules; with larger guests (six or more C atoms) it forms hexagonal channel-shaped inclusion lattices.[36] Urea crystallizes in its pure form in "fairly loose" tetragonal lattice structures; in urea adducts, on the other hand, a hexagonal lattice is present which makes the formation of stronger hydrogen bonds between the urea molecules, as well as a denser molecular packing, possible (cf. ref. [4c]).

Host flexibility and induced fit are found as characteristic features in numerous biochemical host/guest processes—albeit in solution. Thus, for example, the specificity of the enzyme(hexokinase)-catalyzed phosphorylation of glucose with ATP is due to a substrate-induced conformational change of the enzyme.[37]

4. Chiral Onium Host Compounds: Clathrates and Enantiomeric Enrichment

Enantiomeric resolution by means of noncovalent interactions is a further, more recent aspect of host/guest chemistry. Well-investigated examples with broad applications include enantiomeric enrichment using optically active crown ethers[38] in crystallization, extraction, or membrane transport processes,[39] chromatography on optically active adsorbents[40] involving the formation of diastereomeric electron-donor-acceptor complexes,[41] diastereomeric $Cu^{2\oplus}$-amino-acid chelates,[42] and chiroselective inclusions (e.g., in triacetylcellulose, polyacrylamides, and polymethylacrylamides).[43]

In contrast, the use of clathrate chemistry to produce precise, crystalline, chiroselective guest inclusions is still in its infancy. The basic prerequisite is the inclusion of chiral species in chiral crystal cavities. Numerous chiral clathrands are unable to resolve enantiomers. In fact, some even lose their inclusion ability in pure enantiomeric form.[18,44]

Isolated examples of enantiomeric enrichment via the formation of inclusion complexes with optically active host compounds have been described, for example, between chiral carboxylic esters and cyclodextrins,[45] between propargyl alcohols and brucine,[46] and between 1-amino-1-phenylethane and tetraacetyl-α-glucose.[47] Tri-*o*-thymotide **3** crystallizes in its pure form in an achiral lattice, one-half of which consists of plus and the other half of minus propeller conformations. In solution, the two enantiomeric conformers readily interconvert. Upon formation of an inclusion compound, spontaneous "enantiomeric resolution" occurs, so that a chiral environment is offered to the guest molecules in the crystal.[48] By co-crystallization with a chiral species, one of the enantiomers from a racemic mixture can undergo preferential inclusion. The enantiomeric excess per clathratization step is usually higher for the cage-type clathrates of tri-*o*-thymotide **3** (e.g., 2-bromobutane, 37% *ee*) than for channel-like inclusions (e.g., 2-bromononane, 5% *ee*).[49]

Achiral compounds as host crystals can also effect a discrimination of enantiomers. For instance, hexagonal urea crystallizes spontaneously in left- and right-handed helix structures, each of which preferentially forms an adduct with only one enantiomer of a racemic mixture.[51] The azulenebis(ammonium) salt **6** crystallizes, for example, with butanol in a chiral conformation (C_2 symmetry, cf. Fig. 6); the crystal lattice, however, is achiral, since both enantiomers are present.

The structural features (bulkiness, limited conformational flexibility) of the chiral onium compounds that are displayed in Figure 10 illustrate the construction principle of many effective clathrate-forming molecules (cf. Fig. 3). The modified Tröger's bases **38**–**43**[51] and the enantiomerically pure quaternized alkaloid bases **44** and **45**[52] have an extensive inclusion ability (Table 3). Particularly noticeable is the wide range of clathrates formed by the ammonium salts **38**, **39**, and **41** with *aromatic* guest substances.

The (−)-*N*-methyl- and (−)-*N*-benzylquininium salts **44** and **45**, respectively, which were obtained by quaternization of bases from the "pool" of optically active natural

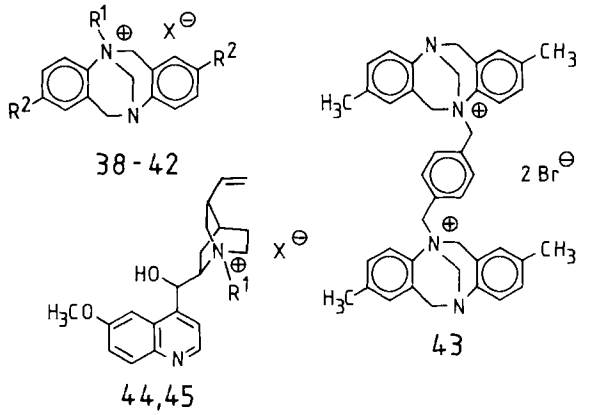


Fig. 10. Chiral onium clathrands **38**–**43** [51] and **44**, **45** [52].

	R^1	R^2	X
38	CH_3	CH_3	I/CH_3SO_4
39	CH_3	CH_2–CH=CH_2	Br
40	CH_3	CH_2–(*p*-C_6H_4)–CH_3	Br
41	OCH_3	CH_3	I/CH_3SO_4
42	OCH_3	CH_2–(*p*-C_6H_4)–OCH_3	Br
44	CH_3	—	I
45	CH_2–Ph	—	Cl

substances, form inclusion compounds with a chiral species (2-butanol) in the stoichiometric ratio 1 : 1, as well as with other short-chained guest compounds. Recrystallization of the enantiomerically pure clathrands from racemic 2-butanol and subsequent declathration by heating to 50 °C at 0.01 torr yields optically active distillates: **44**, (+)-(*S*)-2-butanol, 16% *ee*; **45**, (−)-(*R*)-butanol, 25% *ee*.[25] The reversibility of the clathration/declathration process and the relatively high enantiomeric excess indicate that higher enantiomer enrichments are possible.

Figure 11 shows the crystal structure of the methanol clathrate of **44**. The guest molecules are enclosed within the cage cavity of the quaternized host alkaloid. The hydroxyl group of the host compound is coordinated to the oxygen atom of the guest methanol via a hydrogen bond (coordinato clathrate[17a]).

Table 3. Clathrates of the chiral host compounds **38**–**45**.

Clathrand [a]	Molar ratio host : guest	Guest molecules	Ref.
38, **39**, **41**	1 : 1	benzyl alcohol	[51]
	2 : 1	benzene, toluene, *o*-, *m*-, *p*-xylene, ethylbenzene, chlorobenzene, 4-chlorotoluene, benzaldehyde, D,L-1-phenylethanol, cyclohexanone, dioxane	
	3 : 1	mesitylene, acetophenone	
	3 : 2	cyclohexanol	
40, **42**	1 : 1	ethanol, benzene, toluene, dioxane	[51]
	2 : 1	acetone	
	3 : 2	1-butanol	
43	1 : 1	benzene, dioxane	[51]
44	1 : 1	methanol, ethanol, 1-propanol, 2-propanol, 1-butanol, 2-butanol, trichloromethane, tribromomethane, acetonitrile, 2-nitropropane	[52]
45	1 : 1	ethanol, 1-propanol, 2-propanol, 2-butanol, trichloromethane	[52]
	2 : 3	2-nitropropane	

[a] The inclusion properties of the host compounds **38**, **39** and **41** and of **40** and **42** are identical.

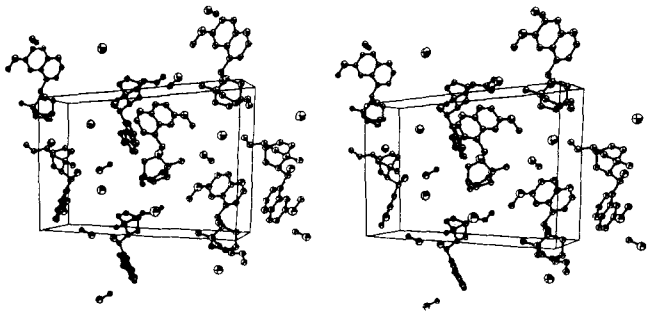


Fig. 11. Unit cell of the methanol clathrate of **44** (stereoscopic picture) [52].

5. Triiodomethane and TCNQ Complexes of Organic Onium Compounds Having Electrical (Semi-)Conductivity

It has been known for a long time that triiodomethane forms solid adducts with onium salts;[31] however, it also forms solid adducts with neutral molecules.[53] The crystalline products with 1,4-dioxane, 1,4-dithiane, and other π-donor substances could be identified as charge-transfer complexes.[53,54] IR and ^{1}H-NMR measurements indicate that the association of tetraalkylammonium halides and triiodomethane in weakly solvating media may also be attributed to electron-donor-acceptor interactions.[55]

Most of the onium compounds whose clathrate-forming qualities have been investigated form solid adducts with HCI_3.[33] Unlike the crystallization of "true" clathrates, which usually takes place slowly from alcoholic solution or requires the addition of inert solvents (e.g., diethyl ether), the reaction with triiodomethane to form solid adducts takes place readily, usually within a few minutes. In Table 4, the molar ratios of onium compounds to triiodomethane in the crystalline complexes are listed.

Table 4. Electron-donor-acceptor complexes of several host compounds with triiodomethane [33].

Onium compound	Molar ratio salt : HCI_3	Onium compound	Molar ratio salt : HCI_3
6	1:2	**23**	1:1
7	1:2	**29**	1:2
8	1:2	**30**	1:4
9	1:3	**31**	1:2
10	1:2	**32**	1:1
11	1:2	**33**	1:4
13	1:2		

X-ray analyses of the adducts (as well as Raman measurements) confirm the existence of electron-donor-acceptor complexes (Fig. 12–14): a) The $I^{\ominus}\cdots I$ distances are about 75 pm shorter than the calculated van der Waals distances; b) the C–I bond lengths in the complexes are slightly longer than in pure HCI_3; c) the $I^{\ominus}\cdots$I–C arrangements are in all cases roughly linear.

The crystal structures of the complexes show that the triiodomethane molecules are in all cases linked to the $I^{\ominus}$ ions via iodine atoms. Since every $I^{\ominus}$—as well as every HCI_3 unit—can be linked one, two, or three times, depending on the crystal packing, three-dimensional cross-linked structures (Fig. 12 and 14) as well as smaller $I^{\ominus}\cdots HCI_3$ units (Fig. 13) result.

An interesting anomaly appears in the NMR spectrum of the complexes in solution. Whereas, the addition of halide ions results in increased shielding of the proton in the ^{1}H-NMR spectrum of HCI_3 (in [D$_6$]DMSO), a significant deshielding of about 10 ppm is observed in the ^{13}C-NMR spectrum. This anomaly can be interpreted satisfactorily by structural changes in the HCI_3 molecule (see above) as a result of the charge transfer from the $I^{\ominus}$ donor to the HCI_3 acceptor.[33]

In the solid state, the triiodomethane complexes have specific electrical conductivities that lie at the lower end of the semiconductor scale. Interestingly, the specific conductivity increases in the sequence $\mathbf{10}\cdot 2\,HCI_3 < \mathbf{8}\cdot 2\,HCI_3 < \mathbf{32}\cdot HCI_3$ with the extent of the three-dimensional $I^{\ominus}\cdots HCI_3$ linking.

The dependence of the $I^{\ominus}\cdots HCI_3$ cross-linking in the crystal on molecular packing and the fact that a part of the onium halide is not able to form corresponding adducts indicate that, in addition to the electron-donor-acceptor interaction, structural characteristics also decisively influence the formation of adducts.

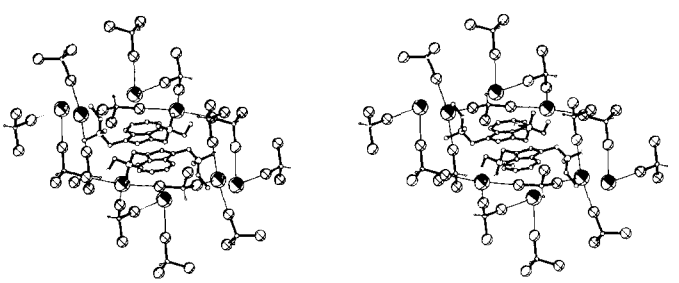


Fig. 12. Section of the unit cell of the complex $\mathbf{8}\cdot 2\,HCI_3$; iodide ions shaded (stereoscopic picture) [33].

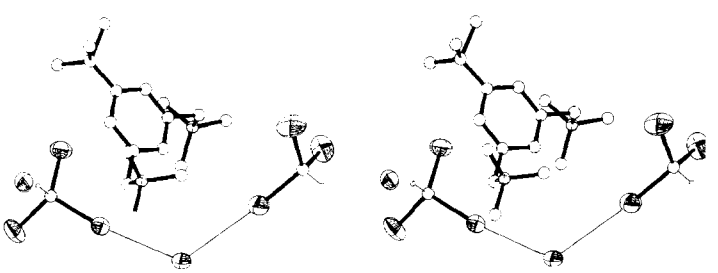


Fig. 13. Crystal structure of the complex $\mathbf{10}\cdot 2\,HCI_3$ with isolated $I^{\ominus}$ and $(I\cdot 2\,HCI_3)^{\ominus}$ units (stereoscopic picture) [33].

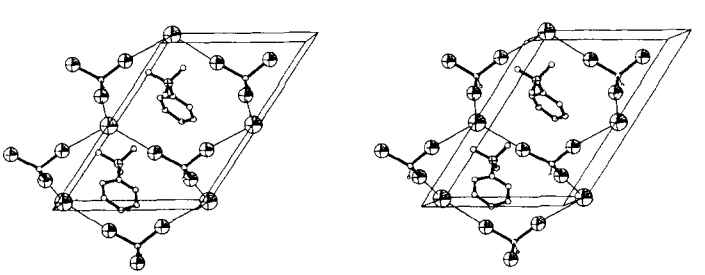


Fig. 14. Unit cell of the complex $\mathbf{32}\cdot HCI_3$ (stereoscopic picture) [33].

In organic conductors and semiconductors based on tetracyanoquinodimethane (TCNQ), the alignment of the TCNQ molecules or radical anions in stacks with overlapping π orbitals is of decisive importance for electrical conductivity.[57] Accordingly, the specific conductance depends sensitively on the molecular packing in the crystal and therefore on the structure of the cation. Generally, one distinguishes between simple salts $M^{n\oplus}(TCNQ^{\ominus})_n$ and complex salts $M^{n\oplus}(TCNQ^{\ominus})_n(TCNQ)_m$ ($M^{n\oplus}$ = metal or organic onium ion).[58] Planar structures like *N*-methylphenazinium **46**, protonated acridine **47**, or quinoline **48** (Fig. 15) have proved to be especially convenient counterions in TCNQ (complex) salts.[57]

How do "clathratogenic" structural features affect the molecular packing and the electrical conductivity of organic TCNQ salts? Reaction of the onium compounds with excess LiTCNQ results in typical "simple salts" as well as in complex salts (**6**, **7**, **30**) of general composition $M^{(n+m)\ominus}(TCNQ^{\ominus})_n(X^{\ominus})_m$.[59] The unusual but reproducible stoichiometry of the complex salts that contain TCNQ and radical ions in addition to halide ions may be ascribed to crystal packing effects.

The conductivity data of a small selection of onium TCNQ salts and complexes (Fig. 3, 4, 15) are listed in Table 5. The complex salt of the cation **30** has an electrical conductivity that is unusually high for simple salts.[59]

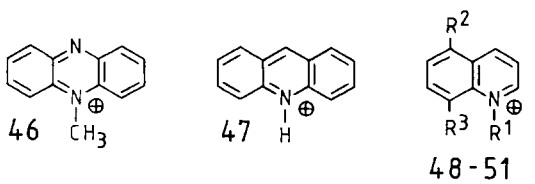


Fig. 15. Selection of some organic cations in TCNQ radical salts and complexes.

	R^1	R^2	R^3
48	H	H	H
49	CH_3	H	H
50	CH_3	Cl	$O(CH_2)_2OH$
51	H	Cl	$O(CH_2)_2OH$

Table 5. Specific conductivities of some TCNQ radical anion salts and complexes of organic onium cations.

Cation of	n	$M^{(n+m)\ominus}(TCNQ^{\ominus})_n(X^{\ominus})_m$ m	$X^{\ominus}$	σ [Ω^{-1} cm^{-1}]	Ref.
6	0.75	1.25	$I^{\ominus}$	$3\cdot10^{-6}$ [a]	[59]
7	0.75	1.25	$Br^{\ominus}$	$1.4\cdot10^{-7}$ [a]	[59]
30	1	1	$I^{\ominus}$	$1.6\cdot10^{-2}$ [a]	[59]

Cation of	n	$M^{n\oplus}(TCNQ^{\ominus})_n(TCNQ)_m$ m	Solvent inclusion	σ [Ω^{-1} cm^{-1}]	Ref.
46	1	—	—	143 [b]	[62]
47	1	1	—	70 [b]	[63]
48	1	1	—	100 [b], 4 [a]	[64]
49	1	0.5	$2CH_3CN$	0.29 [a]	[61]
49	1	0.5	$C_2H_5COCH_3$	0.26 [a]	[61]
50	1	1	CH_3CN	$7.4\cdot10^{-2}$ [a]	[60]
51	1	—	—	$3.7\cdot10^{-6}$ [a]	[60]

[a] Conductivity measurements on a crystal powder pellet. [b] Conductivity measurement on a single crystal.

Solvent molecules often undergo inclusion in the complex TCNQ radical-anion salts (Table 5).[60,61] Upon removal of the acetonitrile from the adduct with **50** (70°C/high vacuum) and from that with **49** (103°C), the conductivities decrease to about 1.2×10^{-4} Ω^{-1} cm^{-1}. Obviously, the solvent molecules in the crystal support a stack-shaped alignment of the TCNQ molecules (cf. structure of **50**·CH_3CN in ref. [59]) which is favorable for the electrical conductivity. This example clearly demonstrates the possible effects of structural and electronic interactions on the formation of crystalline complexes and clathrates.

6. Macrocyclic Onium Compounds with Hydrophobic Cavities as Inclusion Forming Molecules in Aqueous Solution

Host molecules with intramolecular cavities capable of incorporating uncharged guest molecules are interesting with regard to their suitability as selective inclusion forming compounds and as enzyme and receptor models. Beside the well-investigated cyclodextrins,[65] synthetic and semisynthetic molecules, such as modified cyclodextrins,[66] crown compounds,[67] calixarenes,[68] and many-membered cyclophanes,[69] are able to form inclusion compounds with neutral guest molecules.

Of the abiotic host compounds, particularly macroheterocyclic onium compounds of the phane type (Fig. 16–18, 20–22) significantly reflect the basic characteristics of enzymes[1,70] such as substrate specificity, saturation kinetics, and catalysis. The ammonium centers that are already present or are formed by protonation of amine or pyridine nitrogen atoms serve the purpose of ensuring or increasing the water solubility of the host molecules. At least four positive charges are required because of the size of these host molecules and their lipophilic components.

In aqueous medium, steric adaptation (induced fit) and van der Waals, electrostatic, and hydrophobic interactions[71] play decisive roles (multiple recognition[17b,72]) as driving forces for the binding of lipophilic guest molecules inside host molecules with nonpolar cavities. The macrocyclic onium compounds shown in Figures 16 and 17 have the following advantages over open-chained analogues as model compounds (cf. **120**, **121** in Fig. 22[17b]):

a) As a result of the rigid structure units that function as spacers and the repulsion of the positive charges, cavities of strictly defined size and structure are formed in aqueous solution.
b) As a result of their polar exterior, dispersed host macrocycles are soluble in water, i.e., formation of micelles is avoided within a relatively large concentration range.
c) The host molecules have a hydrophobic interior and therefore offer the guest molecules a nonpolar microenvironment.
d) The electropositive potential allows the stabilization of anionic transition states and therefore favors catalytic activity.
e) In the compounds **78**–**82** and **85**–**87**, the hydrophobic quaternary ammonium groups point away from the cavity, so that, on inclusion of nonpolar guest molecules, no interference by water molecules occurs.

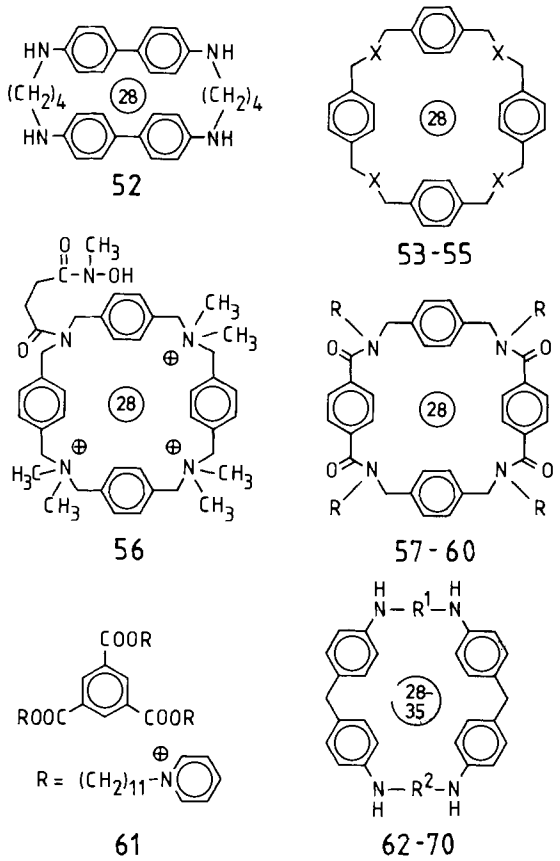


Fig. 16. Host molecules that are water soluble or whose protonated form (acid) is water soluble and host cations with hydrophobic cavities: **52** [73], **53-55** [86], **56** [100] (see also [82]), **57-60** [85, 99], **61** [83c], **62-70** [82c, d].

	X or R
53	NCH_3
54	$\overset{\oplus}{N}(CH_3)_2$
55	$\overset{\ominus}{S}CH_3$
57	$(CH_2)_{10}CO_2H$
58	$(CH_2)_{10}\overset{\oplus}{N}(CH_3)_3$
59	$(CH_2)_{10}\overset{\oplus}{N}(CH_3)_2$–$CH_2$–4-imidazolyl
60	$[(CH_2)_{10}\overset{\oplus}{N}H(CH_3)_2]_{2/4}$ and $[(CH_2)_{10}\overset{\oplus}{N}(CH_3)_2$–$CH_2$–4-imidazolyl$]_{2/4}$

	R^1	R^2
62	$(CH_2)_3$	$(CH_2)_3$
63	$(CH_2)_4$	$(CH_2)_4$
64	$(CH_2)_5$	$(CH_2)_5$
65	$(CH_2)_3$	$(CH_2)_5$
66	$(CH_2)_4$	$(CH_2)_5$
67	$(CH_2)_5$	$(CH_2)_6$
68	$(CH_2)_5$	$(CH_2)_8$
69	CH_2-1,4-phenylene-CH_2	CH_2-1,4-phenylene-CH_2
70	CH_2-1,4-cyclohexylene-CH_2	CH_2-1,4-cyclohexylene-CH_2

Whereas the benzene adduct of **52**,[73] which had long been considered as an intramolecular inclusion compound, turned out, on X-ray analysis, to be an extramolecular benzene inclusion in the crystal (i.e., a clathrate)[74] other host/guest compounds of cyclophanes could be identified as intramolecular inclusions of nonpolar guest molecules (i.e., as cavitates).[16] Thus, for example, the cyclic hexamer **83** with trigonal symmetry forms niches above and below the plane of the macrocycle, in which chloroform molecules are incorporated just as in a lock-key relation and the H

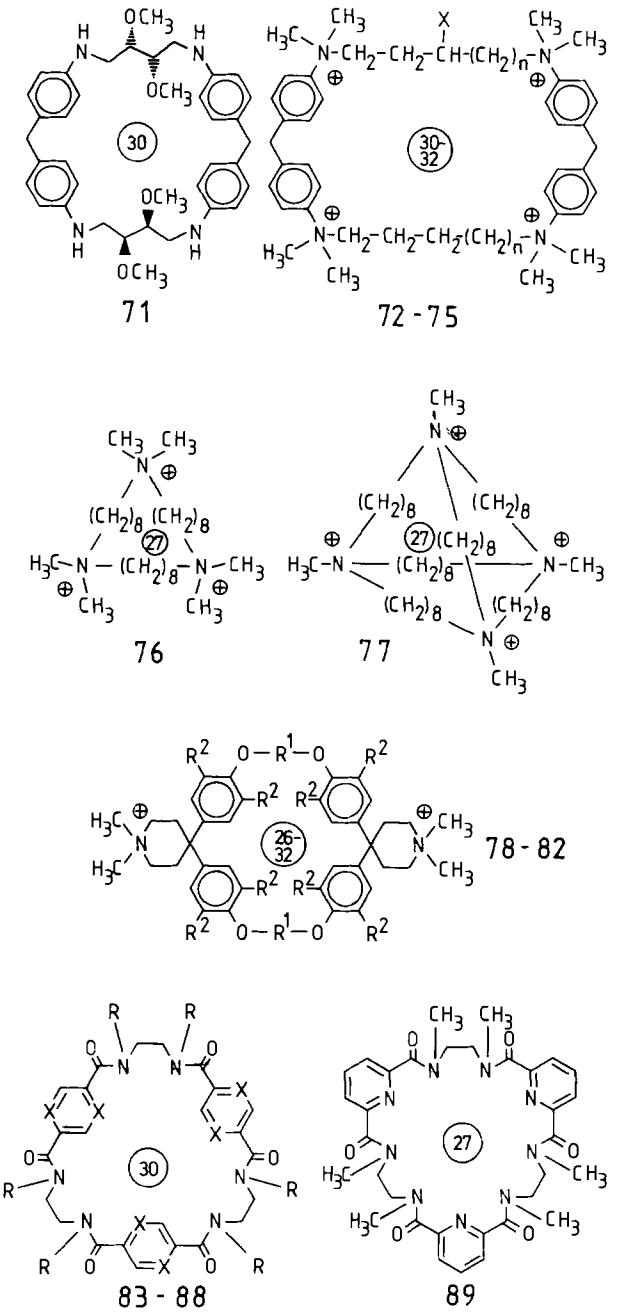
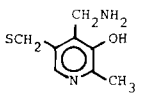
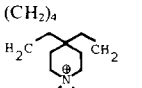


Fig. 17. Host molecules that are water soluble or whose protonated form is water soluble and host cations with hydrophobic cavities: **71** [97], **72-75** [101], **76**, **77** [98], **78-82** [83a, b], **83-89** [87].

	n	X		R^1	R^2
72	1	H	**78**	$(CH_2)_2$	H
73	2	H	**79**	$(CH_2)_3$	H
74	2	$SCOCH_3$	**80**	$(CH_2)_4$	H
			81	$(CH_2)_4$	CH_3
75	2		**82**		CH_3

	X	R
83	CH	CH_3
84	CH	Benzyl
85	CH	CH_2-2-pyridyl
86	CH	CH_2-3-pyridyl
87	CH	CH_2-4-pyridyl
88	N	CH_3

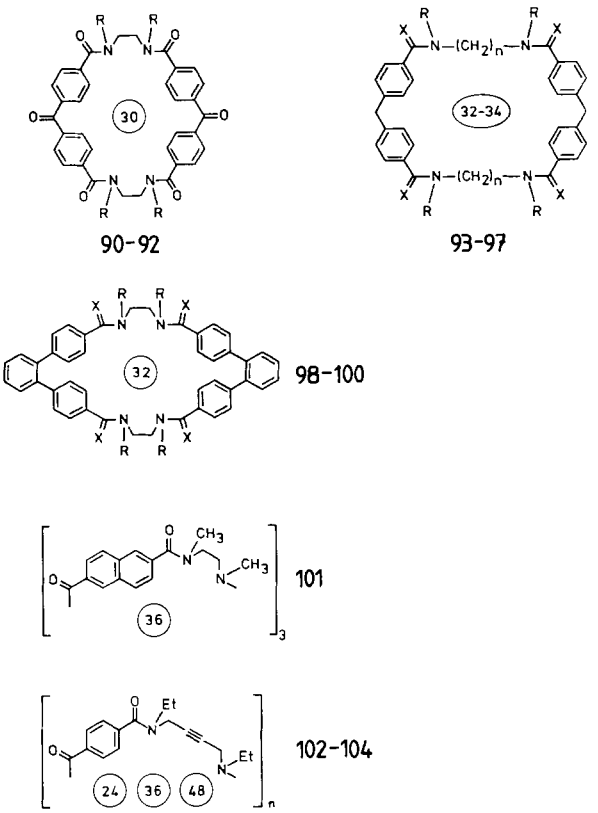


Fig. 18. Host molecules with large cavities, which have been converted into ammonium salts by protonation, and reference compounds [93].

	X	R	n		X	R	n
90	—	CH_3	—	**97**	H_2	C_2H_5	4
91	—	CH_2-phenyl	—	**98**	O	CH_3	—
92	—	CH_2-3-pyridyl	—	**99**	O	CH_2-3-pyridyl	—
93	O	C_2H_5	3	**100**	H_2	CH_3	—
94	O	CH_2-3-pyridyl	3	**102**	—	—	2
95	H_2	C_2H_5	3	**103**	—	—	3
96	O	C_2H_5	4	**104**	—	—	4

atom of the guest molecule points toward the center of the cavity.[75] The inclusion of chloroform was also confirmed for the adduct in solution by nuclear Overhauser effects between host and guest protons, by the splitting of the chloroform signal at −60°C in the ^{1}H-NMR spectrum, and by measurements with ion-selective liquid membrane electrodes.[76]

A dish-shaped conformation is exhibited by the azaparacyclophane **53** in its inclusion compound with 1,4-dioxane.[77]

The question arises as to how guest molecules in neutral or acidic aqueous medium are enclosed in the host molecules. The onium cyclophanes offer a cavity of sufficient depth if the aromatic compounds are in an "all-face" conformation.[78] This is favored as a result of the intramolecular π-interactions of the diphenylmethane units in the ring.[79] In its crystalline inclusion compound with durene, the tetraammonium salt **63** · 4 HCl shows a corresponding "all-face" conformation, in which the plane formed by the four benzene rings is aligned perpendicular to the main plane of the macrocycle. The durene guest molecule is found exactly in the middle of the cavity.[80]

Are the complex geometries of the crystalline intramolecular inclusion compounds (cavitates) also observed in solution? Fluorescence and nuclear magnetic resonance measurements in aqueous medium indicate this to be the case. In the presence of the cyclophanes **53**–**55**, **62**–**70**, **72**, **75**, or **78**–**82** in acidic or neutral aqueous solution, the emission spectra of 8-anilino-1-naphthalenesulfonate and other fluorescence probes undergo changes; the quantum yields increase strongly, and the shift of λ_{max} corresponds to switching to nonpolar media.[82,83,86,101] In the ^{1}H- and ^{13}C-NMR spectra of host and guest molecules, signal displacements are observed that suggest specific geometric alignments of the host/guest associates.[83] Theoretical calculations of the chemical displacement support a "pseudoaxial" inclusion of 2,7-dihydroxynaphthalene in **63**[84] (Fig. 19a), whereas in the large cavities of **67** and **70** "equatorial" alignments of naphthalene derivatives are supposedly present[78,79] (Fig. 19b).

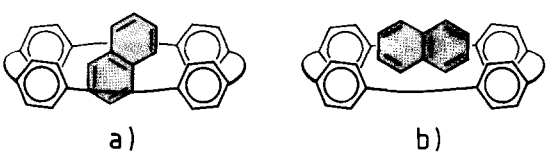


Fig. 19. a) "Pseudoaxial" and b) "equatorial" alignment of naphthalene in the cavity of a schematic cyclophane host in the "all-face" conformation.

In addition to the spectroscopic results, the comparatively high stability constants,[82b] the immobilization of guest molecules in the cavity,[85] the increased solubility of guest substances, and kinetic measurements[86] indicate an intramolecular inclusion in the host cavities.

The fact that **63** prefers β-substituted naphthalene (pseudoaxial inclusion) and **67** and **70** prefer α-substituted naphthalenes (equatorial inclusion) as well as the discrimination between benzene and naphthalene derivatives by **85**–**87** show[87] that even simple structural modifications in cyclophanes of this type result in different substrate selectivities.

Compared with **63** and **64**,[84] the octamethyl compounds **72**–**74**[101] have the advantage of being soluble in neutral aqueous solution.[89]

The inclusion capability of such hosts has been demonstrated by the high-field shifts of the protons of the guest naphthalene in the ^{1}H-NMR spectra as well as by fluorescence and NMR shifts upon titration. The energy of complexation in water decreases strongly with increasing percentage of organic solvent. Furthermore, it has been discovered that the mechanism of the binding of hydrophobic substrates in lipophilic cavities is similar to that of the dissolving of hydrocarbons in water. After immobilization of the azacyclophane **72** (n = 3) by adsorption on silica gel, chromatographic applications are possible.[89] Substrates such as naphthalenesulfonic acid, which is complexed particularly well by **72** (n = 3), are more strongly bound by the host in methanol as eluent than by untreated silica gel; this corresponds to a decreasing R_F value.

Attempts to catalyze the chlorination of hydrocarbons by binding a halide-transferring iodophenyl group to such

a tetraazacyclophane failed because of relative instability and insolubility of the hosts.[88]

In the reaction of 2-(bromomethyl)naphthalene with sodium nitrite in the presence of the 34-membered host **72** (n = 3), an acceleration of the reaction by a factor of 20 was observed compared with the uncatalyzed reaction.[90] Also, the product distribution [R-ONO]/[R-NO_2] obtained with this ambident nucleophile changes from 0.5 : 1 to 0.16 : 1. This product control can be explained by an accumulation of the nitrite ions at the positively charged centers of the host, thereby favoring S_N2 reaction and resulting in attack on nitrogen rather than on oxygen.

With host molecules such as **82**, 1 : 1 complexes could also be obtained with aromatic guest substances that are not readily soluble in water:[91] perylene, fluoroanthrene, pyrene, durene, and azulene. The highest binding constant ($pK = 7.2$) was found for the perylene complex. The weaker binding of adamantanol in methanol and the lack of complex formation in dimethyl sulfoxide as solvent indicate that hydrophobic interactions are the decisive driving forces for this type of host/guest binding.

A unique feature of the hexalactam host compounds **85**–**87** is their ability to complex aliphatic guests such as cyclohexane and adamantane derivatives, in addition to aromatic guests, in acidic aqueous solution, as shown by ^{1}H-NMR spectroscopy.[87]

By combination of the various diphenylmethane hosts (cf. **62**, **72**, **78**) according to the oligolactam concept (cf. **83**–**89**), new hosts having lactam structures (**90**–**94**, **96**, **98**, **99**, **101**–**104**) and—by reduction of the lactams—amine structures (**95**, **97**, **100**) with 30- to 48-membered rings became available[92] (cf. Fig. 18).

If the amine nitrogen atoms are in the benzylic position, as in **95**, **97**, and **100**, rather than in the aryl position, as in the hosts of *Koga* et al. (e.g., **62**–**70**), the complexation ability is completely retained. The high-field ^{1}H-NMR shifts that are observed for different aromatic guests are often very large. Besides phenols and naphthols, aliphatic guest molecules such as *trans*-1,4-cyclohexanediol and *trans*-1,4-cyclohexanedicarboxylic acid are complexed, in particular, by the *o*-terphenyl hosts **98**–**100**.

However, the host substances **102**–**104**, which have been made more rigid by the introduction of triple bonds, do not exhibit high-field shifts under comparable conditions. Fluorescence spectroscopic comparisons of the binding of the guest 8-anilino-1-naphthalenesulfonic acid (ANS) to different hosts[92] support the ^{1}H-NMR results: replacement of the diphenylmethane unit in **63** by the more lipophilic *o*-terphenyl unit in **100** results in an increase of the complexation constant from $pK = 3.8$ to 4.3. Even the rings **102**–**104**, which contain triple bonds, are possible host substances for ANS, although weaker bonding results from increasing ring size.

Like the macrocycles **85**–**87**, the pyridyl-substituted hosts **92**, **94**, and **99** strongly catalyze the H/D exchange in 2,7- and 2,6-naphthalenediol.[93]

Diederich and *Dick* studied the macrobicyclic hosts **105** and **106** with regard to their ability to complex neutral arenes such as pyrene and naphthalene in aqueous solution in cavities (Fig. 20).[94] In weakly acidic solution, **105** has a nonpolar cavity since the solvation-mediating ammonium centers lie at the periphery of the host. Pyrene and naphthalene can be dissolved by **105** in water using solid/liquid extraction. The complexation constants are $pK = 6.6$ for pyrene and 4.1 for naphthalene. In the ^{1}H-NMR spectrum, the signals of the complexed arene are strongly high-field shifted. Presumably, the guest is oriented in the plane of **105**, which includes the three spiro carbon atoms. The exchange between host and pyrene is sufficiently slow so that the ^{1}H-NMR signals of the free and uncomplexed pyrene can be recognized.

Easily available *in/out*-isomeric, spherical large-cavity compounds (**107** and **108**) were recently reported that differ only in cavity size and shape (Fig. 20);[95] their chemical constitutions and chemical properties are otherwise identical. Both hosts are able to complex polar aromatic compounds such as 2,7- and 2,6-naphthalenediol in acidic aqueous solution, as shown by the high-field ^{1}H-NMR shifts. Moreover, unsubstituted aromatic hydrocarbons such as naphthalene are complexed with similar binding constants by both hosts; however, the larger durene undergoes inclusion neither by **107** nor by **108**. Furthermore, with **107** but not with **108** it was possible for the first time to dissolve and efficiently complex a nonfunctionalized *aliphatic* hydrocarbon—adamantane—in aqueous medium by solid/liquid extraction.

This ability, which has up to now only been observed for cyclodextrins, and the marked differences in selectivity compared with the smaller and distorted cavity of the *out/in* isomer **108** are explained by the suitable size and shape of the host cavity of **107**, which is able to enclose the spherical adamantane completely. Accordingly, adamantanethiol is also complexed by **107** but not by **108**. A further confirmation of the different complexation abilities of the isomeric hosts is provided by the fact that the complexation constant of **107** with ANS ($pK = 4.6$) is considerably larger than that of **108** with ANS (4.0).

In contrast to **62**–**70** and to **108**, the *out/out* isomer **107** catalyzes the H/D exchange of the 1-protons of the guests 2,6- and 2,7-naphthalenediol. Presumably, **107** encloses the guest more favorably than **62**–**70** and **108**, resulting in activation of the 1-position.

Recently, the basket-shaped host molecules **109**–**111** were synthesized for the first time; these hosts have a bottom as well as a nearly 30-membered cyclic wall (Fig. 21).[96] The free host amine **111** forms the first inclusion complex with tetrahydrofuran (THF) in neutral water as shown by the high-field ^{1}H-NMR shifts of the THF protons and attempts to liberate the THF. ^{1}H-NMR investigations of the hexalactam **109** in deuterated glacial acetic acid as solvent with different phenols as guests did not result in any significant high-field shifts. On the other hand, an H/D exchange of each of the guest protons in the 1-position was observed for 1,3-naphthalenediol and, particularly, for resorcinol as guest substrates within a few minutes, but not for a large number of other phenols and naphthalenediols. No significant deuteration is observed with reference substances even after one day.

The water soluble paracyclophane **71**[97] permits discrimination between optically active isomers. It has a chiral hydrophobic cavity which is formed by two diphenylmethane units and by two C_4 bridges that are derived from

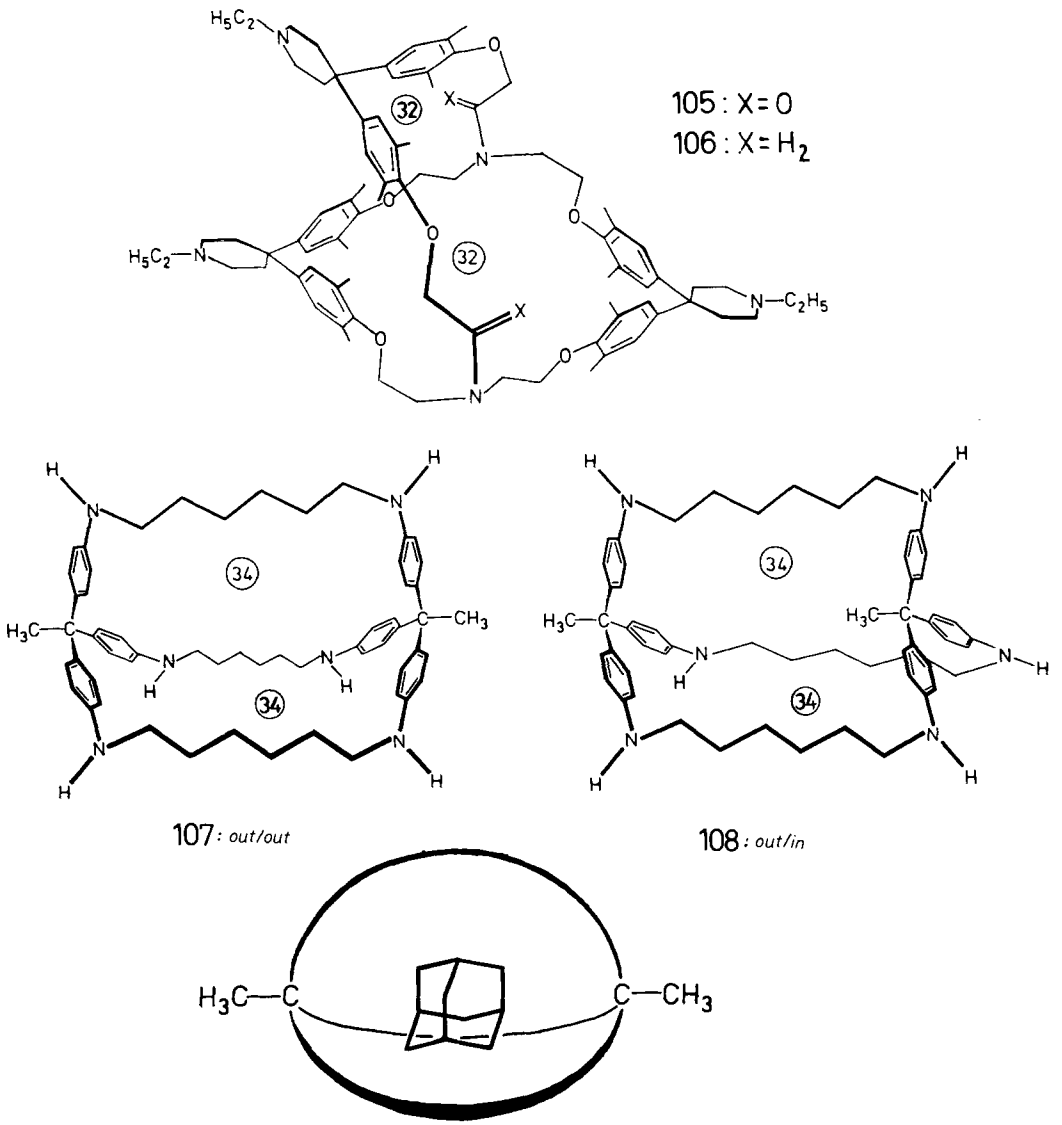
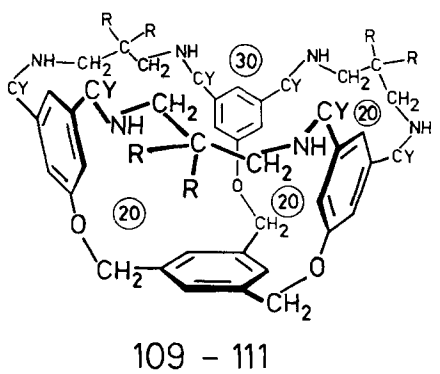


Fig. 20. Spherical large-cavity host compounds [94, 95] and drawing of the adamantane inclusion in **107**.

L-tartaric acid. Enantiomeric guest molecules containing hydrophobic moieties are selectively incorporated by the host to form diastereomeric host/guest compounds (chiral recognition[72]). Thus, for example, the ^{1}H-NMR signals of (*R*)- and (*S*)-mandelic acid or (*R*)- and (*S*)-1-amino-1-(1-naphthyl)ethane show different high-field shifts in a solution of **71** in acidic D_2O (pD = 1.2).[97]



109 - 111

Fig. 21. Basket-shaped host molecules [96]. **109**: Y = O, R = CH_3; **110**: Y = O, R = H; **111**: Y = H_2, R = CH_3.

The formation of a host/guest complex as a result of favorable steric and electronic adjustment is the first important step in enzymatic reactions (substrate discrimination). In order to go from host/guest chemistry to biomimetic chemistry, in which organic reactions are carried out analogously to enzyme-catalyzed reactions, further criteria must be fulfilled: a) suitable substrate orientation and positioning of the functional groups ("active sites") on the host; b) steric and/or electronic stabilization of transition states.[1,37,70]

A few cyclic onium compounds have been investigated with regard to their catalytic activity. Thus, for example, the tricyclic ammonium compound **77** accelerates the reactions of 2,4-dinitrofluorobenzene and iodomethane with azide ions by factors of 20 and 37, respectively, and kinetically controls the elimination of HBr from 2,3-dibromo-3-phenylpropionate.[98] The desolvation of the reaction partners and the stabilization of the anionic transition state are presumably of decisive importance here. The enzyme-like behavior of this so-called "artificial enzyme"[98] is emphasized by its substrate and reaction specificity and by the saturation kinetics.

The cyclophanes **112**–**114**, **118**, and **119** (Fig. 22) catalyze the hydrolysis of *p*-nitrophenyl esters of long-chained aliphatic carboxylic acids and sulfuric acids;[99] **54**–**56** catalyze the hydrolysis of the *p*-nitrophenyl and the α- and β-naphthyl esters of chloroacetic acid.[86, 100]

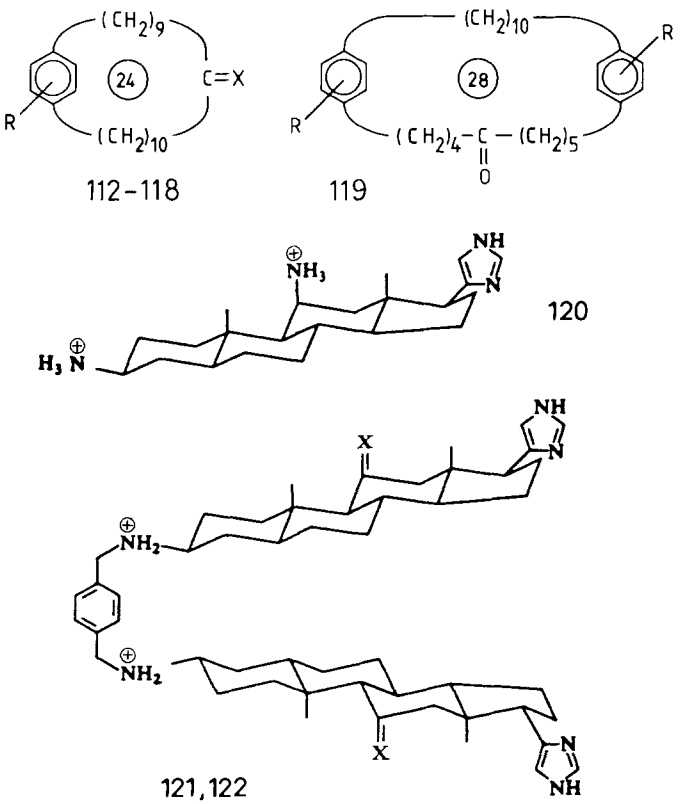
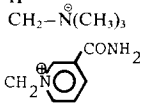


Fig. 22. Cyclic [98, 101] and open-chained ammonium compounds [17b] as enzyme models and reference compounds.

	X	R
112	N–OH	H
113	N–OH	$COO^{\ominus}$
114	N–OH	$CH_2-\overset{\oplus}{N}(CH_3)_3$
115	O	H
116	O	$CH_2-\overset{\ominus}{N}(CH_3)_3$
117	O	
118	O	CONH–$(CH_2)_2$–4-imidazolyl
119	–	CONH–$(CH_2)_2$–4-imidazolyl
121	O	–
122	H, β-$\overset{\oplus}{N}H_3$	–

The amination of phenyl pyruvate to give phenylalanine is accelerated by the macrocycle **75** by a factor of 31 in comparison with pyridoxamine.[101]

The cyclophane **119**, with imidazole residues as functional auxiliary groups, catalyzes the extremely rapid liberation of *p*-nitrophenolate from *p*-nitrophenyl esters in neutral aqueous solution in the presence of $Cu^{2\oplus}$ ions.[102] Possibly, a $Cu^{2\oplus}$ ion is coordinated to one of the two imidazole rings and drives both the transacylation and the hydrolysis.[102]

In contrast to other cyclic ammonium salts (e.g., **63** · 4 HCl) and open-chained reference compounds,[93] the pyridyl-substituted macrocycles **85**–**87**, **92**, **94**, and **99**, the macrobicycle **107** · 6 HX, and the macrotricycle (hexalactam) **109** catalyze a substrate-selective, strongly accelerated H/D exchange in bound hydroxy aromatic compounds in acidic aqueous medium. Apparently, the flexible pyridinium side arms or the carbonyl oxygen atoms function as active sites for this catalysis. The enzymatic character of these phanes is shown clearly by their (cyclo)peptide-like structure and their ability to bind physiologically important metal cations.[87]

Finally, it should be pointed out that *onium* compounds are not only bound as hosts but also in a variety of ways as *guest* substances with suitable host compounds: *ammonium salts as guests* in crown-ether-like host compounds have been thoroughly investigated, particularly as regards enantiomeric differentiation and resolution.[103, 104] Physiologically relevant ammonium compounds could be enclosed by hosts of the crown-ether type as well as, only recently, by anionic large-cavity compounds;[104] non-heterocyclic polyanions have also been used.[105]

7. Outlook

Although host/guest chemistry of heterocationic organic compounds is still in its infancy, the results of the investigations show that this field of research offers a valuable and versatile approach for present and future ways of looking at problems. As a result of the broad applicability of the onium clathrate concept and the fact that suitable host compounds are easy to synthesize, this host family may develop into one of the most widely used clathrate-forming systems and will be useful to both basic and applied research. Furthermore, the ready availability of completely synthetic chiral onium hosts and pure enantiomeric host compounds from the "pool" of optically active natural compounds allows for the first time the application of a clathrate family in the field of enantioselective host/guest systems.

Macrocyclic onium compounds with "exohydrophilic" and "endolipophilic" cavities are already established as simple, abiotic enzyme and receptor models. Even though the "functions" of the completely synthetic catalysts still do not even begin to approach the complexity of biological enzymes and receptors, individual important features are imitated in a significant way. Substrate discrimination (selectivity) and structure changes (induced fit) are of primary interest as initial steps in imitating receptor functions and enzyme action. Substrate orientation and catalytic activity—if necessary, with the aid of functional groups as active sites—are further "minimal characteristics" of enzyme models.

But who does not think in connection with synthetic enzymes of their use in technical processes? With such specific catalysts, chemical transformations—like enzymatic reactions—can be carried out more swiftly, under milder conditions, with higher yields, and fewer by-products, and, if necessary, with stereochemical control.

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Transition Metal Polysulfides: Coordination Compounds with Purely Inorganic Chelate Ligands

By Mark Draganjac and Thomas B. Rauchfuss*

It has been long known that certain transition metal sulfides dissolve in aqueous ammonium polysulfide. Although it was assumed that they thereby formed metal polysulfides, attention was first paid to such compounds only a few years ago. In recent years a host of new complexes with polysulfido chelate ligands have been isolated and characterized. The complexes are of interest not only regarding their structure and reactivity but also in view of their potential uses; they can be used for the directed preparation of sulfur rings of a given size, and there are indications that they will find applications in catalysis.

1. Introduction

The topic of this review, which covers an interface between main group and coordination chemistry, was officially born about 80 years ago with a report on $(NH_4)_2PtS_{15}\cdot 2H_2O$ and related compounds.[1] However, it was not until the 1960's that synthetic, spectroscopic, and structural techniques had evolved sufficiently to allow the systematic study of metal complexes of polysulfides. As coordination chemists turn increasingly toward organic chemistry in their search for new ligands, the discovery or rediscovery of a new class of inorganic chelating agents is a relatively rare phenomenon.

This review covers the syntheses, structures, and reactivity of molecular transition metal compounds containing polysulfido ligands. Important aspects of this chemistry in-

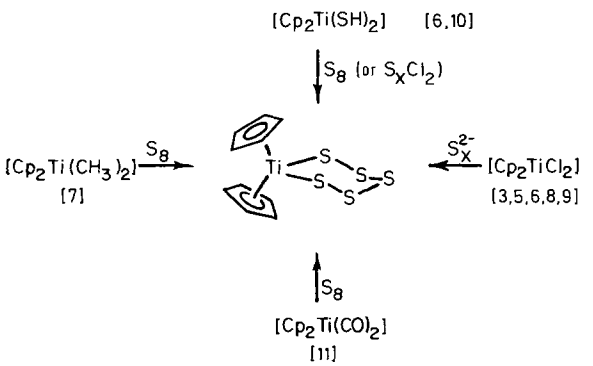
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volve compounds with disulfido ligands. The coordination chemistry of the disulfides has been reviewed recently[2] and will be discussed only insofar as it directly relates to polysulfides. The review is divided into two portions, the first half provides a survey of the syntheses and structures of the polysulfido complexes reported to date. In the second half, we discuss the reaction chemistry of two important classes of these compounds.

2. Synthetic and Structural Aspects of Transition Metal Polysulfides

2.1. The Titanium and Vanadium Triads

Cp_2TiS_5 ($Cp=\eta^5$-C_5H_5), first reported by *Samuel*[3] and *Schmidt*,[4] is one of the most easily prepared polysulfide complexes and has been the subject of numerous studies. With some refinements,[5] *Köpf* and *Schmidt*'s synthesis[6] from aqueous ammonium polysulfide and Cp_2TiCl_2 remains the most convenient way to prepare this compound on a large scale. Several other synthetic routes are available,[7-11] the diversity of which is testament to the stability of this complex and reflects the considerable level of interest in its chemistry (Scheme 1).



Scheme 1. Synthesis of Cp_2TiS_5.

Cp_2TiS_5 is a dark red, practically odorless, crystalline solid which is stable towards air and water. While this compound is sufficiently soluble for many synthetic purposes, the alkyl substituted derivatives such as the MeC_5H_4 and $iPrC_5H_4$ analogues are considerably more soluble and are also easy to prepare.

Early work suggested that the size of the polysulfide ring in the Cp_2TiS_x system could be adjusted by the nature of the polysulfide reagent.[12] Subsequently, these reports were shown to be incorrect; the reaction of Cp_2TiCl_2 with Na_2S_x ($x<5$) simply leads to diminished yields of the pentasulfide complex and negligible quantities of S_2 and S_3 derivatives.[8] This also holds in the case of many other polysulfido chelates: Very rarely can kinetically stabilized polysulfido chelates be selectively prepared through the use of sulfur transfer reagents. A possible exception to this rule, at least for a selenium system, is the reaction of Li_2Se_2 with $(MeC_5H_4)_2TiCl_2$, which affords the dimeric complex $[(MeC_5H_4)_2TiSe_2]_2$ in excellent yield with little formation of the known pentaselenido complex[13] [Eq. (1)].

$$2\ (CH_3C_5H_4)_2Ti\begin{matrix}Cl\\Cl\end{matrix} + 2\ Li_2Se_2 \xrightarrow[-4\ LiCl]{} (CH_3C_5H_4)_2Ti\begin{matrix}Se\text{–}Se\\Se\text{–}Se\end{matrix}Ti(CH_3C_5H_4)_2 \quad (1)$$

On the other hand, in the case of kinetically labile polysulfido complexes, such as those of copper and zinc, the size of the MS_x ring appears to be a function of the ratio of metal to total sulfur and cannot otherwise be controlled.

Two crystalline modifications of Cp_2TiS_5 have been characterized by single-crystal X-ray diffraction and the results of both structural studies are essentially in agreement.[14,15] The structure of this prototypal polysulfido complex is reproduced in Figure 1.

The TiS_5 ring adopts the chair conformation and the S–S distances and angles are within the range observed for other polysulfides, including S_8 itself.[16] Steric factors involving $Cp\cdots S$ interactions appear to be significant, but it has not proven necessary to invoke special electronic effects to rationalize the structural details. The stability of the S_5^{2-} chelate is a consequence of the 95° S–Ti–S angle and the Ti–S distance of 2.45 Å;[15] for comparison the S–S–S angle in α-S_8 is 107° and the S–S distance is 2.048 Å.[16]

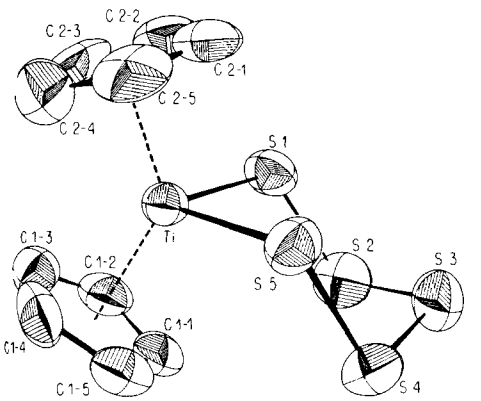


Fig. 1. ORTEP plot of $(C_5H_5)_2TiS_5$ [15].

NMR spectroscopic findings suggest that the chair conformation of the TiS_5 ring is retained in solution.[6] The energetics of this ring inversion, as analyzed by variable temperature NMR spectroscopy, is approximately 76 kJ/mol.[17]

As already mentioned, substitution of the Cp ligands generally enhances the solubility of polysulfides of the group IV elements without impinging on the structural or reactivity characteristics of the polysulfido chelate. An important exception, however, is provided by the decamethyltitanocene derivative, which is obtained as the monomeric trisulfide $(C_5Me_5)_2TiS_3$[18] (Fig. 2).

No evidence has been obtained for the S_5 or S_4 derivatives of the sterically encumbered $(C_5Me_5)_2Ti$ moiety. The barrier for ring inversion of the trisulfidotitanium complex and its zirconium analog is 40 kJ/mol, about half that for the corresponding Cp_2TiS_5 species.

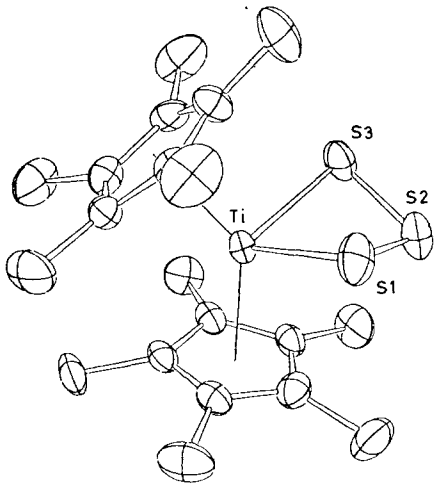


Fig. 2. ORTEP plot of $(C_5Me_5)_2TiS_3$ [18].

Steric factors and not electronic effects dictate the size of the TiS_x rings. This assertion is supported by the fact that, in contrast to the decamethyltitanocene complex, "Cp_2TiS_3" exists as a stable eight-membered Ti_2S_6 ring.[19] 1,5-$[(Cp_2Ti)_2S_6]$ and the six-membered ring compound 1,4-$(Cp_2Ti)_2S_4$ are formed upon desulfurization of the pentasulfido complex. The influence of the steric bulk of the substituents on ring size is often observed in organic systems and, to a lesser extent, in nonmetal rings as well.[20]

In the solid state, 1,5-$[\{(MeC_5H_4)_2Ti\}_2S_6]$ adopts the chiral D_2 conformation (Fig. 3). This same geometry is retained in solution. Thus, its ^{1}H-NMR spectrum shows four resonances indicative of the absence of a time-averaging of the halves of the MeC_5H_4 rings; at higher temperatures these resonances begin to merge, but coalescence has not been observed. With a visible absorption maximum of 610 nm, the blue Ti_2S_6 species somewhat resembles two well-known sulfur compounds, S_3^-[21] and S_8^{2+}.[22] $[Cp_4Ti_2S_6]$ may in fact be related to S_8^{2+} since its conformation lends itself to the formation of an incipient transannular S···S interaction as observed in S_8^{2+}. Such interactions would be induced by the electron-deficient character of the 16-electron titanium centers which possess acceptor orbitals suitably positioned for titanium-sulfur multiple bonding.

Other group IV analogues of Cp_2TiS_5 are known and do not appear to differ structurally. Since the precursor compounds Cp_2ZrCl_2 and Cp_2HfCl_2 are fairly moisture sensitive, the preparation of their polysulfides precludes the use of the aqueous reagents used for the titanium compound. *Shaver* and *McCall* solved this problem through recourse to anhydrous polysulfide reagents generated by using Li-BEt_3H ("superhydride")[23] [Eq. (2)].

$$2\,LiBHEt_3 + 5/8\,S_8 \longrightarrow Li_2S_5 + H_2 + 2\,BEt_3$$
$$Cp_2MCl_2 + Li_2S_5 \longrightarrow Cp_2MS_5 + 2\,LiCl\ (M = Ti, Zr, Hf, V) \qquad (2)$$

This superhydride methodology[24] continues to prove extremely versatile for the preparation of early transition metal polysulfido (and selenido) complexes. The free energy barriers for inversion of the three Cp_2MS_5 compounds are 76.3 (M = Ti), 48.6 (M = Zr), and 58.0 kJ/mol (M = Hf).[23]

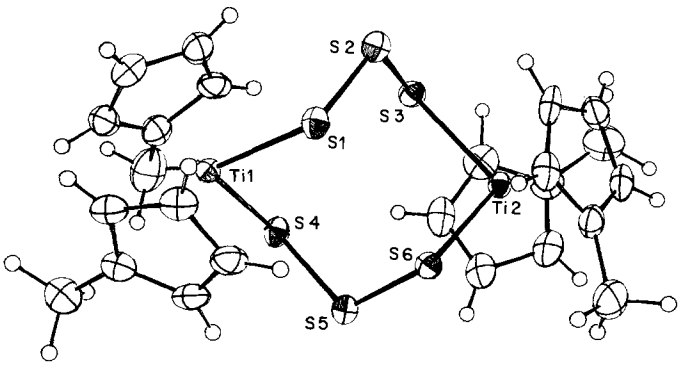


Fig. 3. ORTEP plot of $[(MeC_5H_4)_2TiS_3]_2$ [19].

There is no obvious explanation for these variations in the ring inversion barriers.

The preparation of the black Cp_2VS_5 is completely analogous to that for the titanium complex.[15,25] The structural and spectroscopic characterization of this 17-electron complex was instrumental in determining the spatial distribution of the frontier orbitals of Cp_2ML_2 compounds.[26] Structurally, this compound is isomorphous with the titanium complex, though its S-M-S angle is smaller by 5°. As a result of this angular compression, decamethylvanadocene forms a stable S_2[27] complex, unlike the analogous titanium system where the S_3 species is formed.

No molecular polysulfide chelates of niobium or tantalum have been reported so far, but further investigations in this direction are justified, for two reasons: The first monometallic S_2 complex prepared was Cp_2NbS_2Cl[28], and, as a rule, disulfido complexes presage the existence of related, stable polysulfido chelates. A second incentive for further study of niobium polysulfides derives from possible connections with the solid state chemistry of niobium and tantalum polyselenides and polytellurides, which exhibit unusual electrical properties. The one-dimensional polymer Nb_2Se_9 features Nb_2Se_4 octahedra bridged by Se_5 units.[29]

2.2. The Chromium Triad

Binary metal molybdenum sulfide chemistry represents one of the most fruitful specialties in this area of coordination chemistry.[30] The present inventory of known molecular binary molybdenum sulfides includes $[MoS_4]^{2-}$,[31] $[MoS(S_4)_2]^{2-}$,[32] $[Mo_2(\mu\text{-}S_2)_2(S_2)_4]^{2-}$,[33] $[Mo_2(\mu\text{-}S)_2(S)_2(S_2)_2]^{2-}$,[34] $[Mo_2(\mu\text{-}S)_2(S)_2(S_2)(S_4)]^{2-}$,[32b,35] $[Mo_2(\mu\text{-}S)_2(S)_2(S_4)_2]^{2-}$,[32b] $[Mo_3(\mu\text{-}S)_4(S)_5]^{2-}$,[36] and $[Mo_3(S)(S_2)_6]^{2-}$;[37] note the existence of two structural isomers of "$[Mo_2S_{12}]^{2-}$" (Fig. 4).

Three of these compounds contain S_4 ligands. All of the dimeric compounds are clearly interrelated structurally,

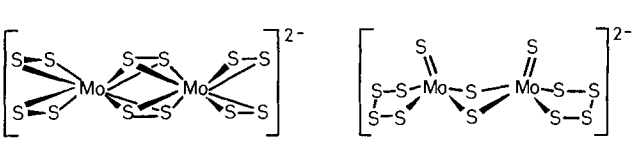


Fig. 4. Two isomers of $[Mo_2S_{12}]^{2-}$.

and, to a limited extent, they appear to be interconvertible.

The reaction of $[MoS_4]^{2-}$ with sources of elemental sulfur affords the $[MoS_9]^{2-}$ ion. The most convenient source of sulfur is dibenzyl trisulfide, and the product obtained in the reaction can be isolated as the PPh_4^+[38] or NEt_4^+[32] salt, both of which have been characterized by X-ray diffraction. Furthermore, the oxo ion $[MoOS_8]^{2-}$ can be prepared either by hydrolysis of $(Et_4N)_2[MoS_9]$[32] or by reaction of $[MoO_2S_2]^{2-}$[38] or $[MoOS_3]^{2-}$[39] with elemental sulfur. In the $[MoS_9]^{2-}$ ion, molybdenum is coordinated in a distorted square pyramidal fashion by a terminal sulfide and two bidentate S_4^{2-} ligands[32] (Fig. 5). The Mo-S1 distance of 2.12 Å is 0.20–0.25 Å shorter than the Mo-S2 (S2′, S5, S5′) distances. Although it is consistent with substantial multiple bond character it is one of the longest Mo-S(terminal) distances known.

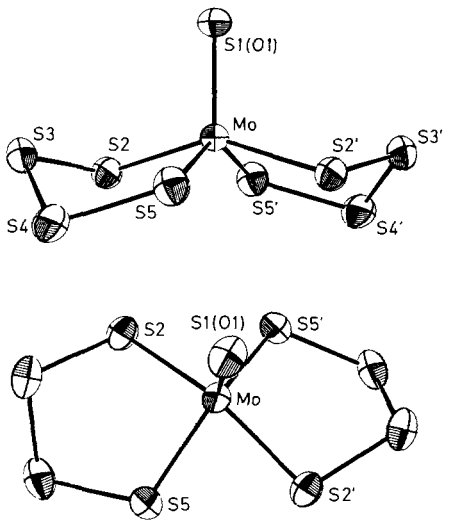


Fig. 5. ORTEP plots of $[MoS_9]^{2-}$ and $[MoOS_8]^{2-}$ [32]. Top: side view; bottom: plan view.

The Mo-S(S_4) distances are only slightly changed upon replacement of the terminal sulfide by an oxide. The S_4 ligands in $[MoX(S_4)_2]^{2-}$ exhibit the unusual envelope conformation, which appears to result from nonbonded contacts between the basal sulfur atoms. In contrast, the half-chair conformer is observed for the pseudotetrahedral species Cp_2MoS_4[40,41] and $[Zn(S_4)_2]^{2-}$, which may be less sterically crowded.

There has been some interest in elucidating the factors responsible for the alternation in S–S bond distances in tetrasulfido chelates. *Coucouvanis* et al. noted that the central S–S bond lengths in $(Et_4N)_2[MoS_9]$ are ca. 0.13 Å shorter than the remaining S–S bonds.[32] In complexes other than $[MoS_9]^{2-}$, the S2–S3 distances are typically 0.06 Å shorter than the flanking S1–S2 and S3–S4 distances.[42] In contrast, no such alternation is observed in the solid state structure of Na_2S_4, and the effect is less pronounced in Cp_2WS_4.[40b] The results of a qualitative molecular orbital calculation on $Pt(S_4)(PH_3)_2$ are consistent with the presence of a weak butadiene-like π-network in the S_4 ligand.[42] π-Donation from S_4^{2-} to the metal effectively depopulates the HOMO, thereby lessening the antibonding interaction between S2 and S3.

Reaction of $[Mo_2(\mu\text{-}S_2)_2(S_2)_4]^{2-}$ with PhS^- affords the unsymmetrical $[Mo_2(S)_2(\mu\text{-}S)_2(S_2)(S_4)]^{2-}$ ion, which can be isolated as the $AsPh_4^+$ salt (Fig. 6). In this compound the coordination sphere of the Mo_2S_4 core is completed by di- and tetrasulfido chelates. Although a crystallographic disorder problem limits the accuracy of the structural data, it is clear that the S_4 chelate adopts a puckered conformation with little bond alternation.[35]

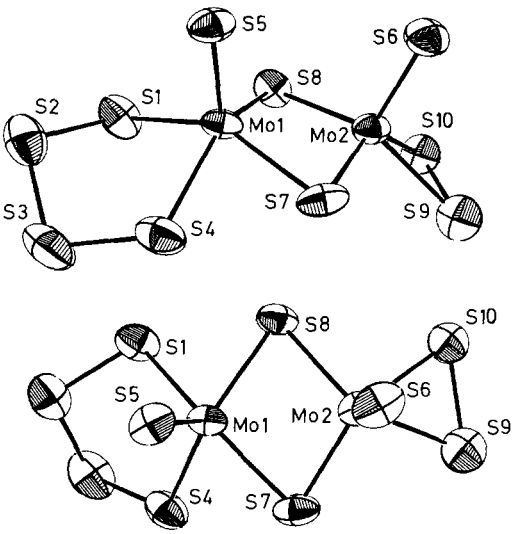


Fig. 6. ORTEP plots (two views) of $[Mo_2S_{10}]^{2-}$ in $(PPh_4)_2[Mo_2S_{10}]$ [32b].

The structure of the PPh_4^+ salt of $[Mo_2S_{10}]^{2-}$, obtained from dibenzyl trisulfide and $(PPh_4)_2[MoS_4]$, is also structurally disordered, but in a different way: here, one-fourth of the disulfido ligands are replaced by an S_4 ligand owing to cocrystallization of $[Mo_2S_{12}]^{2-}$. The Mo–S distances in $[Mo_2S_{10}]^{2-}$ appear to be similar for both ends of the molecule, suggesting that, at least in this case, the electronic effects of the tetrasulfido and disulfido ligands are comparable.[32b,35]

Müller's group has isolated a number of unusual compounds from various combinations of hydroxylamine, $[MoS_4]^{2-}$, and sulfur.[43] One such species is $[Mo_2(NO)_2(S_2)_3S_5(OH)]^{3-}$, which features an S_5 unit strapped across the Mo_2OS_2 core, forming the basket-like structure shown in Figure 7.[44]

Tetrathiomolybdate is not only reactive towards most compounds which contain S–S bonds, but also toward a host of related nonmetal rings and cages.[45] A reaction of

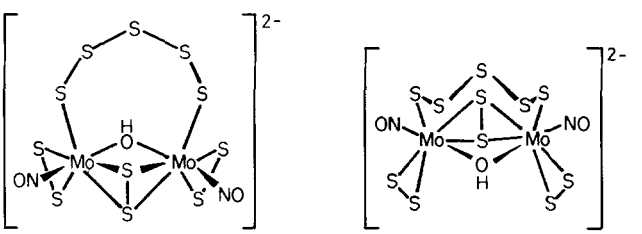


Fig. 7. Two views of $[Mo_2(\mu\text{-}S_2)(\mu\text{-}OH)(\mu\text{-}S_5)(NO)_2(S_2)_2]^{3-}$ [44].

this type, which has afforded a structurally spectacular polysulfur compound, involves As_4S_4[46] and $(PPh_4)_2[MoS_4]$. The product of this reaction is the "crowned" complex shown in Figure 8. The oxo ligands arise from hydrolysis during work-up.

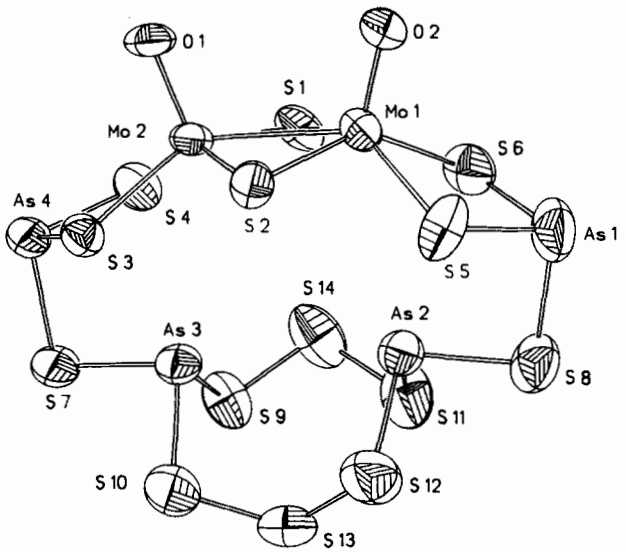


Fig. 8. Structure of the $[Mo_2O_2S_2(As_2S_{12})]^{2-}$ ion [47].

The compound, which has been characterized by X-ray diffraction, features a $Mo_2O_2S_2$ core strapped by the novel $[As_4S_{12}]^{4-}$ chelating unit. This dimolybdenum cage compound reacts readily with $[MoS_2O_2]^{2-}$ to give $[Mo_4O_4As_4S_{14}]^{3-}$, which is thought to possess a 16-membered ring.[47]

Reaction of Cp_2MH_2 or $Cp_2M(SH)_2$ (M = Mo, W) with elemental sulfur affords the tetrasulfido complexes Cp_2MS_4.[41] The rationale for this stoichiometry (vis-a-vis the Cp_2MS_5 stoichiometry observed for Ti, Zr, Hf, and V) invokes the stereochemically important, nonbonding pair of valence electrons in an orbital which leads to compression of the S-M-S angle. The same argument explains the differing metal : sulfur ratio in the sulfidodecamethylmetallocenes of titanium and vanadium.[27]

2.3. The Manganese Triad

Relatively little work has been carried out in this area. $[Mn(SPh)_4]^{2-}$ reacts with excess dibenzyl trisulfide to afford crystals of $(PPh_4)_2[MnS_{11}]$, which has been structurally characterized (Fig. 9). The X-ray structural analysis reveals a tetrahedrally coordinated Mn center bound to S_5 and S_6 ligands, the positions of which are interposed in the lattice.[48]

Herberhold et al. have described the isolation of three sulfido complexes, $CpRe(CO)_2(S_2)$, $Cp_2Re_2(CO)_4(\mu\text{-}S)$, and $Cp_2Re_2(CO)_2(\mu\text{-}S_2)(\mu\text{-}S_3)$, from the reaction of $CpRe(CO)_3$ with elemental sulfur or carbonyl sulfide. The latter complex consists of two CpRe(CO) centers bridged by both a disulfide and the relatively rare trisulfido ligand[49] (Fig. 10). This chiral dimer is formally electron-deficient but the Re-S distances are quite short,[50] indicating substantial S to Re π-donation.

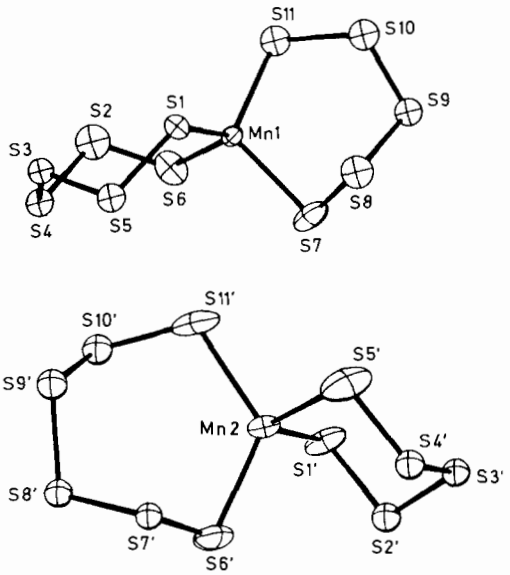


Fig. 9. Two views of the structure of the $[MnS_{11}]^{2-}$ ion [48].

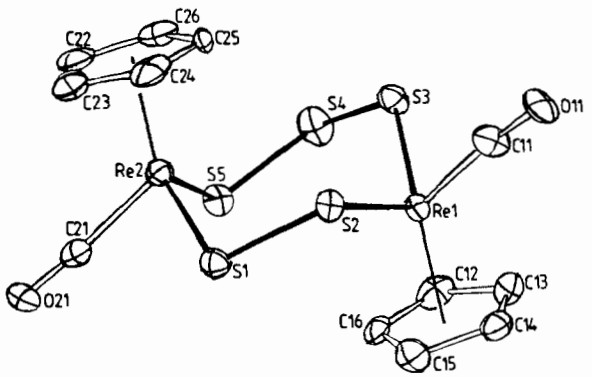


Fig. 10. ORTEP plot of $Cp_2Re_2(CO)_2(\mu\text{-}S_2)(\mu\text{-}S_3)$ [48].

2.4. The Iron Triad

The use of dibenzyl trisulfide as a reagent for the preparation of sulfur-rich complexes is illustrated by *Coucouvanis*' preparation of the $[Fe_2S_{12}]^{2-}$ species[51a] (Fig. 11).

In this and related applications the organic trisulfide functions as a conveniently soluble source of inorganic sulfur, which oxidatively replaces labile mercaptido li-

$$[Fe(SPh)_4]^{2-} \xrightarrow{RzSz} [Fe_2(\mu\text{-}S)_2(S_5)_2]^{2-} \quad (3)$$

gands [Eq. (3)]. Each iron in $[Fe_2S_{12}]^{2-}$ is tetrahedrally coordinated to four sulfur ligands[51b] similar to that found in the naturally occurring ferredoxin dimers and their synthetic analogues.[52] A related compound is $[(S_5)Fe(MoS_4)]^{2-}$[53] (and the W analogue), which, in turn, is a close relative of $[Cl_2FeS_2MoS_2]^{2-}$,[54] emphasizing the pseudohalide character of the polysulfido ligand. An X-ray structural analysis of $(PPh_4)_2[FeMoS_9]$ revealed the presence of ca. 30% occupancy of the decasulfide, $[FeMoS_{10}]^{2-}$, which contains an S_6 chelate.[53b]

The absence of a mononuclear iron polysulfide is the major gap in the coordination chemistry of polysulfides.

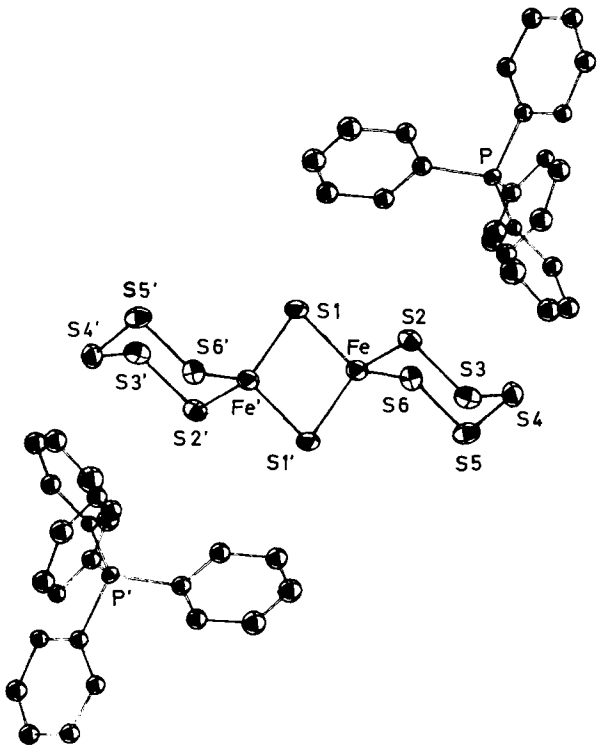
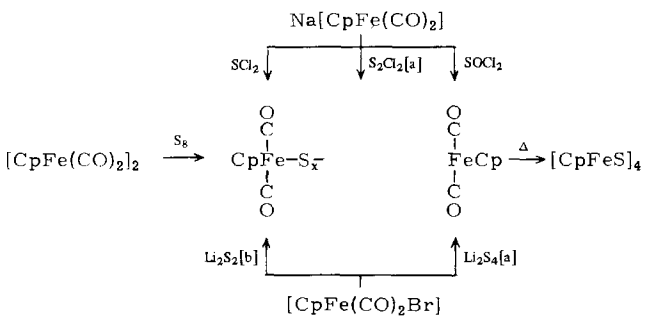


Fig. 11. ORTEP plot of $(PPh_4)_2[Fe_2S_{12}]$ [51a].

On the basis of the results discussed in this review a pseudo-tetrahedral species such as $[Fe(S_6)_2]^{2-}$ might be expected to be stable.[55] The most abundant binary iron sulfide, iron pyrite, features octahedral iron bound to six disulfide ligands. Another important sulfur-rich compound of iron is marcasite, again featuring octahedral iron bound to six disulfide ligands.[56] These minerals do not dissolve in ammoniacal polysulfide solutions.

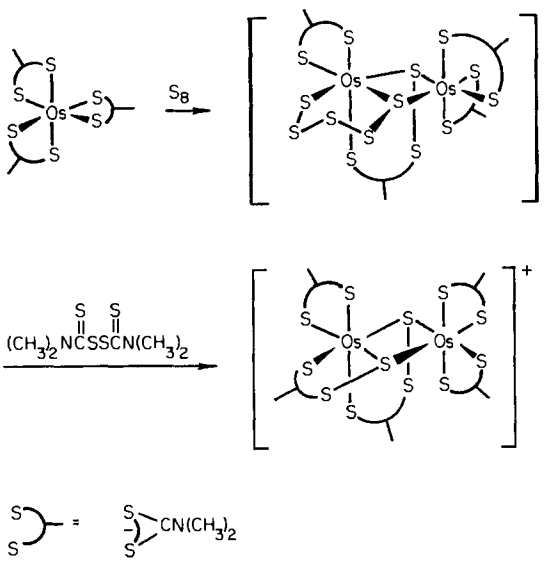
In a simple and instructive study of organometallic polysulfides, *McAllister* et al. prepared members of the series $[CpFe(CO)_2]_2S_x$, where x = 1–4 (Scheme 2). It is necessary to conduct these reactions at low temperatures in order to minimize redox reactions. The structures of the trisulfido and tetrasulfido complexes were determined by single-crystal X-ray methods.[57] The trisulfido complex undergoes decarbonylation in refluxing toluene, affording the well known[58] cubane $Cp_4Fe_4S_4$.

The two known examples of polysulfidoosmium complexes have both set precedents. The compound



Scheme 2. Synthesis of $[CpFe(CO)_2]_2S_x$. [a] x = 3, 4. [b] x = 2, 3. Not specified: x = 3.

$Os_2(Me_2dtc)_3(Me_2dtcS)(S_5)$, ($Me_2dtc$ = *N*,*N*-dimethyldithiocarbamate) was obtained in high yield on reaction of elemental sulfur with $Os(Me_2dtc)_3$.[59] In the dinuclear compound one finds two octahedral Os^{III} centers bridged by one end each of the S_5^{2-} ligand and a perthiocarbamate. Judging by the structural parameters, the bridging interaction does not seem to have any major effect on the S–S bonds. The pentasulfido complex is an intermediate in the formation of the bis(trithiocarbamate) complex, $[Os_2(Me_2dtc)_3(Me_2dtcS)_2]^+$, as shown in Scheme 3.



Scheme 3. Synthesis of $Os_2(\mu\text{-}S_5)(\mu\text{-}Me_2dtcS)(Me_2dtc)_3$ and its reaction with tetramethylthiuram disulfide yielding $[Os_2(Me_2dtcS)_2(Me_2dtc)_3]^+$.

The clean formation of a trithiocarbamato complex on reaction of the pentasulfido species with thiuram disulfide (but not dithiocarbamate anion) implicates polysulfido intermediates in the formation of the sulfur-rich trithiocarbamate ligands. Related complexes may function as sulfur transfer agents in the metal-catalyzed vulcanization of polyolefins.[60]

The compounds $M(PMe_3)_3(PMe_2CH_2)H$ (M = Ru, Os) are interesting substrates for oxidative addition chemistry because they are sources of the exceptionally nucleophilic 16-electron $M(PMe_3)_4$ moieties[61] (which are isoelectronic with $[Ir(R_2PCH_2CH_2PR_2)_2]^+$). Reaction of the ruthenium and osmium phosphane complexes with elemental sulfur initially affords products of the formula $M(PMe_3)_3S_6$, which upon recrystallization give $M(PMe_3)_3S_7$. These are the only known examples of heptasulfido complexes and are particularly novel because the S_7 ligand is coordinated in a tridentate manner (Fig. 12).

The ^{31}P-NMR spectrum of the compound is indicative of an AB_2 system. However, the dynamics have not yet been studied in detail. The two S–S bonds to the central sulfur are unusually long (2.20 and 2.15 Å).[62] In contrast, even though S_8^{2+} has a similar conformation all of the S–S bond lengths are within the normal range of 2.05 Å. This osmium compound may represent a model for the early stages of the reaction of S_8 with metals. To a certain extent this S_7 ligand resembles the tridentate S_4N_3 ligand found in $[PtCl(S_4N_3)]$.[63]

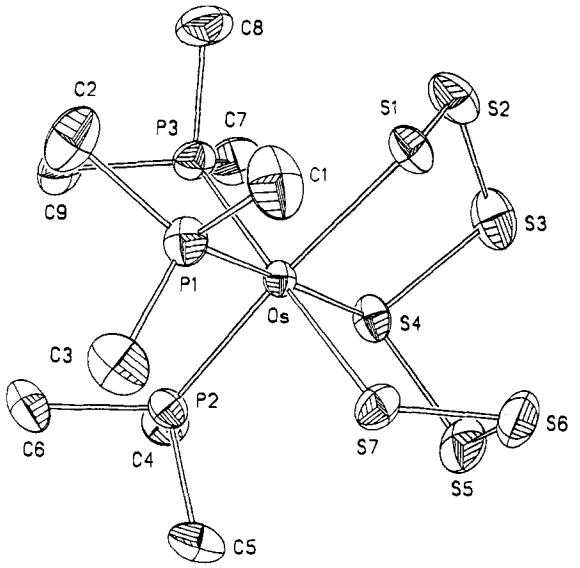
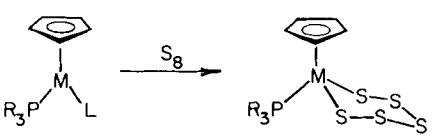


Fig. 12. ORTEP plot of $OsS_3(PMe_3)_3$ [62].

2.5. The Cobalt Triad

Several classes of polysulfido chelates have been described for the cobalt triad: anionic binary sulfides, cyclopentadienyl derivatives, and those containing phosphane chelates. Binary sulfido-cobalt complexes have not yet been reported, and, though the species $[M(S_5)_3]^{3-}$ (M = Ir, Rh)[64-66] and $[RhS_{10}]^{-}$[65] have been described, they remain poorly characterized. There is little doubt that some very novel chemistry is involved here, and increased activity in this area can be anticipated following recent reports that rhodium and iridium sulfides are good hydrodesulfurization catalysts.[67]

Reaction of $CpM(PR_3)(L)$ (M = Co,[68] R = Me, L = CS_2; M = Rh,[69] R = Ph, L = CO) with elemental sulfur furnishes the oxidative addition product $CpM(PR_3)(S_5)$ in good yields [Eq. (4)].



(4)

Both the trimethylphosphanecobalt and triphenylphosphanerhodium compounds have been structurally characterized. These compounds are relatives of Cp_2TiS_5, in which a Cp in the latter has been replaced by a phosphane ligand.

The first structurally characterized molecular S_2 complex was prepared from $[Ir(Ph_2PCH_2CH_2PPh_2)_2]^+$ and elemental sulfur;[70] related compounds containing selenium have also been described.[71] Recently, *Ginsberg* and coworkers have examined the addition of Se_8 to the very basic $[Ir(dmpe)_2]^+$ (dmpe is 1,2-bis(dimethylphosphino)ethane); $[Ir(Se_4)(dmpe)_2]^+$, which features an Se_4 chelate, is formed.[72] (A related S_4 complex is p_3CoS_4, in which p_3 is the tripod ligand 1,1,1-tris(diphenylphosphinomethyl)-ethane.[73]) Upon treatment with phosphane desulfurizing agents, $[Ir(Se_4)(dmpe)_2]^+$ is converted into the Se_2 complex.[72] These and other observations suggest that polychalcogen chelates may in fact be intermediates in the formation of other mono- and dichalcogenido complexes. In support of this theory, one observes that the kinetically stabilized products obtained from the reactions of low valent metal complexes with S_8 and Se_8 generally contain more E–E bonds (E = S, Se) than are found in thermally equilibrated systems. Some particularly notable examples of such kinetically stabilized species (in addition to $[Ir(Se_4)(dmpe)_2]^+$) are $[MoS_9]^{2-}$,[32] $[(C_5Me_5)_2Mo_2(S_2)_5]$,[74] $[(C_5Me_5)_2Mo_2(S)_2(S_2)]$,[75] and $[Mo_2(S_2)_6]^{2-}$.[33]

2.6. The Nickel Triad

Several examples of polysulfido chelates can be found in this triad, some of which date back to 1903. The structural characterization of *Hofmann*'s and *Höchtlen*'s $(NH_4)_2PtS_{15}\cdot 2H_2O$ in 1967[76] was a major turning point in the development of this area of chemistry.

There are four principal structural types for the polysulfides of this triad. Preeminent is $[Pt(S_5)_3]^{2-}$, which consists of a Pt(IV) moiety octahedrally coordinated to three bidentate S_5^{2-} ligands (Fig. 13).

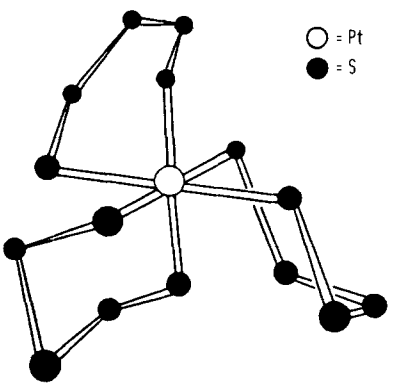


Fig. 13. Structure of the $[PtS_{15}]$ ion (see M. Schmidt, *Angew. Chem. 85* (1973) 474; *Angew. Chem. Int. Ed. Engl. 12* (1973) 445).

In the crystallographically characterized potassium[77] and ammonium[76] salts, the chelate rings adopt a chair conformation. ^{195}Pt-NMR studies on methanol solutions of $[Pt(S_5)_3]^{2-}$ indicate the presence of a 17.2 : 1 mixture of diastereoisomers which are thought to arise from the presence of both $(chair)_3$ and $(chair)_2(boat)$ conformers.[78] Unlike the situation for organic chelates, conformational diastereoisomers are expected to be common in polysulfido complexes because of the high barriers for rotation about S–S bonds. *Gillard* et al. have reported the partial optical resolution of $[Pt(S_5)_3]^{2-}$, thereby providing a very rare example of an optically active inorganic molecule.[79]

Desulfurization of $[Pt(S_5)_3]^{2-}$ with S^{2-}, SO_3^{2-}, PPh_3, and OH^- yields the $[PtS_{10}]^{2-}$ ion, which can be isolated as its water-soluble potassium and ammonium salts or its organic-soluble tetraalkylammonium salts.[80,81] It is probable that $[PtS_{10}]^{2-}$ consists of square planar Pt^{II} bound to two S_5^{2-} chelates. Should these S_5 chelates adopt the chair conformation, then the ^{195}Pt-NMR spectrum would reveal the presence of a 1 : 1 mixture of two diastereoisomers.

Further treatment of $[PtS_{10}]^{2-}$ with triphenylphosphane yields the well characterized square planar complex $Pt(S_4)(PPh_3)_2$,[80,82] which can also be prepared from elemental sulfur and $Pt(SH)_2(PPh_3)_2$[83] or $Pt(PPh_3)_3$.[42,84] There are a large number of closely related species in this class of compounds.[85]

In the early 1960's, *Schrauzer* and *Mayweg* pointed out the differing reactivities of stoichiometric and nonstoichiometric (sulfur-rich) nickel sulfides.[86] Very recently, the first binary polysulfidonickel complex, $(Et_4N)_2[Ni(S_4)_2]$, was reported by two groups[48,87] (Fig. 14).

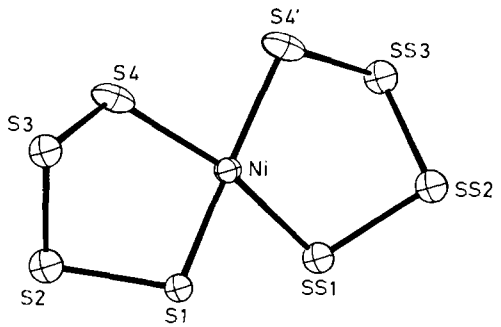


Fig. 14. ORTEP plot of the $[Ni(S_4)_2]^{2-}$ anion in $(Et_4N)_2[Ni(S_4)_2]$ [48]. The atoms marked SS belong to one of the two crystallographically disordered S_4^{2-} ligands which take up the same place and have atom S4' in common.

The complex can be prepared metathetically using polysulfide ions[87] or with the neutral sulfur transfer agent dibenzyl trisulfide.[48] The anion consists of square planar nickel; and the palladium complex[87] is presumably quite similar. The complex $[Ni(S_4)_2]^{2-}$ is quite reactive towards carbon disulfide and acetylenes, forming perthiocarbonate and alkenedithiolate complexes.[48]

2.7. The Copper Triad

The salts of CuS_4^- and AuS_3^- have been known since the beginning of the century[1], but only recently have they been examined in any detail. The structure of NH_4CuS_4,[88,89] shown in Figure 15, features a CuS_4 ring,

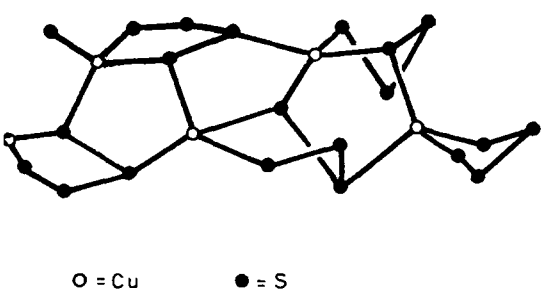


Fig. 15. Structure of the $[CuS_4]_n$ chain in $NH_4[CuS_4]$ [88].

wherein the polysulfido ligand forms bridges to other copper centers. Bridging polysulfide ligands are unusual for most elements but appear to be prevalent for the sulfido clusters of copper(I). Reaction of ethanolic polysulfide solutions with $Cu(CH_3CO_2)_2 \cdot 2H_2O$ yields crystals of $(Et_4N)_3[Cu_3(S_6)_3]$.[90] One end of each of the S_6 chelates is bridging, giving a Cu_3S_3 ring (Fig. 16).

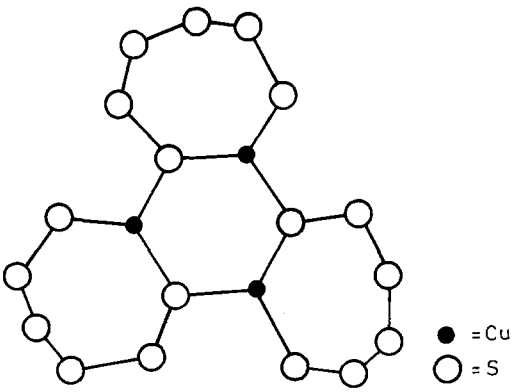


Fig. 16. ORTEP plot of the $[Cu_3S_{18}]^{3-}$ anion [90].

Closely related to $[Cu_3(S_6)_3]^{3-}$ is $[Cu_3(S_4)_3]^{3-}$.[91] The bridging nature of the S_4 and S_6 ligands in these trimetallic anions is similar to the S_5 chelate found previously in $Os_2(dtc)_3(dtcS)S_5$.[59] Three coordinate copper(I) is also found in $[Cu_2S_{20}]^{4-}$, which features two CuS_6 rings linked by an S_8 chain.[87b,91] The analogous silver complex, $[Ag_2S_{20}]^{4-}$, has also recently been prepared.[92]

A new class of inorganic sulfido clusters contain a tetrahedral Cu_4 core with S_4 and S_5 bridging chelates. There are reports of the isolation and crystallographic characterization of each member of the series $[Cu_4(S_4)_{3-x}(S_5)_x]^{2-}$ $(x=0-3)$[93-96] (Fig. 17).

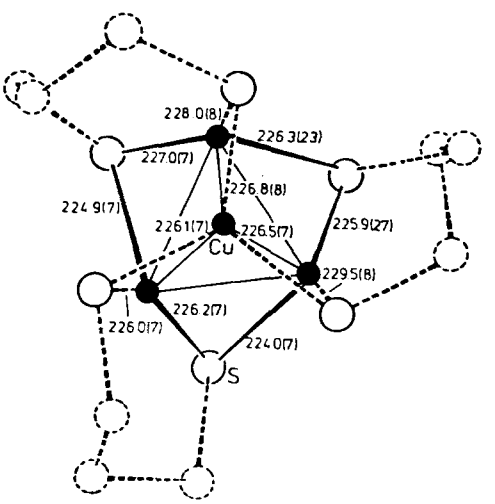


Fig. 17. ORTEP plot of the $[Cu_4S_{14}]^{2-}$ anion [93-96]. Distances [pm].

The $[Cu_4S_{15}]^{2-}$ and $[Cu_4S_{14}]^{2-}$ ions cocrystallize, a rare example of the coexistence of both S_4 and S_5 chelates.[95] Structurally, the most spectacular polysulfide cluster is $[Cu_6S_{17}]^{2-}$ (Fig. 18).

The molecule comprises an edge-shared bitetrahedral array of copper atoms with three tetrasulfido and one pentasulfido subunits. The S_4 ligands are like those seen in the aforementioned Cu_4 clusters, whereas the S_5 ligand is bound to four metal ions. The molecule contains a twofold axis through the central (non-coordinated) sulfur atom of the S_5 chelate.[97,98]

The record size for a metal polysulfide ring is currently held by the $[AuS_9]^-$ ion isolated by *Strähle* and *Mar-*

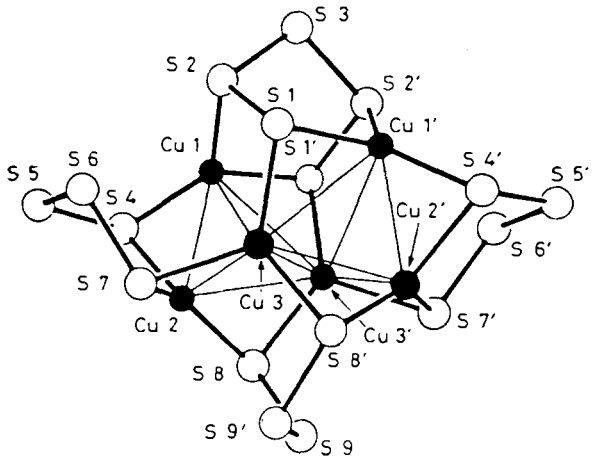


Fig. 18. ORTEP plot of the $[Cu_6S_{17}]^{2-}$ anion [97, 98].

bach.[99] In this molecule the catenating abilities of sulfur and the linear coordination geometry preferred by gold(I) stabilize the S_9^{2-} strap (Fig. 19). The S–Au–S angle is 176° and the S–S bond lengths are in the normal range of 2.03 Å.

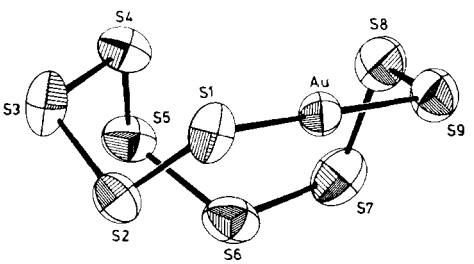


Fig. 19. ORTEP plot of the $[AuS_9]^-$ anion [99].

The bimetallic species $[Au_2S_8]^{2-}$ contains a ten-membered ring; each gold atom is again accomodated with a linear coordination environment. Here the two S_4-bridged gold centers are separated by 3.120 Å[95] (Fig. 20).

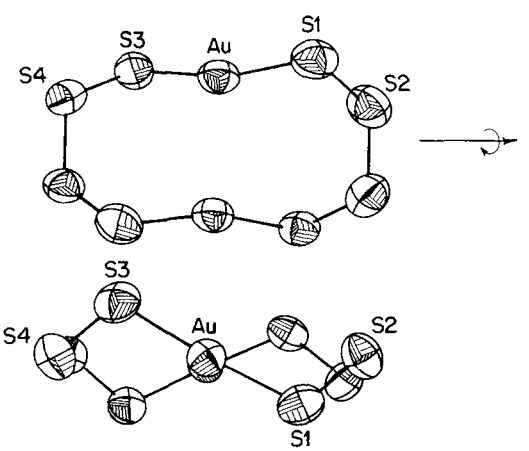


Fig. 20. ORTEP plot of the $[Au_2S_8]^{2-}$ anion [95].

The analogous $[AgS_9]^-$ ion has been prepared recently as the Ph_4P^+ salt; however, the anion is severely disordered in the crystal lattice. *Müller* et al. have also isolated the $[Ag_2(S_6)_2]^{2-}$ complex, under similar reaction conditions. The S_6 ligands coordinate in a fashion similar to that observed in $[Cu_3(S_6)_3]^{3-}$, such that a planar Ag_2S_2 ring is formed (Fig. 21).[100]

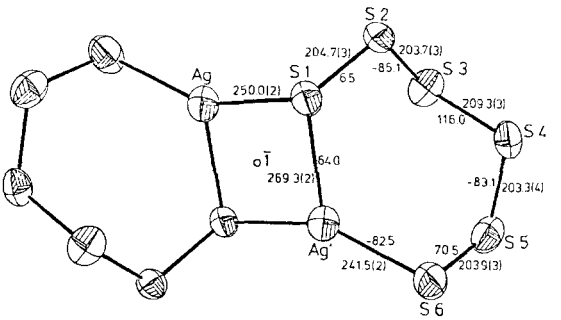


Fig. 21. ORTEP plot of the $[Ag_2(S_6)_2]^{2-}$ anion [100]. Distances [pm], angles [°].

2.8. The Zinc Triad

The stepwise reaction of dibenzyl trisulfide with $[Zn(SPh)_4]^{2-}$ has recently been reported by *Coucouvanis* et al.[48] Initially the mixed ligand complexes $[Zn(SPh)_2(S_4)]^{2-}$ and $[Zn(SPh)_2(S_5)]^{2-}$ are formed, additional sulfur gives $[Zn(S_5)_2]^{2-}$ and eventually $[Zn(S_6)_2]^{2-}$ (Scheme 4).

$$[Zn(SR)_4]^{2-} \xrightarrow{S^\circ} [Zn(SR)_2(S_4)]^{2-} \xrightarrow{S^\circ} [Zn(SR)_2(S_5)]^{2-}$$

$$\xrightarrow{S^\circ} [Zn(S_5)_2]^{2-} \xrightarrow{S^\circ} [Zn(S_6)_2]^{2-}$$

$$[Zn(S_5)_2]^{2-} \xrightarrow{Ph_3P} [Zn(S_4)_2]^{2-}$$

Scheme 4. Formation of polysulfide ligands by stepwise addition of sulfur to $[Zn(SPh)_4]^{2-}$ and its derivatives.

Under the same conditions employed for the synthesis of $(PPh_4)_2[Zn(SPh)_2(S_5)]$, $(Et_4N)_2[Zn(SPh)_4]$ is converted into $(NEt_4)_2[Zn(S_4)_2]^{2-}$ (Fig. 22).

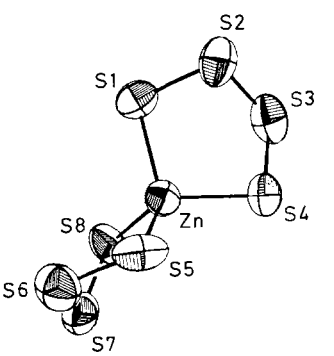


Fig. 22. ORTEP plot of the $[ZnS_8]^{2-}$ anion [48].

These results highlight the importance of counterion effects on the stoichiometry of compounds crystallized from solutions of such kinetically labile ions. Starting with $[Cd(SPh)_4]^{2-}$, *Coucouvanis* et al. obtained $(PPh_4)_2[Cd(SPh)_2(S_5)]$ using reactant ratios employed for

the synthesis of both $(PPh_4)_2[Zn(SPh)_2(S_x)]^{2-}$ complexes, with $x = 4$ or 5. This difference may result from the larger ionic radius of the Cd^{2+} ion which stabilizes the S_5 chelate ring. Contrary to this facile explanation, however, is the fact that the $[Cd(S_6)_2]^{2-}$ ion, unlike the situation for zinc and mercury(II), is not observed. The dianion $[Hg(S_6)_2]^{2-}$ can be prepared from mercuric acetate and aqueous polysulfide.[109] This molecule closely resembles the $[MnS_{11}]^{2-}$ ion.

2.9. f-Element Polysulfides

The compound $(C_5Me_5)_2ThS_5$ has recently been prepared from $(C_5Me_5)_2ThCl_2$ and Li_2S_5. In the solid state, the molecule features a twist conformation for the ThS_5 ring (Fig. 23). This structure is maintained in solution, as revealed by a DNMR study on $(C_5Me_4Et)_2ThS_5$, whose low temperature ^{1}H-NMR spectrum consists of four methyl singlets. The calculated $\Delta G^{\neq}$ for the ring inversion process (racemization) is 58 kJ/mol (Scheme 5).[102]

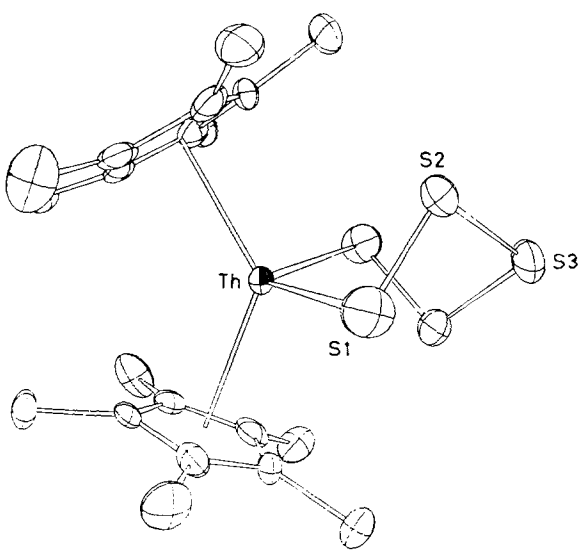
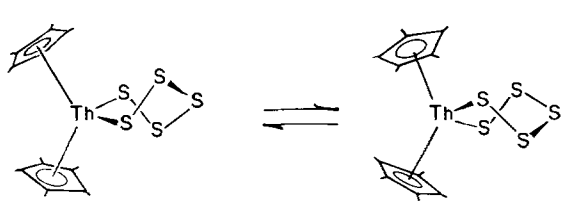


Fig. 23. ORTEP plot of $(C_5Me_5)_2ThS_5$ [102].



Scheme 5. Racemization of $(C_5Me_5)_2ThS_5$ via ring inversion.

Two aspects of the $(C_5Me_5)_2ThS_5$ structure warrant further discussion. First, why does this thorium complex exist as a pentasulfide while the corresponding transition metal compounds, e.g. $(C_5Me_5)_2MS_3$ (M = Ti, Zr), are trisulfides? This difference is probably due to the more open coordination environment about the actinoid. The Th–S distance of 2.77 Å is 0.33 Å longer than the corresponding distance in Cp_2TiS_5, while the C_5Me_5–Th–C_5Me_5 angle is 4° smaller than that for Cp–Ti–Cp, and the S–Th–S angle of 113.5° is 18° wider than the S–Ti–S angle. As already mentioned, the structure of Cp_2TiS_5 features short C···β-S contacts (cf. Section 2.1). These contacts would become intolerably short in the hypothetical $(C_5Me_5)_2TiS_5$, but apparently not so in its thorium analogue.

The second and more intriguing aspect of $(C_5Me_5)_2ThS_5$ is the twist conformation of the ThS_5 ring. This ring geometry had not been observed previously in any of the transition metal polysulfides and is presumed to be a consequence of bonding between Th and the β-sulfur atoms (3.04 Å). The twist conformation may be stabilized by a cog wheel effect induced by the nesting of the methyl groups.

3. Reactions of Polysulfide Complexes

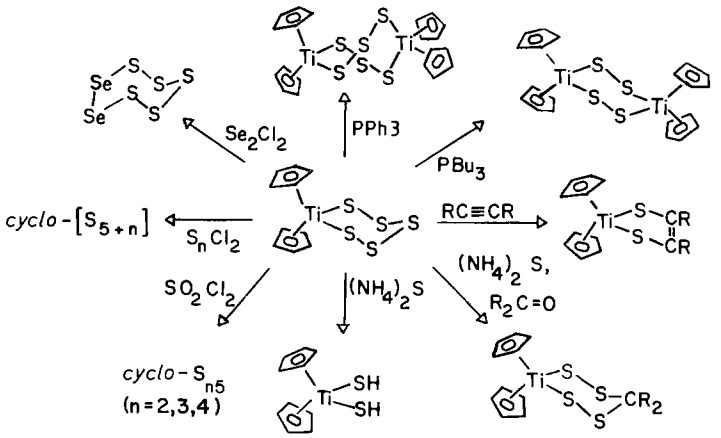
Polysulfides are reactive ligands. Mechanistic studies have largely involved kinetically stable complexes, particularly those derived from titanium, molybdenum, and platinum.[80,81,85a] On the other hand, the synthetic applications of this class of compounds have thus far been restricted to titanium.

3.1. The Chemistry of the Bis(cyclopentadienyl)titanium Pentasulfides

The reaction chemistry of Cp_2TiS_5 is extensive (Scheme 6). Because of the oxophilicity of titanium, the sulfur ligand in Cp_2TiS_5 is easily displaced by oxide or, more importantly, halide. This was the basis for the S_5 transfer reaction of *Schmidt* et al., which was first demonstrated in the high yield syntheses of *cyclo*-S_6 and *cyclo*-S_7.[103] The reaction of Cp_2TiS_5 with chlorosulfanes is ideally suited for the directed synthesis of polysulfide compounds since it gives relatively few products and little S_8. Subsequent to *Schmidt*'s original report in 1968, Cp_2TiS_5 has emerged as a standard reagent in the synthesis of new polysulfur rings.[104–109]. It is interesting to note that unlike the situation with organic synthesis, organotransition metal reagents are rarely employed in the synthesis of main group compounds. Sulfur homocycles can also be obtained from the reaction of S_2Cl_2 with KI or by extraction of supercooled sulfur melts followed by careful fractional crystallization. In contrast to the titanium-mediated chemistry, however, these methods afford primarily even-numbered sulfur rings, especially S_6, S_{12}, and S_{18}, together with large amounts of S_8.[16]

Mechanistic insights into the course of chelate transfer reactions of Cp_2TiS_5 are being gained from investigations by *Steudel* et al.[5] It is found that the reaction of SO_2Cl_2 gives *cyclo*-S_{10} in good yields, some *cyclo*-S_{15}, and, depending on the rate of the addition, varying amounts of *cyclo*-S_{20}. The addition of SO_2Cl_2 to a solution containing both Cp_2TiS_5 and *cyclo*-S_7 gave no *cyclo*-S_{12}, suggesting that these reactions do not involve the coupling of small ring intermediates such as *cyclo*-S_5. Further insight into these reactions is provided from the synthesis of heterocycles from Cp_2TiS_5. Thus, oxaloyl chloride reacts with the pentasulfide to give a 14-membered C_4S_{10} ring compound.[105] Reaction of Cp_2TiS_5 with Se_2Cl_2 initially gives *cyclo*-1,2-

Se_2S_5, which was identified by Raman spectroscopy.[107] This selenasulfide appears to undergo a highly selective ring expansion reaction, giving *cyclo*-1,2,3-Se_3S_5 as the principal Se-rich product, possibly via the intermediacy of a spirobicyclic Se^{IV} species.[108] Such experiments represent a significant step towards elucidating the mechanisms of the basic reactions of inorganic sulfur.



Scheme 6. Selected reactions of Cp_2TiS_5 showing its synthetic usefulness in preparing novel titanium complexes and new *cyclo*-sulfur compounds.

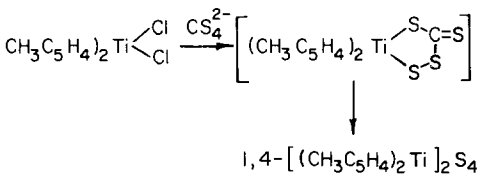
It should be noted that Cp_2TiSe_5 has also emerged as a useful chalcogen transfer reagent. This is an important development for selenium chemistry since Cp_2TiSe_5 and particularly its derivatives (i.e., $(MeCp)_2TiSe_5$) are soluble in a range of organic solvents giving thermally stable purple solutions. In contrast red selenium is only modestly soluble in a limited number of solvents. The syntheses of the following Se compounds have been accomplished using Cp_2TiSe_5: 1,3-$(IB)_2Se_3$, $(Bu_2B)_2Se_2$, $[Ir(Se_2)(Ph_2PC_2H_4PPh_2)_2]^+$, $Cp_2TiSe_2C_2R$ ($R_2=(CO_2Me)_2$; H, CO_2Me; $(CF_3)_2$), V(Se)(porphyrin), and *cyclo*-Se_7.[9, 16, 109]

The mechanism of the classic reaction of elemental sulfur with nucleophiles such as phosphanes was studied in detail several years ago by *Bartlett* et al.[110] The reaction rate obeys bimolecular kinetics consistent with nucleophilic opening of the S_8 ring and concomitant formation of a thiophosphonium intermediate. The latter decomposes to the phosphane sulfide and an undetermined, presumably labile, homocyclic sulfide. Insight into this classical reaction is provided by the products formed in the reaction of phosphanes with Cp_2TiS_5. These reactions are facile and it is unlikely that they involve direct coordination of the phosphane to the titanium atom. The two products formed in the desulfurization of Cp_2TiS_5 are not interconvertible under the experimental conditions used, and the type of products formed depends noticeably on the nucleophilicity of the phosphane employed. This chemistry highlights one of the very interesting aspects of these titanium polysulfides: the S–S bonds are reactive in the normal way but the M–S bonds are resistant to attack by phosphanes. The products of such desulfurizations are dimers of the type 1,4-$[(MeC_5H_4)_2TiS_2]_2$[111] and 1,5-$[(MeC_5H_4)_2TiS_3]_2$[19] [Eq. (5)].

These compounds could arise via either ionic (open chain) or neutral (small ring) intermediates. Ionic species would be expected to react readily with activated acetylenes; indeed, the addition of phosphanes to solutions containing both Cp_2TiS_5 and dimethylacetylenedicarboxylate (DMAD) affords the dithiolene even at 0 °C.[111] While this trapping experiment is consistent with the presence of ionic intermediates, the synthesis of the Ti_2S_4 ring in high yield via the perthiocarbonate route implies that it is neutral, strained ring compounds which actually dimerize[111] [Eq. (6)].

$$(MeC_5H_4)_2TiS_5 \xrightarrow{+3.3\ \text{equiv. } PR_3} \begin{matrix} 1,4\text{-}[(MeCp)_2Ti]_2S_4 & \mathbf{1} \\ + & \\ 1,5\text{-}[(MeCp)_2Ti]_2S_6 & \mathbf{2} \end{matrix} \quad (5)$$

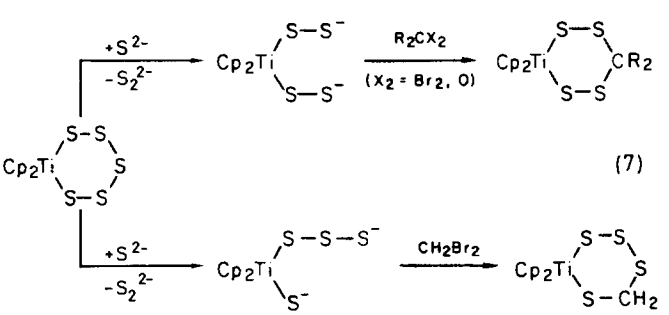
PR_3	Yield of **1** [%]	Yield of **2** [%]
$P(C_6H_5)_3$	trace	38
$P(C_6H_5)_2CH_3$	22	23
$P(C_6H_{11})_3$	35	trace
$P(C_4H_9)_3$	43	trace



(6)

Related dimerization reactions have been observed in the desulfurization of benzo-1,2,3-trithiacyclopentane, which affords the 1,2,5,6-tetrathiadibenzocyclooctane[112], and the $SbCl_5$-induced dimerization of S_6O, which yields 1,7-$S_{12}O_2$.[113]

Sulfur anions, like phosphanes, are very good thiophiles. Although Cp_2TiS_5 can be prepared from ammonium polysulfide, it is also rapidly degraded by the sulfide ion, giving $Cp_2Ti(SH)_2$ (see Scheme 5).[114] Ionic intermediates arising from the cleavage of the TiS_5 ring with sulfides can be trapped with aliphatic ketones to give perthiolato complexes.[115] Two regioisomers of the methylene derivative can be prepared from methylene bromide, Cp_2TiS_5, and ammonium sulfide [(Eq. (7)].



(7)

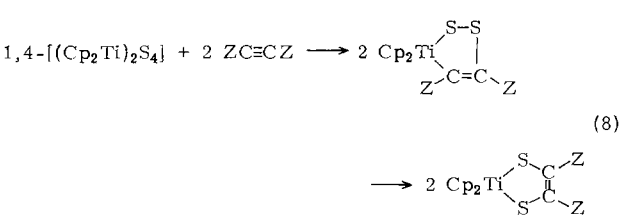
The existence of the symmetrical isomer of $Cp_2TiS_4CH_2$ has been proven by an X-ray structure analysis, while the structure of the other isomer was established by NMR studies, which revealed the absence of a plane of symmetry in the methylcyclopentadienyl derivative. In view of the numerous applications of Cp_2TiS_5 for the preparation of novel sulfur rings, it would appear that these isomeric alkylidene bisperthiolates could evolve as synthetically and mechanistically useful reagents. In general, they appear to

be more stable than the pentasulfides and are less reactive towards sulfides and phosphanes.

The reaction of the titanium polysulfides and polyselenides with acetylenes has been studied in some detail.[9, 111] The following rules apply:

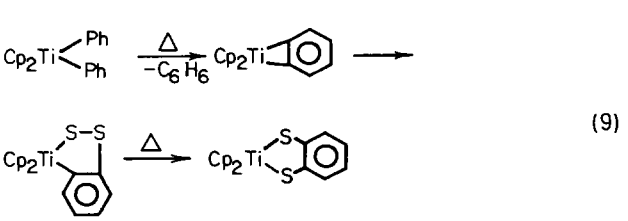
1. Only activated acetylenes participate in these reactions; these include dimethylacetylenedicarboxylate (DMAD), hexafluorobutyne, and methyl propiolate.
2. The selenides react faster than the sulfides and the reactivity of the rings increases with decreasing E/M ratio (e.g. the Ti_2S_4 compound is much more reactive than is Cp_2TiS_5).
3. The reactions proceed via an associative pathway, the rates of the reactions being linearly dependent on the concentrations of both the acetylene and the titanium precursor.

These are beautiful reactions to witness as they involve the conversion of the red or purple chalcogenidotitanium into the brilliant green dithiolenes and diselenenes. The first methylcarboxylate substituted dithiolenes were prepared in this way. It now appears that this type of dithiolene will emerge as the most readily accessible ligand of this type. The mechanism proposed for the reaction of Cp_2TiS_5 with acetylenes is a not an obvious one and was only revealed through kinetic studies on 1,4-$[(Cp_2Ti)_2S_4]$. Reaction of the latter with DMAD proceeds at room temperature to give a green compound isomeric with the "normal" dithiolene[111] [Eq. (8)]. The rate of this reaction is first order, both for the titanium dimer and for the acetylene, and there is no evidence for a predissociation of the $Cp_4Ti_2S_4$ species into Cp_2TiS_2 fragments.



(8)

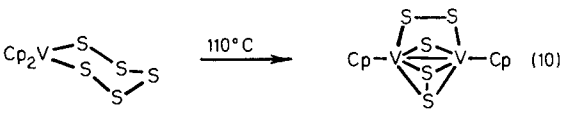
The structurally characterized vinyl disulfide isomer then rearranges in a first order reaction to give the normally observed isomer. Similar types of intermediates have been observed by *Halbert* et al.[116a] who reacted $[Mo_2O_2(S)_2(S_2)_2]^{2-}$ with DMAD, and by *Tebbe* who studied the insertion of sulfur into a titanium-benzyne species[116b] [Eq. (9)].



(9)

Many of the currently recognized metal-promoted dithiolene syntheses may proceed via similar insertion mechanisms. Furthermore, this mechanism may be applicable to the addition of sulfur to metal disulfides yielding tetrasulfides.

It has been known for several years that Cp_2VS_5 undergoes a facile thermal rearrangement[117] to give the dinuclear complex $Cp_2V_2S_5$. [By heating Cp_2VS_5 in toluene, 85% yield [Eq. (10)].]



(10)

The selenium compound behaves similarly. The structures of both products have been determined by X-ray crystallography. It is probable that these transformations involve the formation of organochalcogen intermediates. This suggestion is supported by studies on the thermolysis of Cp_2TiS_5.[118] Heating the titanium complex in boiling xylene for one day followed by gel permeation chromatography affords a black fraction which contains sulfidotitanium clusters and a red fraction containing an isomer of Cp_2TiS_5. While the red color of this isomer is (deceptively) similar to that for its precursor, its ^{1}H-NMR spectrum is decidedly more complex. The X-ray structural analysis of the compound reveals that a cyclopentadienyl fragment has migrated to the sulfur atoms (Figure 24).

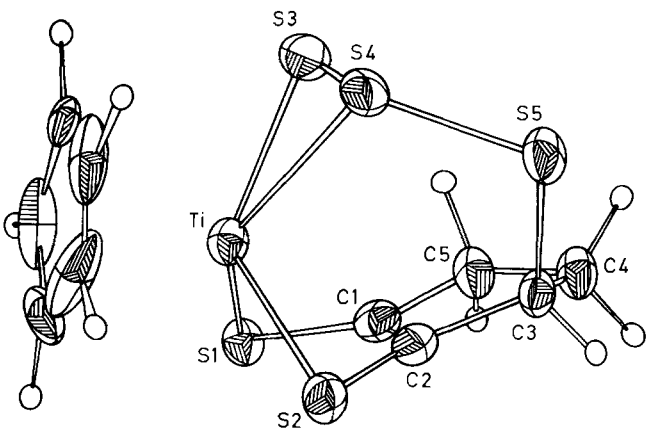


Fig. 24. ORTEP plot of β-$C_{10}H_{10}TiS_5$ [102].

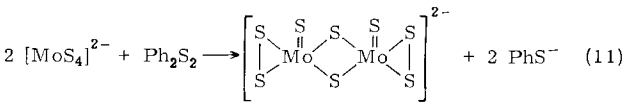
It is also interesting that this rearrangement involves both the formation of three new carbon-sulfur bonds as well as the migration of two hydrogen atoms. The tetradentate $C_5H_5S_5$ ligand binds to the titanium atom via an η^2-trisulfide and a dithiolene, whereby the latter is so distorted that it appears to be coordinated in an η^4 fashion. This rearrangement of Cp_2TiS_5 provides a further example of the migration of an organic ligand from the metal to sulfur.

3.2. Polysulfidomolybdenum Compounds

In molybdenum chemistry one observes several reactions involving interconversions between S, S_2, and S_4 ligands which proceed with a change in the formal oxidation state of the molybdenum. This novel type of redox reaction highlights the inappropriateness of the oxidation

state formalism for these compounds and suggests the near electronic equivalence of S_2 and S_4 ligands.

The reaction of $[MoS_4]^{2-}$ with organic disulfides affords the $[Mo_2S_8]^{2-}$ ion together with two equivalents of the reduced organosulfur compound[34] [Eq. (11)].



$$2\ [MoS_4]^{2-} + Ph_2S_2 \longrightarrow \left[\begin{array}{c}S\\ \|\\ S-Mo-S\\ |\ \ \ |\\ S-Mo-S\\ \|\\ S\end{array}\right]^{2-} + 2\ PhS^- \qquad (11)$$

Evaluation of the changes in the formal oxidation state in this and related systems can be confusing, and for "bookkeeping purposes" one can analyze this reaction by considering the valence isomer of $[MoS_4]^{2-}$, namely $[Mo(S)_2(S_2)]^{2-}$. In this way the two-electron reduction of $(PhS)_2$ is coupled with the two-electron oxidation of a pair of Mo^{IV} compounds.

In the oxidation of $[MoS_4]^{2-}$ with sulfur-rich compounds such as elemental sulfur or dibenzyl trisulfide one obtains the $[MoS_9]^{2-}$ ion.[32] Similarly, the reduction of $[MoS_9]^{2-}$ with thiolates generates the oxidized species $[MoS_4]^{2-}$.[36b] Here again, changes in the formal oxidation state of the metal ion occur concomitant with the making and breaking of sulfur-sulfur bonds. Little is known about the mechanisms of these reactions and the problem, at least as it is described in the literature, is a formidable one. For example, the addition of solutions of PPh_4Cl to acetonitrile solutions of $(Et_4N)_2[MoS_9]$ yields crystals of $(PPh_4)_2[Mo_2S_{10}]$. Similarly, it has been demonstrated that the reverse reaction occurs when solutions of Et_4NCl are added to $(PPh_4)_2[Mo_2S_{10}]$.[32b]

The $[MoS_9]^{2-}$ species has been the subject of a series of studies by the *Coucouvanis* group. $[MoS_9]^{2-}$ appears to function as a source of $[MoS(S_2)_2]^{2-}$ in its reactions with carbon disulfide, affording perthiocarbonate complexes.[119] Two isomers of $[MoS(CS_4)_2]^{2-}$ are obtained in this reaction. However, the lack of appropriate analytical techniques has precluded any mechanistic insight into the implied interconversion (Fig. 25).

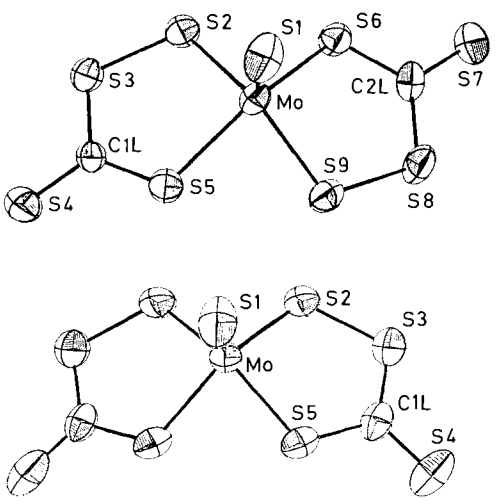
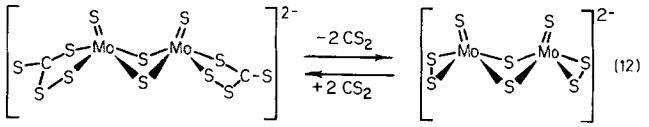


Fig. 25. Structure of the two isomers of $[MoS_9C_2]^{2-}$ formed on reaction of $[MoS_9]^{2-}$ with CS_2 [38].

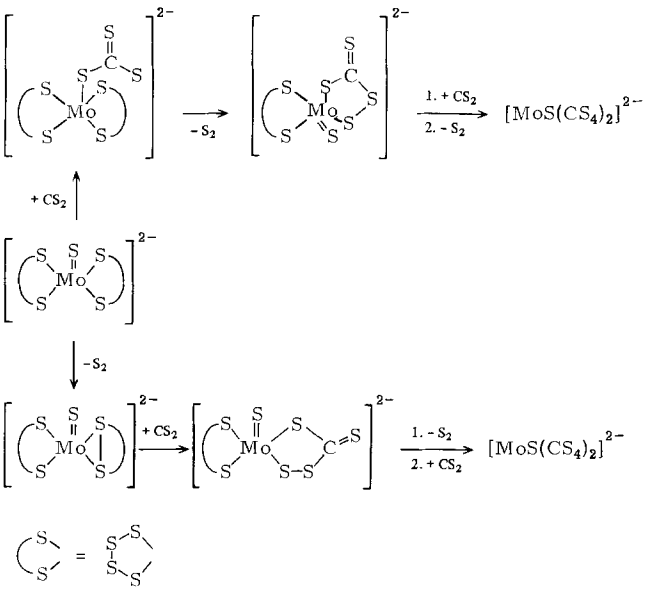
Also formed in these reactions is the dimer $[Mo_2S_4(CS_4)_2]^{2-}$, which reversibly evolves CS_2 in vacuo to give the bis(disulfido) compound $[Mo_2S_8]^{2-}$ [Eq. (12)].



$$\left[\begin{array}{c}S\\ \|\\ S-Mo-S\\ |\ \ \ |\\ S-Mo-S\\ \|\\ S\end{array}\right]^{2-} \underset{+2\,CS_2}{\overset{-2\,CS_2}{\rightleftharpoons}} \left[\begin{array}{c}S\\ \|\\ S-Mo-S\\ |\ \ \ |\\ S-Mo-S\\ \|\\ S\end{array}\right]^{2-} \qquad (12)$$

CS_2 can also be removed from solutions of the $[MoS(CS_4)_2]^{2-}$ ion, whereby $[MoS_4]^{2-}$ is formed;[38] it would be of special interest to attempt this removal of CS_2 in the solid state. As shown by *Coucouvanis* et al., this CS_2 addition reaction appears to be of some generality as it is observed with the polysulfido complexes of nickel, zinc, and manganese.[48] In the case of manganese, the product formed from the addition of CS_2 to only one polysulfido ligand, $[Mn(S_6)(CS_4)]^{2-}$, has also been characterized.

$[MoS_9]^{2-}$ reacts with DMAD to give the trigonal prismatic $[Mo(dithiolene)_3]^{2-}$.[120] It is noteworthy that $[MoOS_8]^{2-}$ does not give the tris(dithiolene) complex upon treatment with DMAD. Furthermore, this oxo complex also fails to react with carbon disulfide.[38] These observations suggest involvement of the nucleophilic terminal sulfido ligand in these addition reactions (Scheme 7).



Scheme 7. Two possible routes for the conversion of $[MoS_9]^{2-}$ into $[MoS(CS_4)_2]^{2-}$.

The oxidation of polysulfido chelates has not been examined in detail and only a few oxo derivatives of *cyclo*-S_x are known.[113] Certain disulfur complexes undergo oxidation to give S_2O or S_2O_2 complexes.[121] Recently, *Müller* has reported the structural characterization of an S_3O_2 complex $(PPh_4)_2[Mo_2(O)_2(\mu\text{-}S)(S_2)(S_3O_2)]$; crystals of this compound are obtained when solutions of simple thiomolybdates are exposed to oxygen[122] (Fig. 26).

Binary molybdenum-sulfur complexes participate in various equilibria: Treatment of $[MoS_4]^{2-}$ with $(NH_4)_2S$ is

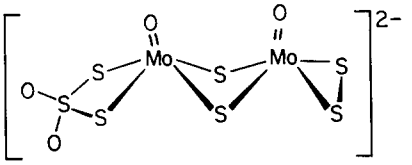


Fig. 26. Structure of $[Mo_2O_2(\mu\text{-}S)_2(S_2)(S_3O_2)]^{2-}$, the first dithiosulfate complex [122].

reported to give $[Mo_3S_{13}]^{2-}$ and small amounts of $[Mo_2(S_2)_6]^{2-}$; the addition of more sulfur to such mixtures favors the binuclear compound at the expense of the trimer. Addition of Et_4NCl to mixtures of $[MoS_4]^{2-}$ and $(NH_4)_2S_x$ yields the $[MoS_9]^{2-}$ ion in the form of a crystalline salt.[32b] PPh_4Cl reacts with solutions of $[Mo_2(S_2)_6]^{2-}$ in acetonitrile to give crystals of $(PPh_4)_2[Mo_2S_4(S_4)_2]$.[38] These few results demonstrate the complexity of this chemistry and reveal that the choice of counterions can have a decisive effect on the structure of the crystallized product. Despite the large number of structurally characterized binary molybdenum sulfides, there has never been a comprehensive study of the solution equilibria involved, primarily because of a lack of appropriate analytical techniques. ^{95}Mo-NMR spectroscopy could prove to be a useful probe for these systems.

4. Conclusions

The study of polysulfido chelates has developed rapidly in the past few years and stable derivatives have been prepared for most of the transition metals. These ligands are found in a number of ring sizes and bonding modes, but they are of special interest since they are so reactive. This area of research has already proven valuable to the transition metal chemist (how do thio- and disulfido ligands arise in the reactions of S_8) and the main group specialist (the directed syntheses of S_x rings ($x \neq 8$); Cp_2TiS_5 as a mechanistic model for S_8). Polysulfidometal compounds promise further development as synthetic reagents and as precursors to new materials[29] and catalysts.[123]

Opportunities abound for further extensions of polysulfido-transition metal chemistry. The recent preparation of $(C_5Me_5)_2ThS_5$[102] points to the f-elements as a novel source of compounds. Main group polysulfide chemistry has in large measure remained untouched.[124] No polytellurido and only very few polyselenido complexes are known. In view of the dramatic structural differences between $(NMe_4)_2Te_5$[125] and Cs_2Te_5,[126] the polytellurido chelates may prove very novel.[129] It has already been demonstrated that the ^{77}Se-NMR of metal polyselenides is structurally useful[112] and this approach could eventually resolve some of the mechanistic issues in this area of coordination chemistry. S-N[63, 127] and $(PR)_n$[128] chelates have been known for several years, but have seldom been subjected to reactivity studies.

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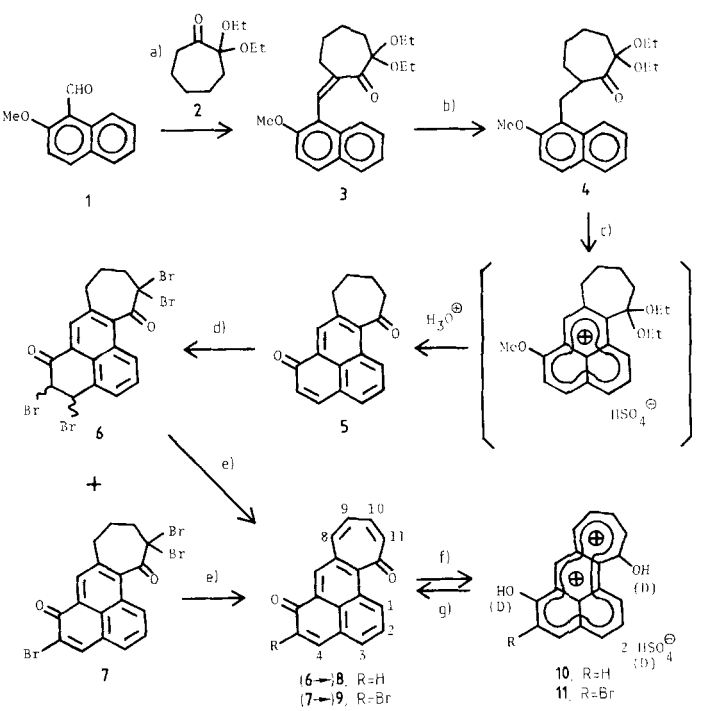
Synthesis of Cyclohepta[*a*]phenalene-6,12-dione

By *Shigeyasu Kuroda,* Yuriko Fukuyama, Tomohiko Tsuchida, Eishi Tanaka,* and *Syuzi Hirooka*

Although many types of nonbenzenoid quinones have been investigated, little is known about polycyclic quinones containing more than three rings.[1] Herein we report on the first synthesis and the properties of the novel tetracyclic quinone cyclohepta[*a*]phenalene-6,12-dione **8** and its dication **10** as well as the corresponding 5-bromo derivatives **9** and **11**, respectively. It is also of interest to know the tropicity of these species. They should show opposite tropicity to the unknown parent hydrocarbon cyclohepta[*a*]phenalene, which is predicted to be aromatic,[2] since an analogous alternation of tropicity is found for the heptalene system.[3]

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The reaction of 2-methoxy-1-naphthaldehyde **1** with 2,2-diethoxycycloheptanone **2** in the presence of NaOMe in refluxing tetrahydrofuran furnished **3** (78% yield, Scheme 1). The catalytic hydrogenation of **3** provided the satu-



Scheme 1. a) NaOMe, anhydrous tetrahydrofuran, reflux, 3 h. b) H_2/PtO_2, 2.7 atm., 3 h. c) 85% H_2SO_4, 45°C, 25 min. d) $C_5H_5NHBr_3$, $CHCl_3$. e) 2.5 equiv. *LiCl*, *dimethylformamide*, 90°C, *30 min*. f) conc. H_2SO_4 *or* D_2SO_4. g) H_2O in excess.

rated ketone **4** (>90%). The cyclodehydration of **4** gave **5** (60%), which was brominated with pyridinium tribromide in chloroform at 10°C in ca. 12 h to give **6** (93%) and **7** (traces). Under more vigorous conditions (50°C, 3 h), **7** was obtained as the major product (63%) along with **6** (23%). On treatment of **6** with LiCl in dimethylformamide,[4] the parent quinone **8** was obtained in one step as air-stable needles in 80% yield. The same treatment transformed **7** into the 5-bromoquinone **9** (73%).

Table 1. Some physical properties of quinones **8**, **9** and their dications.

8, yellow needles, m.p. = 209–212°C; IR (KBr): ν = 3040, 1640 (C=O), 1618, 1580 (C=O), 840 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 90 MHz): δ = 8.67 (dd, J = 1.5, 8.5 Hz, 1-H), 8.62 (s, 7-H), 7.70 (d, J = 9.8 Hz, 4-H), 7.67 (m, 2-H), 7.54 (m, 3-H), 7.48 (d, J = 10.0, 8-H), 6.92 (m, 9,10,11-H), 6.65 (d, J = 9.8 Hz, 5-H); ^{13}C-NMR ($CDCl_3$, 90 MHz): δ = 191.2 (C=O, C-12), 184.7 (C=O, C-6), 143.1 (C-4), 137.1 (C-8), 134.5 (C-10), 133.0 (C-7), 132.7 (C-11), 131.9 (C-3), 130.4 (C-1), 128.8 (C-9), 128.4 (C-3), 127.6 (C-2), 140.0, 133.4, 130.8, 130.6, 128.4, 128.0 (quart. C); UV (hexane): λ_{max} = 416 (lgε = 3.86), 319 (3.97), 268 nm (4.14); MS: m/z 258 (M^+).—**10**, ^{1}H-NMR (conc. D_2SO_4/CH_2Cl_2, 200 MHz): δ = 10.25 (s, 7-H), 10.16 (d, J = 8.7 Hz, 1-H), 9.36 (bd, J = 10.1 Hz, 8-H), 9.34 (bd, J = 9.3 Hz, 4-H), 8.90 (dd, J = 8.8, 10.9 Hz, 10-H), 8.90 (d, J = 7.8 Hz, 3-H), 8.70 (d, J = 10.9 Hz, 11-H), 8.62 (dd, J = 8.8, 10.1 Hz, 9-H), 8.42 (dd, J = 7.8, 8.7 Hz, 2-H), 7.85 (d, J = 9.3 Hz, 5-H); ^{13}C-NMR (conc. D_2SO_4/CH_2Cl_2, 200 MHz): δ = 182.7 (C-OH, C-12), 181.9 (C-OH, C-6), 165.2 (C-4), 154.9 (C-10), 152.5 (C-8), 148.0 (C-1), 146.9 (C-3), 141.8 (C-7), 138.5 (C-5), 132.7 (C-11), 131.4 (C-9), 120.1 (C-2), 140.2, 138.1, 129.7, 127.2, 126.4, 125.0 (quart. C); UV (conc. H_2SO_4): λ_{max} = 548 (lgε = 2.25), 493 (2.98), 268 nm (3.14)

9, yellow needles, m.p. = 225°C (decomp.); IR (KBr): ν = 1655 (C=O), 1610, 1582 (C=O), 795 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 90 MHz): δ = 8.85 (s, 7-H), 8.67 (dd, J = 1.8, 8.0 Hz, 1-H), 8.27 (s, 4-H), 7.78 (dd, J = 1.8, 8.0 Hz, 3-H), 7.64 (t, J = 8.0 Hz, 2-H), 7.60 (dd, J = 2.0, 10.5 Hz, 8-H), 6.98 (m, 9,10,11-H); ^{13}C-NMR spectrum could not be obtained due to low solubility of **9**. UV(CH_2Cl_2): λ_{max} = 425 (lgε = 4.08), 332 (4.08), 295 nm (4.28); MS: m/z 338 (M^+).—**13**, ^{1}H-NMR (conc. D_2SO_4/CH_2Cl_2, 90 MHz): δ = 10.39 (s, 7-H), 10.23 (d, J = 8.6 Hz, 1-H), 9.65 (s, 4-H), 9.41 (d, J = 10.0 Hz, 8-H), 9.03 (md, 3-H, 10-H), 8.72 (m, 11-H, 9-H), 8.48 (dd, J = 7.5, 8.5 Hz, 2-H); ^{13}C-NMR (conc. D_2SO_4/CH_2Cl_2, 90 MHz): δ = 182.9 (C-OH, C-12), 176.2 (C-OH, C-6), 165.9 (C-4), 155.6 (C-10), 152.5 (C-8), 150.3 (C-1), 139.0 (C-3), 138.9 (C-7), 132.1 (C-11), 131.9 (C-9), 114.8 (C-2), C-5: signal intensity too weak, 140.3, 138.5, 130.0, 127.2, 126.3, 123.9 (quart. C); UV (conc. H_2SO_4): λ_{max} = 580 (lgε = 3.76), 504 (4.26), 376 nm (4.46)

The structures of **8** and **9** were assigned on the basis of their spectra (Table 1). The ^{1}H-NMR chemical shifts of the seven-membered ring of **8** are very close to those of 5-benzocycloheptenone ("benzo[2,3]tropone")[4] and those of the phenalenone moiety are in almost the same region as those of **5** except for 1-H and 7-H, which are shifted to lower field by the deshielding effects of the carbonyl groups (Fig. 1, above). The ^{1}H-NMR spectrum of **9** is essentially identical to that of **8** but is slightly shifted to lower field. The coupling constants J (8-H, 9-H) of **8** and **9** indicate that the bond alternation of the cycloheptatrienone (tropone) moiety is smaller than that of 5-benzocycloheptenones.

The reduction potentials of **8** and **9** are $^1E_{1/2} = -1.05$, $^2E_{1/2} = -1.44$ and $^1E_{1/2} = -0.90$, $^2E_{1/2} = -1.37$ V (vs. SCE), respectively.[5] These values are similar to those of anthraquinones.[1]

The ^{1}H-NMR spectra of **8** and **9** in conc. D_2SO_4 indicate the formation of the dications **10** and **11** (Fig. 1, below). The changes in the ^{1}H-NMR chemical shifts of the seven-membered-ring protons ($\Delta\delta$ = 1.83 ppm) and of the other protons ($\Delta\delta$ = 1.35 ppm) in going from **8** to **10** are larger than those for the corresponding hydroxytropylium ion ($\Delta\delta$ = 1.50 ppm) and hydroxyphenalenylium ion ($\Delta\delta$ = 1.00 ppm),[6] respectively. This is presumably due to the diatropicity of the dications, since only small differences are observed for the corresponding $\Delta\delta$(^{13}C) values of these compounds.

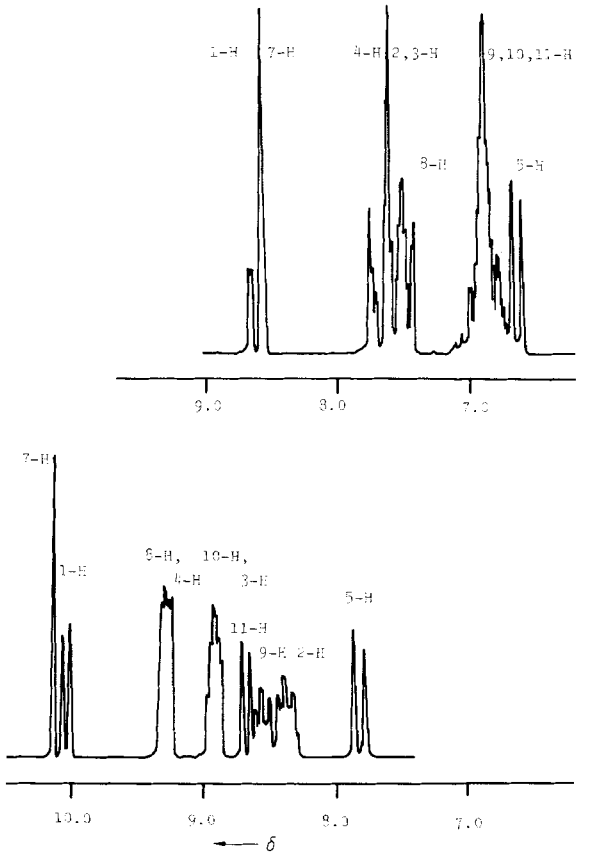


Fig. 1. Above: ^{1}H-NMR spectrum of the quinone cyclohepta[*a*]phenalene-6,12-dione **8** ($CDCl_3$, 90 MHz, δ values). Below: ^{1}H-NMR spectrum of the dication 6,12-dihydroxycyclohepta[*a*]phenalenediium **10** (conc. D_2SO_4, 200 MHz, δ values).

From the above results, it is concluded that the quinones **8** and **9** are formally composed of a tropone moiety and a phenalenone moiety; however, the dicationic species are not merely composed of hydroxytropylium and hydroxyphenalenylium ions, but are, contrary to expectation, novel dicationic diatropic compounds.

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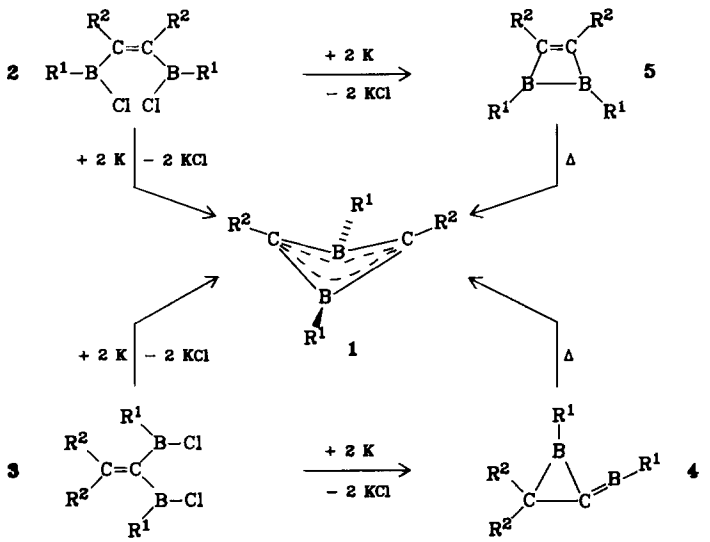
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1,2-Bis(diisopropylamino)-1,2-dihydro-1,2-diborete**

By *Manfred Hildenbrand, Hans Pritzkow*, and *Walter Siebert**

Dedicated to Professor Karl Dimroth on the occasion of his 75th birthday

According to MO calculations for the $C_2B_2H_4$ system, the folded 1,3-dihydro-1,3-diborete structure **1** is the energetically favored isomer.[1] **1** has been prepared via several routes[2-5] and its structure confirmed by X-ray analysis of compounds **1c** and **1d**. Dehalogenation of the chloroboranes **2a-c** using Na/K alloy yields **1a-c**; compound **1d** is formed from **3d**, and **1e** is formed via a thermal rearrangement of the initially formed boranediylborirane **4e**. Compound **1f** is obtained, along with other compounds, from *t*Bu-C≡C-*t*Bu, $MeBBr_2$, and C_8K.[5] **1** should also be accessible via a rearrangement of the isomer of type **5**, which is 7-17 kcal/mol[1] higher in energy. After several unsuccessful attempts to synthesize 1,2-dihydro-1,2-diboretes,[3,6] we now report the preparation and structure of **5g**, the first derivative of 1,2-dihydro-1,2-diborete.[4b]



	1a, 2a [2]	1b, 2b [2]	1c, 2c [3]	1d, 3d [4a]	1e, 4e [2]	1f [5]	1g, 2g, 5g
R^1	*t*Bu	*t*Bu	NMe_2	$NiPr_2$	*t*Bu	Me	$NiPr_2$
R^2	Me	Et	*t*Bu	$SiMe_3$	$SiMe_3$	*t*Bu	H

Reaction of 1,2-bis(dichloroboryl)ethene **2** (R^1 = Cl, R^2 = H),[7] obtained from B_2Cl_4 and acetylene, with diisopropylamine affords **2g**,[8] which can be dehalogenated in refluxing benzene using Na/K alloy. Colorless crystals are obtained in 55% yield. That the product obtained, **5g**, is indeed the 1,2-dihydro-1,2-diborete is shown by the NMR data. The ^{1}H-NMR spectrum contains two septets separated by $\Delta\delta = 0.48$, two doublets for the methyl groups of the isopropyl substituents on the nitrogen atom, and a broad singlet ($\delta = 8.87$) for the olefinic protons. Only one septet is expected for a 1,3-arrangement of the boron atoms. The ring carbon atoms are found at $\delta(^{13}C) = 178.8$, whereas, for the 1,3-dihydro-1,3-diboretes, δ values of 37-126[2-5] are obtained. The ^{11}B-NMR shift ($\delta = 46.5$) also lies outside the range ($\delta = 31$-34[3,4b]) found for compounds of type **1**; it supports a dialkyldiaminodiborane(4) compound.[9] Neither in the IR nor in the Raman spectrum is a C=C band observed between 2100 and 1520 cm^{-1} and between 2100 and 1510 cm^{-1}, respectively.

The 1,2-dihydro-1,2-diborete structure derived from the NMR and MS data has been confirmed by an X-ray analysis[10] (Fig. 1).

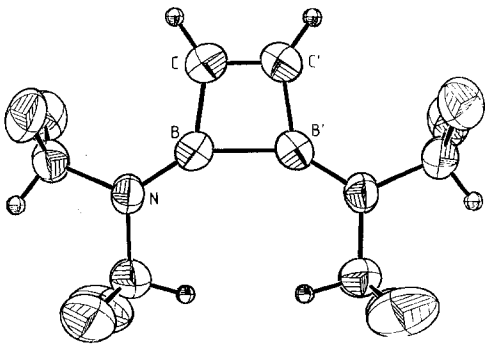


Fig. 1. ORTEP drawing of the structure of **5g** (vibration ellipsoids with 40% probability, arbitrary for the H atoms; methyl H atoms left out). Bond lengths [Å] and bond angles [°] (standard deviations 0.01 Å and 0.5°): CC' 1.31, BB' 1.75, BC 1.58, BN 1.38; CBB' 82.0, BCC' 98.0, NBB' 146.7.

The molecule lies on a crystallographically twofold axis. The C_2B_2 ring is planar (±0.007 Å) and the NC_2 atoms of the amino groups lie in the plane of the ring. The BB distance is longer than in a non-strained 1,2,4,5-tetraborinane.[11] The BC distance is in good agreement with the values for a BC single bond in a 1,3-diboretane[4a] and 1,2,4,5-tetraborinane,[11] but is significantly longer than those in **1c** (1.50 Å) and **1d** (1.52 Å). The calculations[1] for **5** predict a slightly longer CC double bond and a shorter BB single bond.

The rearrangement of **5g** to **1g**, expected on the basis of calculations,[1] takes place upon heating of a sample in [D_8]toluene to 120 °C. In the ^{1}H-NMR spectrum, a new singlet at $\delta = 2.21$ appears after 30 min and grows at the expense of the low-field signal ($\delta = 8.87$). Heating for five hours results in a conversion >95%; the singlet at $\delta = 8.87$ is barely observable and a septet at $\delta = 3.50$ has formed from the two septets originally present for **5g**. In the ^{11}B-NMR spectrum, an upfield shift from $\delta = 46.5$ to 37.3 is observed, and in the ^{13}C-NMR spectrum, an upfield shift from $\delta = 178.8$ to 37.5 for the ring carbon atoms is found. Analogous rearrangements could already take place at the temperature employed for the dehalogenation of other derivatives on account of the lower activation energies, and hence explain the formation of **1** from **2**.

Comparison of the structures of **1c** and **1d** with that of **5g** reveals that both π electrons are delocalized in the folded **1**, whereas they are localized in the CC double bond of the planar **5g**. Our results thus support the theoretical predictions[1] concerning the bonding and relative stabilities of **1** and **5**.

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CAS Registry numbers:
1g, 97826-17-0; **2** (R^1 = N*i*Pr$_2$, R^2 = H), 97826-18-1; **5**, 97826-19-2; $Cl_2BCH{=}CHBCl_2$, 1803-26-5; *i*Pr$_2$NH.

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[8] **2g**: *i*Pr$_2$NH (6.06 g, 60 mmol) in 20 mL of hexane was added with stirring to $Cl_2BCH{=}CHBCl_2$ (2.82 g, 15 mmol) in 30 mL of hexane. The reaction mixture was then refluxed for 2 h. After filtering off the *i*Pr$_2$NH$_2$Cl precipitate, the solvent was removed in vacuum and the residue distilled at 94°C/10^{-3} torr. Yield: 3.48 g (10.9 mmol, 73%), m.p. = 49–51°C (from CH_2Cl_2); ^{1}H-NMR ($CDCl_3$): δ = 1.18 (d, 12H), 1.29 (d, 12H, in each case ^3J(HH) = 6.8 Hz), 3.81 (m, 4H), 6.61 (s, 2H); ^{11}B-NMR ($CDCl_3$): δ = 35.2 (s).—**5g**: **2g** (3.48 g, 10.9 mmol) and NaK_8 (0.89 g, 24 mval) in 20 mL of C_6H_6 were refluxed for 45 min. After filtration, the solvent was removed at 50 torr and **5g** was sublimed from the oily residue at 40°C/10^{-3} torr. Yield: 1.48 g (6 mmol, 55%), m.p. = 54–55°C (from Et_2O); ^{1}H-NMR ($CDCl_3$): δ = 1.16 (d, 12H), 1.24 (d, 12H), 3.40 (sept., 2H), 3.88 (sept., 2H, in each case ^3J(HH) = 6.6 Hz), 8.54 (s, 2H); ^{13}C-NMR ($CDCl_3$): δ = 23.0 (q, 4C, *C*H$_3$), 25.2 (q, 4C, *C*H$_3$, in each case ^1J(CH) = 123 Hz), 46.1 (d, 2C, N*C*), 52.7 (d, 2C, N*C*, in each case, ^1J(CH) = 134 Hz), 178.8 (d, 2C, *C*=*C*, ^1J(CH) = 145 Hz); MS: *m/z* 248 (M^+, 94%), 233 (M^+ − Me, 20%), 205 (M^+ − *i*Pr, 61%), 163 (205 − CMe$_2$, 40%), 121 (163 − CMe$_2$, 38%). – **1g**: ^{1}H-NMR ([D$_8$]toluene): δ = 1.40 (d, 12H), 1.44 (d, 12H), 3.50 (sept., 4H, in each case ^3J(HH) = 6.6 Hz), 2.21 (s, 2H); ^{13}C-NMR ([D$_8$]toluol): δ = 24.0 (q, 4C, *C*H$_3$), 25.3 (q, 4C, *C*H$_3$, in each case ^1J(CH) = 125 Hz), 37.5 (d, 2C, B*C*, ^1J(CH) = 162 Hz), 51.8 (d, 4C, N*C*, ^1J(CH) = 133 Hz); ^{11}B-NMR ([D$_8$]toluene): δ = 37.3 (s).

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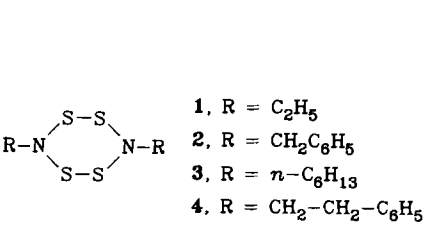
[10] **5g**: space group F2dd, a = 8.267(5), b = 19.372(10), c = 22.466(15) Å, V = 3598 Å^3, Z = 8. 632 observed reflections (Stoe two-circle diffractometer, Mo$_{K\alpha}$ radiation), R = 0.076, R_w = 0.051 (B, C and N refined anisotropically). Further details of the crystal structure investigation are available on request from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2, by quoting the depository number CSD 51382, the names of the authors, and the journal citation.

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The X-Ray Crystal Structures of Two 1,2,4,5-Tetrathia-3,6-diazacyclohexanes**

By *Ray Jones, David J. Williams,* and *J. Derek Woollins**

Eight-membered sulfur-nitrogen rings $S_n(NR)_{8-n}$ are well known and have been extensively studied.[1] Their nitrogen atoms have planar environments and can thus be considered to be sp^2 hybridized and consequently non-basic. It is to be expected that cyclic sulfur-nitrogen compounds with other ring sizes would exist and there has been a brief report on compounds of the type $S_4(NR)_2$.[2] Here we report on the synthesis of compounds **1**–**4** and the crystal structures of **1** and **2**.[3]



1, R = C_2H_5
2, R = $CH_2C_6H_5$
3, R = n-C_6H_{13}
4, R = CH_2–CH_2–C_6H_5

Reaction of disulfur dichloride with primary amines under Ruggli-Ziegler high-dilution conditions gave **1**–**4**; use of *tert*-butylamine or aniline was unsuccessful, giving only polymeric material and the corresponding amine hydrochloride.

The crystal structures of **1** and **2** (Figs. 1 and 2) both reveal six-membered cyclohexane-type rings with the EtN and PhCH$_2$N groups in the 3,6-positions as expected. In both structures there is a crystallographic center of symmetry at the center of the ring. The structures have two unusual features. 1) All the S–N bond lengths (average 1.716 Å) are significantly longer than the previously reported values (ca. 1.67 Å) found for $S_n(NH)_{8-n}$.[4–8] 2) The angles at the nitrogen atoms, SNS = 111.3, CNS = 115.8, 116.8° (average values), reveal a substantial degree of pyramidalization; the nitrogen atoms lie 0.373 Å and 0.392 [0.379] Å from the plane of their substituents in **1** and **2**, respectively (the value in brackets refers to a second crystallographically independent molecule). This pyramidal (sp^3) geometry is in contrast to that observed for cyclic eight-membered sulfur-nitrogen compounds, which are all essentially trigonal.[4–8] The S–S bond lengths (2.054(1) Å) in **1** are marginally longer than those in **2** (2.037(2),

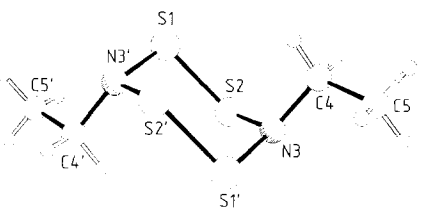


Fig. 1. Crystal structure of **1**. Important bond lengths [Å] and bond angles [°]: S1-S2 2.054(1), S1-N3' 1.714(3), S2-N3 1.716(3), N3-C4 1.475(4), C4-C5 1.506(8); S2-S1-N3' 104.8(1), S1-S2-N3 104.9(1), S2-N3-C4 115.7(3), S2-N3-S1' 111.6(2), C4-N3-S1' 117.3(2), N3-C4-C5 111.6(4).

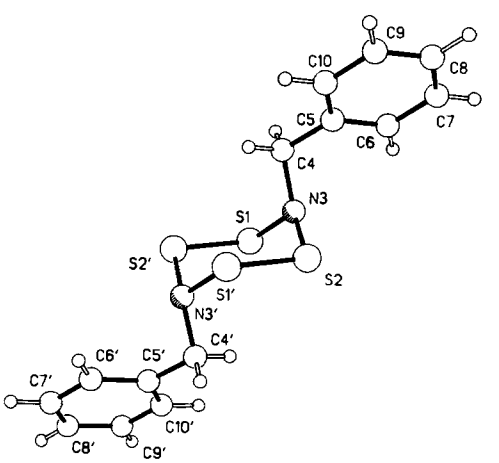


Fig. 2. Crystal structure of **2**. Important bond lengths [Å] and bond angles [°]: S1-S2' 2.037(2) [2.034(2)], S1-N3 1.713(4) [1.717(4)], S2-N3 1.720(3) [1.717(4)], N3-C4 1.479(5) [1.462(6)]; S1'-S2-N3 105.2(1) [105.9(1)]; S2-N3-S1 110.9(2) [111.3(2)], N3-S1-S2' 105.8(1) [105.3(1)], S2-N3-C4 116.7(3) [116.2(3)], S1-N3-C4 115.5(3) [116.5(3)]. Numbers in brackets are for the second crystallographically independent molecule.

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2.034(2) Å). Although these differences are statistically significant, we are unable to rationalize them, particularly since the S–N distances are all equal in **1** and **2**. The SSN angles in both **1** and **2** are normal.

An additional notable feature is the axial substitution of the nitrogen atoms. In **1** there is a close approach (3.33 Å) of S1 to N1 of a neighboring molecule. However, in **2** there are no such close contacts; the shortest approach to N3 is 3.74 Å (to S2 of a neighboring molecule). Thus, it seems unlikely that packing forces are the determining factor in the unexpected axial substitution.

All of the above observations may be rationalized by assuming that **1** and **2** are held together by bonds with very little or no π character. The S–N bond lengths are the longest so far reported for such cyclic sulfur-nitrogen compounds. The axial substitution of the nitrogens may be a result of the importance of lone-pair repulsion between the adjacent nitrogen and sulfur atoms; this repulsion is minimized with the lone pairs of the nitrogen in the equatorial positions.

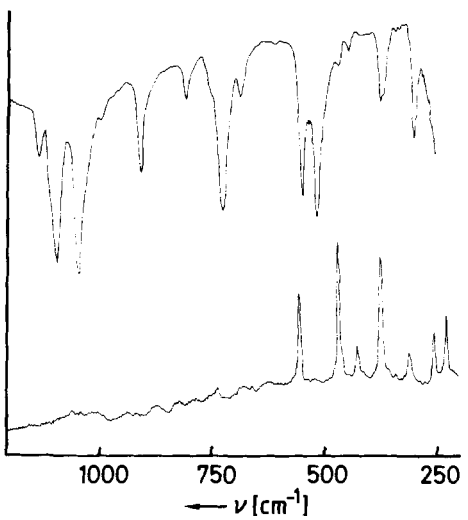


Fig. 3. Upper trace: IR spectrum, lower trace: Raman spectrum of **1**.

Vibrational spectroscopy has proved to be a useful tool for detecting S_n species with different ring sizes. The IR and Raman spectra of **1** are shown in Figure 3. The bands due to ν_{SS} have been correlated with the S–S distance in S_n rings[9] and in **1** the predicted frequency would be 470 cm^{-1}; the band at 473 cm^{-1} is thus readily assigned to ν_{SS}. By comparison with previous reports,[10] we propose that the bands at 738 and 910 cm^{-1} are largely due to ν_{SN}. **2**–**4** have very similar spectra to **1** in these regions; **2**: ν_{SS} = 479 cm^{-1}, ν_{SN} = 730, 905 cm^{-1}.

Experimental Procedure

1: Diethyl ether solutions of S_2Cl_2 (33 mmol in 20 mL) and $EtNH_2$ (100 mmol in 20 mL) were added over 16 h to 600 mL of stirred diethyl ether. The precipitate of $EtNH_3Cl$ was filtered off, and the filtrate was concentrated to ca. 20 mL and cooled (−78°C) to give **1** (1.2 g, 34%) as colorless crystals; m.p. ≈ 37°C. **2**–**4** were prepared in a similar fashion and recrystallized from ethanol or ethanol/diethyl ether; **2**: m.p. = 138°C, yield 26%; **3**: m.p. = 126°C, yield 24%; **4**: m.p. = 110°C, yield 16%.

All compounds gave good elemental analyses and showed the parent ion in mass spectra. **1**: *m/z* 214 (100%, M^+), 171 (65% S_4NEt^+), 108 (10%, S_2NHEt^+), 75 (15%, $SNEt^+$). IR spectra were recorded as KBr discs, Raman spectra were obtained using 647.1-nm excitation (50 mW) with a rotating cell arrangement; **1**, **2**, and **4** were quite stable in the laser beam, whereas **3** decomposed, making its spectrum difficult to record.

Crystals of **1** suitable for X-ray analysis were obtained by slow evaporation of a diethyl ether solution at −15°C; crystals of **2** were obtained from diethyl ether/ethanol.

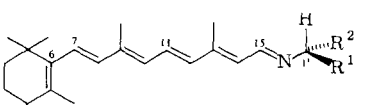
Received: April 9, 1985;
supplemented: June 10, 1985 [Z 1251 IE]
German version: *Angew. Chem. 97* (1985) 778

[1] H. G. Heal, *The Inorganic Heterocyclic Chemistry of Sulfur, Nitrogen and Phosphorus*, Academic Press, New York 1980.
[2] M. Becke-Goehring, H. Jenne, *Chem. Ber. 92* (1959) 1149.
[3] **1**: $P\bar{1}$, $a = 5.936(2)$, $b = 6.458(1)$, $c = 6.478(2)$ Å, $\alpha = 75.27(1)$, $\beta = 73.92(2)$, $\gamma = 88.41(2)°$, $V = 230.5(1)$ Å^3, $Z = 1$, $\rho_{calcd} = 1.63$ g cm^{-3}, $\mu(Cu_{K\alpha}) = 88$ cm^{-1}. **2**: $P2_1/a$, $a = 9.567(2)$, $b = 9.699(2)$, $c = 16.983(4)$ Å, $\beta = 92.70(2)°$, $V = 1574$ Å^3, $Z = 4$. The structure contains two crystallographically independent molecules each centered on a crystallographic center of symmetry; $\rho_{calcd} = 1.43$ g cm^{-3}, $\mu(Cu_{K\alpha}) = 54$ cm^{-1}. Nicolet R3m diffractometer, $Cu_{K\alpha}$ radiation, graphite monochromator, ω-scan. The structures of **1** and **2** were solved by direct methods and all non-hydrogen atoms were refined anisotropically to give, respectively, $R = 0.025$, $R_w = 0.027$ and $R = 0.053$, $R_w = 0.062$ for 426 and 1711 independent, absorption-corrected reflections [$\theta \leq 50°$ and $\theta \leq 55°$, $|F_o| > 3\sigma(|F_o|)$]. Further details of the crystal structures can be obtained from the Director of Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW (England) by quoting the full literature citation.
[4] The average S–N distance in *cyclo*-$S_4N_4H_4$ is 1.674 Å: R. L. Sass, J. Donohue, *Acta Crystallogr. 11* (1958) 497.
[5] The average S–N distance in *cyclo*-S_7NH is 1.676 Å: H. J. Hecht, R. Reinhardt, R. Steudel, H. Bradaczek, *Z. Anorg. Allge. Chem. 426* (1976) 43.
[6] The average S–N distance in *cyclo*-S_5-NH-S-NH is 1.672 Å: H. J. Postma, F. Van Bolhuis, A. Vos, *Acta Crystallogr. B27* (1971) 2480.
[7] The average S–N distance in *cyclo*-S_3-NH-S_3-NH is 1.680 Å: P. F. Van Bolhuis, A. Vos, *Acta Crystallogr. B29* (1973) 915.
[8] The average S–N distance in *cyclo*-S_4-NH-S_2-NH has been reported to be 1.724 Å: J. Weiss, *Z. Anorg. Allg. Chem. 305* (1960) 190. Later workers [6, 7] considered this to be in error as a consequence of disorder.
[9] R. Steudel, *Topics in Current Chem. 102* (1982) 149.
[10] A. J. Banister, L. F. Moore, J. S. Padley, *Spectrochim. Acta 23A* (1967) 2705.

UV and CD Spectroscopic Evidence of the Self-Association of a Schiff Base of all-*trans*-Retinal**

By *Ute Wingen, Lothar Simon, Michael Klein*, and *Volker Buß**

While the structural consequences of hydrogen bonding in solids may be studied directly, one usually has to rely on assumptions with regard to hydrogen bonded aggregates in solution. We have found that certain Schiff bases of all-*trans*-retinal form, in aprotic solvents, aggregates in which according to spectral data the chromophores assume fixed positions with respect to each other.



1a: $R^1 = CH(CH_3)_2$, $R^2 = CH_3$
1b: $R^1 = CH_2OH$, $R^2 = CH(CH_3)_2$

The circular dichroism (CD) of the Schiff base **1a** is practically nil down to 113 K in all solvents investigated; apparently the chiral group on nitrogen is not able to dis-

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criminate sufficiently between conformations that are oppositely twisted with respect to the C(6)–C(7) bond. In contrast, **1b** exhibits a markedly temperature-dependent CD in a mixture of 2,2-dimethylbutane and *n*-pentane. In a 2.45×10^{-4} M solution (Fig. 1, left), a pair of oppositely signed bands at 345 and 390 nm is already observed at room temperature. With decreasing temperature, the amplitudes of these bands grow dramatically and reach their maximum $\Delta\varepsilon$ values of +77 and −74 at 133 K, corresponding to rotational strengths of 210×10^{-40} and -170×10^{-40} cgs, respectively.[1] The increase of the CD upon cooling is accompanied by a long-wavelength shift of the pair of bands and the zero crossing point of about 8 nm.[2]

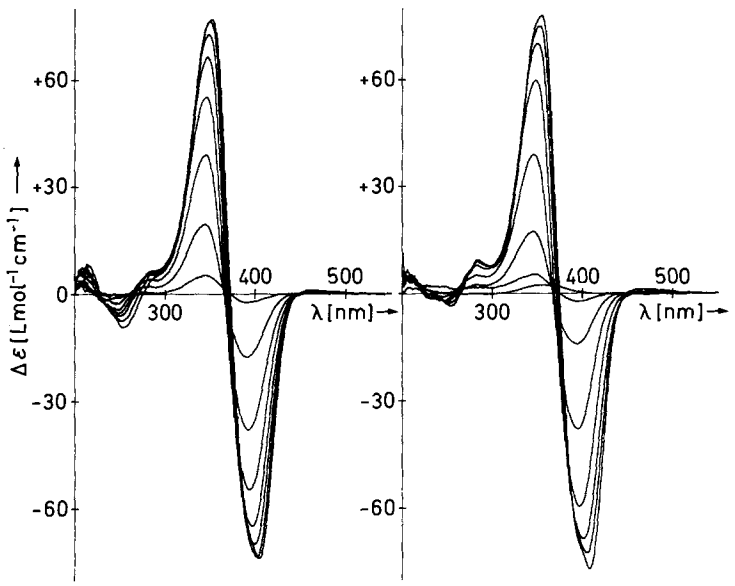


Fig. 1. Temperature- and concentration-dependent CD spectra of **1b** in Rigisolve (2,2-dimethylbutane—*n*-pentane 8:3). Concentration: 2.45×10^{-4} mol/L (left), 2.2×10^{-5} mol/L (right). The amplitude increase in the two series of spectra corresponds to cooling (starting from 283 K) first by 30, then by 20°, down to 133 K. The volume contraction of the solvent is taken into consideration in all spectra.

The CD is concentration dependent: in a solution diluted tenfold (Fig. 1, right), the rotational strengths increase significantly more slowly upon cooling but eventually attain the same final value as in the concentrated solution.

The temperature-dependent UV spectra also support, although less dramatically, an association of **1b** in contrast to **1a** (Fig. 2). At room temperature, the spectra of both compounds are practically identical; they exhibit an intense band with a maximum at 359 nm assigned to the longest-wavelength $\pi\pi^*$ excitation of the retinylidene chromophore. Upon cooling, only the band of **1b** undergoes splitting into an intense, short-wavelength (relative to **1a**) component and a weak component, recognizable only as a shoulder on the long-wavelength side of **1a**.

We formulate the association as a dimerization via hydrogen bonds to give **2**, which contains a ten-membered ring. The interaction of the electronic excitations of the two (identical) chromophores leads, according to exciton theory,[3] to splitting in the UV and the appearance of a pair of bands ("couplet") in the CD with a zero crossing point in the absorption maximum of the monomer **1b**.

Qualitative analysis clearly indicates that the two chromophores form an acute angle and must be arranged in an *M*-helical fashion.[4] An obtuse angle or even a linear arrangement of the retinylidene groups would result in a reversal of the intensity ratios in the UV; *P* helicity would result in the reverse sequence of signs in the CD. With these restrictions, molecular models suggest the structure of the dimer **2** given in Figure 3 with C_2 symmetry. The ten-membered ring assumes a conformation similar to the twist-boat geometry of (*Z*,*Z*)-1,5-cyclooctadiene,[5] the double bonds being replaced by two N···H–O fragments. The two retinylidene moieties extend approximately along the C_2 axis; their π-systems from C(15) to about C(11) are in close contact, which probably contributes to the stability of the aggregate. The absolute configuration of the dimer is fixed by the pattern of substitution of the two asymmetric carbon atoms. The hydrogen atoms on C(1′) and C(15) are nearly eclipsed. In analogues of **1b**, this conformation is especially favorable.[6] The isopropyl group, on the other hand, occupies the position in the dimer that offers the greater amount of space.

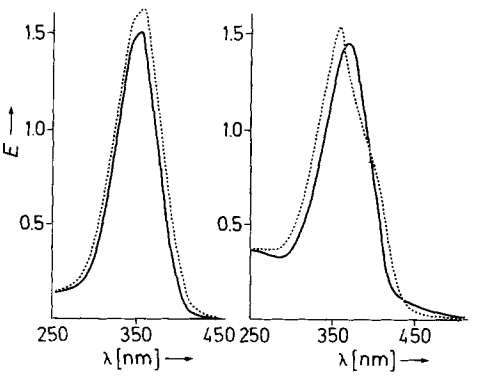
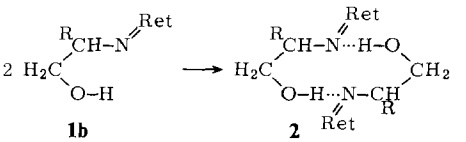


Fig. 2. UV spectra **1a** (——) and **1b** (· · · · ·) in Rigisolve at room temperature (left) and at 113 K (right). Concentrations: **1a**: 3.2×10^{-5} mol/L; **1b**: 3.6×10^{-5} mol/L.



1b **2**

R = $CH(CH_3)_2$, Ret = all-*trans*-retinylidene

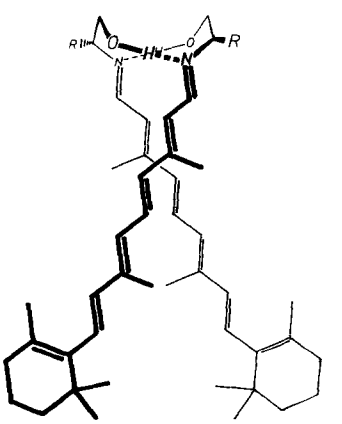


Fig. 3. Model of the structure of the dimeric aggregate **2** of **1b**, R = $CH(CH_3)_2$.

Rotational strengths calculated on the basis of this structure[7] agree well with the experimental values and support our model. The available data do not allow, at this time, a decision to be made as to whether other equilibria, apart from the dimerization, are involved in the formation of the aggregate. The factors that are responsible for the remarkable chiral discrimination and the stability of this system are the subject of further study.

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[1] The integration of the bands to determine their rotational strengths did not take into account their mutual overlap. The values given are therefore lower limits for the actual rotational strengths.

[2] The bathochromic shift of the long-wavelength absorption bands in retinals and retinal derivatives at low temperature is well known and is due to the solvent: R. R. Birge, M. J. Sullivan, B. E. Kohler, *J. Am. Chem. Soc. 98* (1976) 358; P. K. Das, R. S. Becker, *J. Phys. Chem. 82* (1978) 2081.

[3] N. Harada, K. Nakanishi: *Circular Dichroic Spectroscopy—Exciton Coupling in Organic Stereochemistry*, Oxford University Press, Oxford 1983.

[4] See [3], p. 8.

[5] O. Ermer, *J. Am. Chem. Soc. 98* (1976) 3964.

[6] V. Buß, M. Klein, *Tetrahedron Lett. 25* (1984) 4487.

[7] For the conformation shown in Figure 3 (chromophores twisted 60° with respect to each other, separation of the two π-systems 300 pm), we calculated rotational strengths of 670×10^{-40} and -650×10^{-40} cgs for the short- and long-wavelength bands, respectively on the basis of the coupled oscillators model. Since the bands in the CD spectrum overlap strongly, the experimental rotational strengths are definitely several times larger than the values determined by integration.

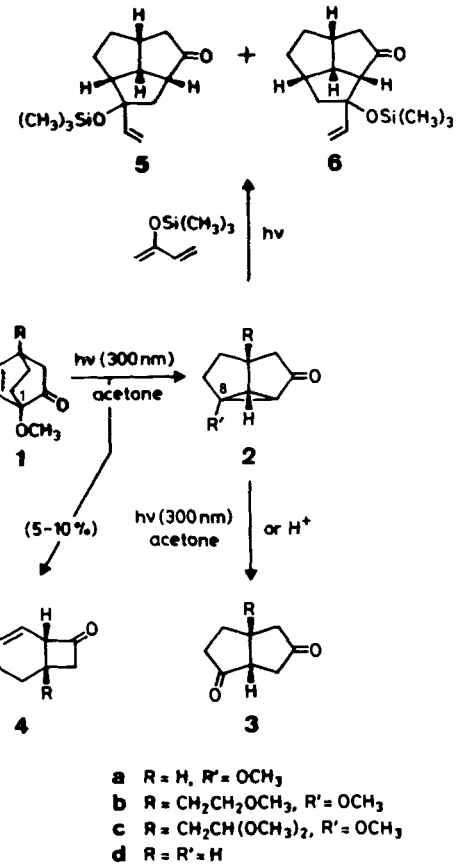
Photochemistry of 1-Methoxybicyclo[2.2.2]octenones; Photolytic Cyclopropane Cleavage of the Initially Formed Tricyclo[3.3.0.0^{2,8}]octan-3-ones**

By *Martin Demuth,* Bernhard Wietfeld, Bipin Pandey,* and *Kurt Schaffner*

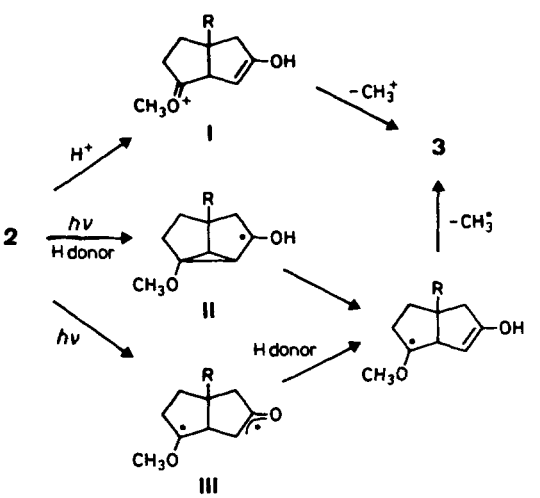
1-Methoxybicyclo[2.2.2]octenones **1a–c** are converted in a triplet-sensitized photoreaction into bicyclo[3.3.0]octanediones **3a–c** (Scheme 1; for **1a**→**3a** see ref. [1]). Diquinanes such as **3** are of synthetic interest.[2,3] Modified derivatives promise to serve as key intermediates for the synthesis of natural products such as the pentalenolactones.[4,5] We have investigated this reaction in order to elucidate the mechanism and to optimize the reaction conditions. We restricted this study to the analogues **1b** and **1c**,[6] which possess synthetically useful angular substituents and which are readily available, each in ca. 30% yield, from *p*-methoxyphenylacetic acid and *p*-methoxybenzyl cyanide, respectively.[2,5]

Irradiation ($\lambda = 300$ nm) of argon-flushed 1% solutions of **1b** and **1c** in 2:1 mixtures of acetone and isopropyl alcohol at room temperature gave **3b** and **3c**, respectively, in ≥75% yields[6] (quantum yields of product formation, $\Phi_{3b} = \Phi_{3c} = 0.03$[7]), along with **4b** and **4c** (5–10%).[6,8]

Rogers et al.[1] had previously postulated that the conversion **1a**→**3a** proceeds via an oxa-di-π-methane rearrangement to **2a**,[8] followed by photolytic cleavage of its three-membered ring[11,12] (Scheme 2: intermediate **III**); the reaction sequence ends with addition of H and loss of CH_3. We have now found that, upon irradiation of **1b** in acetone, **2b** is formed in low yield (ca. 5%). **2b** is also formed in benzene containing acetophenone, but not in benzene containing bicyclo[2.2.2]oct-2-en-2-yl phenyl ketone, which has a similar triplet energy (E_T(O–O) = 73.3 kcal/mol by phosphorescence in ether-isopentane-ethanol at 77 K[13]) but less readily abstractable H atoms. Whereas **2b** is stable in the dark in acetone solution, **2b** gave **3b** upon addition of methanol, isopropyl alcohol, or *p*-toluenesulfonic acid (Scheme 2: **2**→**I**→**3**). This transformation could also be effected in the absence of proton donors



Scheme 1. Photochemical transformations of the 1-methoxybicyclo[2.2.2]octenones **1a–c** and the tricyclo[3.3.0.0^{2,8}]octanones **2a–c** as well as addition of trimethylsiloxybutadiene to **2d** (all chiral compounds racemic).



Scheme 2. Protonolysis and photolysis of **2**. H donor: acetophenone, acetone, etc.

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[**] *B. P.* thanks the Alexander-von-Humboldt Foundation for a fellowship.

by irradiation of **2b** in acetone. Transient **2b** is thus firmly established as an intermediate in the transformation of **1b** into **3b**.

The light-induced step **2b** → **3b** is ca. 1.7 times faster in acetone than in [D_6]acetone. In *both* experiments, C_2H_6 (ca. 80%) and CH_4, but neither CH_3OH nor C_2H_4, were found in the gas phase by GC-MS. The H/D isotope effect shows that hydrogen abstraction is rate determining. The formation of ethane indicates that the 8-methoxy group is homolytically cleaved; moreover, the absence of methanol and ethylene rules out heterolytic cleavage and carbene elimination. Consequently, there are two possibilities for the primary step in the transformation of **2** into **3**: either hydrogen abstraction by the keto group (**2** → **II**) or the regioselective[11] β-cleavage of the cyclopropyl ketone following n→π* excitation (**2** → **III**). For **II**, ring opening would be expected to dominate over hydrogen abstraction from isopropyl alcohol, as has been found even for less strained α-hydroxycyclopropylcarbinyl radicals.[14]

The existence of intermediate **III** is strongly supported by an additional observation: On irradiation of **2d** ($\lambda = 300$ nm, benzene) in the presence of 2-trimethylsiloxybutadiene (spectral cut-off at ca. 290 nm), three of the four possible products with constitutions **5** and **6**[6, 15] are formed in a ratio of 1:2:4. Since direct excitation was used in this experiment, the diene most likely quenched all triplet-excited ketone by intersystem crossing. The conclusion drawn may therefore be valid only for the reaction of the singlet excited state of **2b**. That the addition occurs with poor regioselectivity is in better accord with the trapping of a biradical than a zwitterion. Furthermore, the mechanism of the transformations **2** → **3** is very likely independent of the substitution patterns **a**–**c**.

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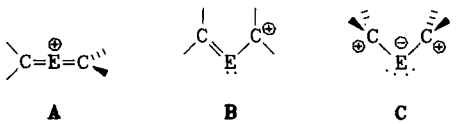
[1] a) S. D. Parker, N. A. J. Rogers, *Tetrahedron Lett. 1976*, 4389; b) T. J. Eckersley, S. D. Parker, N. A. J. Rogers, *Tetrahedron 40* (1984) 3749.
[2] M. Demuth, K. Schaffner, *Angew. Chem. 94* (1982) 809; *Angew. Chem. Int. Ed. Engl. 21* (1982) 820.
[3] L. A. Paquette, *Top. Curr. Chem. 119* (1984) 1.
[4] M. Demuth, *Chimia 38* (1984) 257.
[5] B. Wietfeld, *Dissertation*, Max-Planck-Institut für Strahlenchemie, Mülheim a. d. Ruhr and Universität Bochum 1984.
[6] The analytical data (IR, 400-MHz ^{1}H-NMR, MS) for all new compounds are satisfactory.
[7] Actinometry: W. Amrein, J. Gloor, K. Schaffner, *Chimia 28* (1974) 185; extrapolation to zero conversion.
[8] The oxa-di-π-methane rearrangement and the 1,3-acyl shift are characteristic photoreactions of β,γ-unsaturated ketones [9]. As for bicyclooctenones lacking methoxy substituents [10], the 1,3 acyl shift (→ **4b, c**) under our conditions probably results from residual direct absorption by **1b, c**.
[9] D. I. Schuster in P. de Mayo (Ed.): *Rearrangements in Ground and Excited States, Vol. 3*, Academic Press, New York 1980, p. 167.
[10] M. Demuth, P. R. Raghavan, C. Carter, K. Nakano, K. Schaffner, *Helv. Chim. Acta 63* (1980) 2434.
[11] L. D. Hess, J. L. Jacobson, K. Schaffner, J. N. Pitts, Jr., *J. Am. Chem. Soc. 89* (1967) 3684.
[12] W. G. Dauben, G. W. Shaffer, *Tetrahedron Lett. 1967*, 4415.
[13] W. Amrein, K. Schaffner, unpublished results.
[14] D. C. Neckers, A. P. Schaap, J. Hardy, *J. Am. Chem. Soc. 88* (1966) 1265; D. G. Marsh, J. N. Pitts, Jr., K. Schaffner, A. Tuinman, *ibid. 93* (1971) 333.
[15] The major reaction path of **2d** with trimethylsiloxybutadiene is oxetane formation (>90% at room temperature). The amount of **5** and **6** increased to about 10% at 5°C (the reaction at lower temperatures has not yet been investigated). Recently, *Isobe* et al. [16] photochemically generated and successfully trapped a similar but more delocalized biradical.
[16] N. Isobe, M. Matsuo, J. Miyamoto, *Tetrahedron Lett. 25* (1984) 861.

How is Phosphorus Bound in 2-Phospha- and 2-"Phosphoniaallyl" Cations?**

By *Roberta O. Day, Angela Willhalm, Joan M. Holmes, Robert R. Holmes,** and *Alfred Schmidpeter**

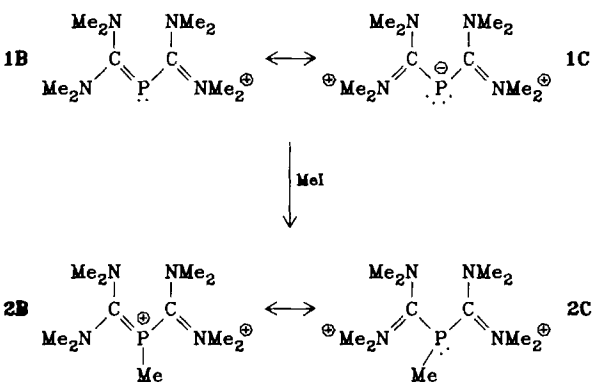
Dedicated to Professor Karl Dimroth on his 75th birthday

The 2-phosphaallyl cations[1, 2] are of practical interest as building blocks in the synthesis of phosphaheterocycles[2] as well as of theoretical interest as models with phosphorus in the center of a potentially conjugated chain.[3] Their bonding system may in principle be described by one of the three possibilities **A**, **B**, and **C** (E = P), which should result in different structures.



A **B** **C**

For E = N,[4] structurally investigated examples cover the range from **A** (2-azaallenium ions) to **B** (2-azaallyl cations) depending on the nature of the substituent at C. For E = P, the linear arrangement **A** was much less feasible from the outset because two-coordinate phosphorus compounds have been found to be bent (by an angle of around 100°, usually less than the tetrahedral angle) in every case up to now. Whereas description **C** would account for such a bond angle, it is consistent with neither the chemical behavior of the 2-phosphaallyl cations, nor with the strong variation of $\delta(^{31}P)$ with the C-substituents.[2] The latter is not understandable in the absence of π-interactions between the phosphide center and the carbenio ligands.



The C-substituents also govern the electrophilicity of phosphorus. Thus, only cation **1** with four amino groups can be methylated by methyl iodide to give the dication **2**. If derived from form **B**, the center in **2** should be planar, as in the homologous biguanide dications[5] and in the isoelectronic tetraaminoallyl cations.[6] On the other hand,

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[**] This work was supported by the Deutsche Forschungsgemeinschaft and Fonds der Chemischen Industrie (*A. S.*) and by the NSF (CHE 8205411) and NIH (GM 21466, *R. R. H.*).

it should be pyramidal if derived from form **C**. With X-ray structural investigations on crystals of the perchlorate of **1**[7] and the diiodide of **2**,[8] it is now possible to compare **1** and **2** and their analogues.

The molecular structure of **1** (Fig. 1, top) shows the usual bent geometry at phosphorus, as well as PC bond lengths that are in accord with a bond order of 1.5, corresponding to **B**. Nevertheless, the coplanarity that would be optimal for **B** is not quite attained. As in the allyl cation, **1** (CH instead of P),[6] the dimethylamino groups are twisted somewhat out of the central plane as a result of their steric interaction, and the interior angles at carbon are considerably larger than the exterior angles. The CN bond lengths also agree with those found for the allyl cation (average, 135 pm).

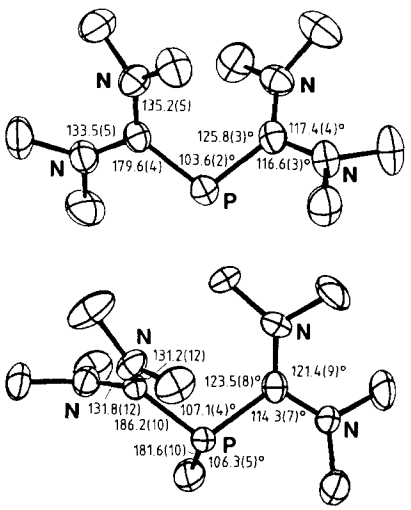


Fig. 1. ORTEP plot of the structures of **1** (top) and **2** (bottom) in the crystals of **1** ClO_4 and **2** I_2. The thermal ellipsoids are shown at the 50% probability level. Hydrogen atoms have been omitted for clarity. Bond lengths [pm] and bond angles [°] (mean values).

The C_2 symmetry that is approximately present in **1** is fully lost as a consequence of methylation to give **2** (Fig. 1, bottom). With a somewhat wider CPC angle than in **1**, the phosphorus coordination is now essentially trigonal pyramidal, and the planes of the two $C(NMe_2)_2$ groups are rotated by an angle of 69° with respect to one another. The PC bonds attain the single bond distance, while the CN bonds are clearly shorter than in **1**.[9]

Accordingly, the methylation of the phosphaallyl cation is well described by **1B**→**2C**. In **1**, where the phosphorus is bicoordinated, there is obviously a normal conjugated allylic system present. In this case, the phosphorus can best be viewed as using its p orbitals for both π- and σ-bonding, the latter of which is consistent with the small bond angle. The lone (s-)electron pair is accordingly not available to an electrophile without considerable promotion energy. It therefore remains in **2** and becomes stereochemically active. Instead, the π-electron pair is involved (at least formally)[10] in the binding of the methyl group. The dication **2**, therefore, is no longer a conjugated allylic system but merely a phosphane substituted with two independent amidinium groups. The conjugated form **2B** would require a nearly planar coordination of the phosphorus, the necessary energy for which is not sufficiently provided by the resonance stabilization. In contrast, in the isoelectronic tetraamino cations and dications with CR and NR, respectively, instead of PMe, the allylic bonds exhibit the highest barriers to rotation.[5, 11]

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[7] Upon combination of concentrated ethanol solutions of **1** Cl [1] and $NH_4^{\oplus}ClO_4^{\ominus}$, **1** ClO_4 crystallizes at first as light yellow needles, then as platelets; m.p. = 168–169 °C. $P2_1/n$ (alternate setting of $P2_1/c$), $a = 6.806(1)$ Å, $b = 12.887(3)$ Å, $c = 19.256(3)$ Å, $\beta = 97.99(2)°$, $Z = 4$. Enraf-Nonius CAD4 diffractometer; graphite-monochromated $Mo_{K\alpha}$ radiation for $2° \le 2\theta \le 50°$; 2045 independent reflections with $I \ge 2\sigma(I)$; $R = 0.061$, $R_w = 0.075$.
[8] From a roughly 0.2 M acetonitrile solution of **1** Cl [1] and two molar equivalents of methyl iodide, a light yellow precipitate of **2** I_2 forms within several days; almost colorless crystals after recrystallization from acetonitrile, 80% yield, m.p. = 207–209 °C, $\delta(^{31}P)(CH_3CN) = -17.4$. $P2_1/n$ (alternate setting of $P2_1/c$), $a = 8.012(2)$ Å, $b = 12.164(3)$ Å, $c = 19.157(3)$ Å, $\beta = 92.31(1)°$, $Z = 4$. Enraf-Nonius CAD4 diffractometer, graphite-monochromated $Mo_{K\alpha}$ radiation for $2° \le 2\theta \le 43°$; 1784 independent reflections with $I \ge 2\sigma(I)$; $R = 0.035$, $R_w = 0.056$. Further details of the crystal structure investigation are available on request from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2, on quoting the depository number CSD 51519, the names of the authors, and full citation of the journal.
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Allylation of Aldehydes with Etherification by Dialkoxydichlorotitanium/Allyltrimethylsilane; an Asymmetric Variant of the Sakurai Reaction**

By *Rene Imwinkelried* and *Dieter Seebach**

Dedicated to Professor Hans Musso on the occasion of his 60th birthday

The preparation of homoallylic alcohols by $TiCl_4$-mediated allylation of aldehydes and ketones with allyltrimethylsilane was first described by *Sakurai* et al. in 1976.[1] We have now found that dialkoxydichlorotitanium reagents behave quite differently from $TiCl_4$ under the same conditions. Treatment of aldehydes with 1.1 equivalents of dialkoxydichlorotitanium at −75 °C,[2] and subsequent addition of 1.2 equivalents of allyltrimethylsilane led to the isolation in good yields of homoallylic ethers **1** (Table 1). The reagents are easily generated in situ either by mixing equimolar amounts of $TiCl_4$ and commercial $Ti(OR')_4$

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[**] Part of the projected Ph. D. thesis of *R. I.*, ETH Zürich.

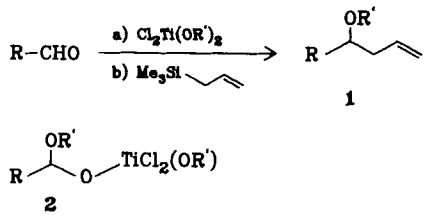


Table 1. Preparation of homoallylic ethers **1** (CH_2Cl_2, −75°C, 30 min; −75 to +20°C).

	R	R′	Yield [%]
1a	C_6H_5	$CH(CH_3)_2$	90
1b	C_6H_5	C_2H_5	95
1c	C_6H_5	CH_2–CH=CH_2	50
1d	$CH_2CH_2C_6H_5$	$CH(CH_3)_2$	65

($R' = C_2H_5$, $CH(CH_3)_2$)[3] or by allowing two equivalents of LiOR′ to react with $TiCl_4$.

In this one-step synthesis of homoallylic ethers,[4, 5] the carbonyl oxygen atom of the aldehyde is replaced by an alkoxy and an allyl group.[6] We assume that the first step is the addition of an alkoxy group to the aldehyde. The resulting (titanated) hemiacetal **2** then undergoes substitution of the former aldehyde oxygen by the allyl group. Quenching with aqueous base before addition of the allylsilane leads to complete recovery of the aldehyde, indicating that acetals $R-CH(OR')_2$ are not involved as intermediates.[5]

The synthesis of homoallylic ethers **3** from chiral, nonracemic alcohols and subsequent cleavage of the ether bond should allow the preparation of optically active homoallylic alcohols **4**. Thus, (*S*)-(−)-1-phenylethanol (96% *ee*)[7] reacted to give the homoallylic ethers **3** with a diastereoselectivity of ca. 90%[8]—racemic 1-phenylethanol produced (±)-**3a** and (±)-**3b** with 97.5% and 89% *ds*, respectively.[9] By mild cleavage of the benzylic ether bond with iodotrimethylsilane,[10] the ethers **3** were converted into the optically active homoallylic alcohols **4** (Table 2).[11]

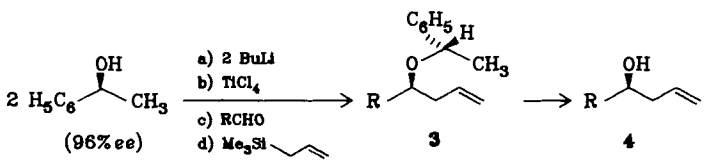
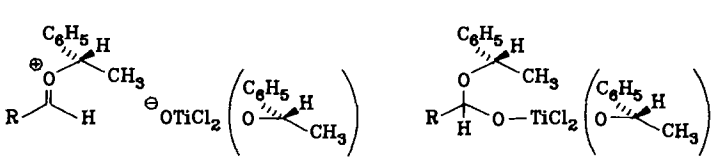


Table 2. Preparation of chiral homoallylic ethers **3** and homoallylic alcohols **4** [8, 11]. For conditions see Table 1.

	R	Yield [%]	*ds* [%]	*ee* [%]	$[\alpha]_D^{20}$ [a]
3a	$CH_2CH_2C_6H_5$	42	91.5		
3b	$CH(CH_3)_2$	50	90		
4a	$CH_2CH_2C_6H_5$	≈75		80 (*R*)	+16.9
4b	$CH(CH_3)_2$	≈75		78 (*S*)	− 2.8

[a] In $CHCl_3$, $c = 1$.

To the best of our knowledge, this is the first asymmetric synthesis of homoallylic alcohols via *open-chain* acetal derivatives.[12] It is not yet clear whether the observed asymmetric induction arises in the reaction of the oxonium ion **5** (addition) or of the hemiacetal derivative **6** (substitution).



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[8] The diastereomeric selectivities (% *ds*) of **3** were determined by GC (OV-1701, 18-m capillary) and by ^{13}C-NMR analysis of the crude products, the *ee* values by ^{19}F-NMR analysis of the Mosher 2-methoxy-2-phenyl-2-trifluoromethylacetic (MTPA) esters.
[9] Twice as many diastereomeric intermediates **5** and **6** can be formed with racemic than with enantiomerically pure 1-phenylethanol (two vs. one for **5** and four vs. two for **6**).
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A New Type of Sandwich Complex Formed by Ag^I and $[Pt_3(\mu_2\text{-}CO)_3(PiPr_3)_3]$**

By *Alberto Albinati, Klaus-Hermann Dahmen, Antonio Togni,* and *Luigi M. Venanzi**

Although many homo- and heteronuclear cluster compounds of gold are known,[1] silver-containing clusters are uncommon.[2] *Briant* et al.[3] recently reported the formation of a gold-platinum cluster in which $[Au\{P(c\text{-}C_6H_{11})_3\}]^+$ caps the Pt_3 fragment $[Pt_3(\mu_2\text{-}CO)_3\{P(c\text{-}C_6H_{11})_3\}_3]$.[4] Fragments of the type $[Pt_3(CO)_3L_3]$ are recurrent building blocks in platinum cluster chemistry[5] and can form sandwich-type complexes in which the central unit can be either Hg or Hg_2, e.g., **1**.[6] We describe here the preparation and X-ray crystal structure of the sandwich complex **2** in which two Pt_3 fragments are joined by Ag^+.

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$[Hg_2\{Pt_3(\mu_2\text{-}CO)_3(PPh\mathit{i}Pr_2)_3\}_2]$ **1**
$[Ag\{Pt_3(\mu_2\text{-}CO)_3(P\mathit{i}Pr_3)_3\}_2](CF_3SO_3)$ **2**

Complex **2** is obtained in 65% yield as air-stable, dark-red prismatic crystals[7] on addition of ca. 1.2 equivalents of $AgCF_3SO_3$ to a CH_2Cl_2 solution of $[Pt_3(CO)_3(P\mathit{i}Pr_3)_3]$. The structure of **2**[8] consists of discrete cations and $CF_3SO_3^-$ anions. The cations (Fig. 1) consist of two Pt_3 fragments joined by a Ag^+ ion placed between them on a crystallographic inversion center. Therefore, the two Pt_3 fragments have a staggered configuration. The structure of the cation is distorted antiprismatic, since two of the Ag-Pt distances to each triangle (2.828(2) Å) are shorter than the third (2.853(2) Å). This type of distortion is observed also in the Hg_2Pt_6 cluster **1**.[6] The Pt-Pt distances within each triangular unit are not equivalent, two of them being longer than those found in the parent Pt_3 cluster[4] and in **1**.[6] The CO ligands symmetrically bridge the platinum atoms and are slightly bent towards the silver ion, while the phosphane ligands bend away from the Pt_3 plane. The mean deviations of the oxygen and phosphorus atoms from this plane are 0.8 and 0.9 Å, respectively.

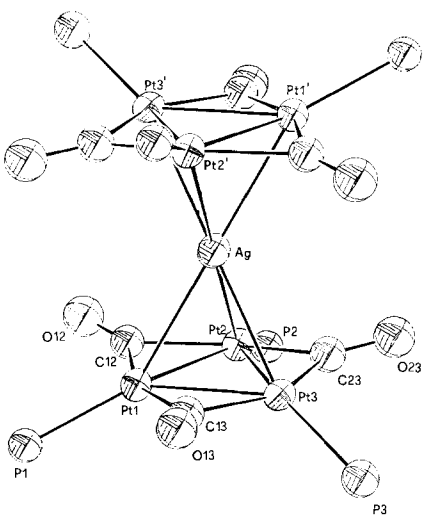


Fig. 1. ORTEP diagram of the structure of the cation of **2** in the crystal [8]. Selected bond lengths [Å] and angles [°]: Ag-Pt1 2.853(2), Ag-Pt2 2.825(2), Ag-Pt3 2.831(2), Pt1-Pt2 2.668(2), Pt1-Pt3 2.657(2), Pt2-Pt3 2.672(2), average Pt-P 2.28(1), average Pt-C 2.00(8); Pt1-Pt2-Pt3 59.68(5), Pt1-Pt3-Pt2 60.08(5), Pt2-Pt1-Pt3 60.24(5), Pt1-Ag-Pt2 56.05(3), Pt1-Ag-Pt3 55.74(3), Pt2-Ag-Pt3 56.38(3).

The ^{31}P- and ^{195}Pt-NMR data are consistent with this structure if one assumes rapid rotation of the Pt triangles on the NMR time scale. The values of the chemical shift and coupling constants[9] fall within the expected ranges.[10] The IR spectrum shows three bands in the carbonyl region.[11]

Sandwich complexes of type **2** can be obtained with several phosphanes (e.g., $PPh\mathit{i}Pr_2$), and clusters of the type $[Pt_3(CO)_3L_3]$ react also with other metal ions (e.g., Cu^+ and Cd^{2+}), giving products that are analogous to **2**.[12] Thus, there appears to be an extensive coordination chemistry based on Pt_3-cluster units.

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[7] Satisfactory C, H, Ag, and Pt elemental analyses as well as Ag/P and Ag/S ratios (determined by X-ray fluorescence) were obtained.

[8] **2**: monoclinic, $P2_1/c$, $a=13.277(4)$, $b=25.413(5)$, $c=12.712(3)$ Å, $\beta=81.27(4)°$, $V=4239.5$ Å^3, $Z=2$. Philips PW 1100 diffractometer, $Mo_{K\alpha}$, $2\theta\leq 37.0°$, $\theta/2\theta$ scan (0.04° s^{-1}), constant scan-width of 1.20°. 2527 observed reflections ($I\geq 3\sigma(I)$). Patterson and Fourier methods, anisotropic temperature factors for Ag, Pt, and P, isotropic factors for the other atoms. The $CF_3SO_3^-$ anions are strongly disordered over many positions and their contributions were not taken into account at this stage of the refinement, which gives $R=0.078$. However, this does not affect the main features of the cation.

[9] ^{19}F-NMR (84.66 MHz, $CFCl_3$ ext., [D$_6$]acetone): $\delta=-79.25$ ($AgCF_3SO_3$: $\delta=-78.8$). The NMR spectra of **2** are similar to those found for $[Pt_3(CO)_3L_3]$ [A. Moor, P. S. Pregosin, L. M. Venanzi, *Inorg. Chim. Acta 48* (1981) 153] but show the additional splittings due to the ^{107}Ag and ^{109}Ag isotopes: $^{31}P\{^1H\}$-NMR (101.25 MHz, H_3PO_4 ext., [D$_6$]acetone, ca. 300 K): $\delta=61$. $^1J(PtP)=5100$, $^2J(PtP)=316$, $^2J(^{107}AgP)=36$, $^2J(^{109}AgP)=42$, $^3J(PP)=22.5$ Hz; $^{195}Pt\{^1H\}$-NMR (53.53 MHz, K_2PtCl_6 ext., [D$_6$]acetone): $\delta=-4776$, $^1J(PtPt)=2136$, $^1J(^{107,109}AgPt)=190$ Hz (br.).

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[11] In nujol: $\nu=1855$ (w), 1799 (vs), 1762 (m) cm^{-1}. Bands due to $CF_3SO_3^-$ (in KBr) are observed at $\nu=1270$ (s), 1220 (m), 1145 (m), and 1030 (m) cm^{-1}.

[12] L. M. Venanzi, K.-H. Dahmen, unpublished results.

Novel High-Nuclearity HgCoRu and HgCoFe Sandwich Complexes. Synthesis and Structure of $[Hg\{RuCo_3(\mu\text{-}CO)_3(CO)_9\}_2]$**

By *Pierre Braunstein,* Jacky Rosé, Antonio Tiripicchio,* and *Marisa Tiripicchio Camellini*

The isoelectronic character of Au^I and Hg^{II} accounts for the structural analogy found between heteronuclear metal-metal bonded complexes of these ions.[1] A particularly interesting and rapidly expanding class of mixed-metal clusters is that in which the $[AuPR_3]^{\oplus}$ ion, isolobal with $H^{\oplus}$, caps the triangular face of a transition metal cluster.[2] The first examples of a similar bonding mode for the isolobal $[HgX]^{\oplus}$ ion have recently been reported for X = Br[3] and $X=Co(CO)_4$.[4] The divalent $Hg^{2\oplus}$ ion has now been found to react with the anionic clusters $[MCo_3(CO)_{12}]^{\ominus}$ (M = Fe, Ru) with formation of the novel sandwich complexes **1** and **2**. In particular, the nonanuclear $Hg(RuCo_3)_2$ cluster is formed in 60% yield as stable black-green crystals[5] upon addition of 2 equivalents of $K[RuCo_3(CO)_{12}]$ to $HgBr_2$ in CH_2Cl_2. It is noteworthy that **2** is also formed—

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along with $HgBr_2$—by ligand disproportionation of $BrHg[RuCo_3(CO)_{12}]$ (CH_2Cl_2, 7 d, 5 °C); **2** precipitates directly in the form of crystals that are suitable for X-ray structure analysis.

$[Hg\{MCo_3(\mu\text{-}CO)_3(CO)_9\}_2]$ **1**, M = Fe; **2**, M = Ru

The structure[6] of the $Hg(RuCo_3)_2$ cluster **2** consists of discrete molecules having an imposed C_i symmetry, in which two $RuCo_3$ tetrahedral units are joined by a $Hg^{2\oplus}$ ion placed sandwiched between the Co_3 planes, at 2.382(1) Å from each plane. Alternatively, this structure can be viewed as consisting of two trigonal bipyramidal metal cores $HgCo_3Ru$ sharing a common vertex. Since $Hg^{2\oplus}$ is on a crystallographic inversion center, the $RuCo_3$ units are staggered and $Hg^{2\oplus}$ is located in a strongly distorted octahedral cavity. The Co–Hg distances range from 2.777(2) to 2.816(2) Å. The other metal-metal distances and the disposition of the carbonyl ligands are similar to those found in related $RuCo_3$ clusters in which the Co_3 face is capped by $[CuPPh_3]^{\oplus}$, $[AuPPh_3]^{\oplus}$[7] or $[HgCo(CO)_4]^{\oplus}$.[4] The structure of **2** can also be compared with that of bimetallic $Hg(Pt_3)_2$ clusters.[8]

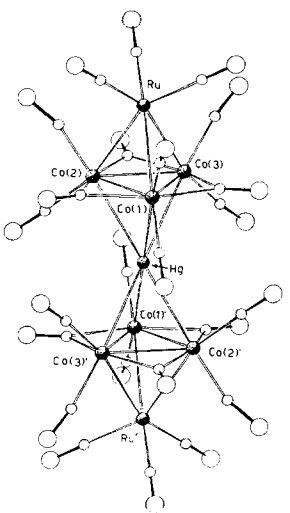


Fig. 1. Crystal structure of **2**. Selected bond distances [Å] and angles [°]: Hg-Co(1) 2.816(2), Hg-Co(2) 2.791(3), Hg-Co(3) 2.777(2), Ru-Co(1) 2.687(3), Ru-Co(2) 2.681(3), Ru-Co(3) 2.689(4), Co(1)-Co(2) 2.522(2), Co(1)-Co(3) 2.547(2), Co(2)-Co(3) 2.520(2), Co(1)-Hg-Co(2) 53.5(1), Co(1)-Hg-Co(3) 54.2(1), Co(2)-Hg-Co(3) 53.8(1), Co(1)-Ru-Co(2) 56.0(1), Co(1)-Ru-Co(3) 56.6(1), Co(2)-Ru-Co(3) 56.0(1), Co(2)-Co(1)-Co(3) 59.6(1), Co(1)-Co(3)-Co(2) 59.7(1), Co(1)-Co(2)-Co(3) 60.7.

Preliminary reactivity studies indicate that heating $Hg(FeCo_3)_2$ in toluene leads to metal-metal bond cleavage with formation of, *inter alia*, metallic Hg and $[(\eta^6\text{-toluene})Co_4(CO)_9]$.[9] Interestingly, Et_4NCl reacts with **1** in CH_2Cl_2 with extrusion of $Hg^{2\oplus}$, affording $Et_4N[FeCo_3(CO)_{12}]$[10] and $HgCl_2$. This opens the way to a number of double-exchange reactions.

$n Bu_4N[FeCo_3(\mu\text{-}CO)_3(CO)_9\{\mu_3\text{-}AuCo(CO)_4\}]$ **3**
$[RuCo_3(\mu\text{-}CO)_3(CO)_9\{\mu_3\text{-}HgCo(CO)_4\}]$ **4**

Attempts to synthesize analogous Au-complexes, using the methods developed above, by reaction of $n Bu_4N[AuI_2]$[11] with $K[FeCo_3(CO)_{12}]$ (THF/H_2O, 0 °C, molar ratio 1 : 2) led to formation of the FeCoAu-cluster **3**, the proposed structure of which is supported by the spectroscopic data presently available[12] and by analogy with the isoelectronic RuCoHg cluster **4**.[4]

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CAS Registry numbers:
1, 97878-85-8; **2**, 97878-86-9; **3**, 97878-88-1; $K[FeCo_3(CO)_{12}]$, 90636-09-2; $[(B)Co_3(CO)_9]$ (B = η^6-toluene, 32698-87-6; $Et_4N[FeCo_3(CO)_{12}]$, 53509-36-7; $K[RuCo_3(CO)_{12}]$, 97878-89-2; $BrHg[RuCo_3(CO)_{12}]$, 97878-90-5; $n\text{-}Bu_4N[AuI_2]$, 50481-03-3; Fe, 7439-89-6; Hg, 7439-97-6; Ru, 7440-18-8; Co, 7440-48-4.

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[5] Correct elemental analysis. **1**: IR (KBr): ν = 2071 (s), 2025 (vs), 1980 (sh), 1920 (w), 1870 (s) cm^{-1}. UV (CH_2Cl_2): λ_{max} = 330, 616 nm; **2**: IR (KBr): ν = 2083 (s), 2033 (vs), 1972 (m), 1912 (w), 1879 (s) cm^{-1}. UV (CH_2Cl_2): λ_{max} = 326, 365, 548 nm.
[6] Philips PW1100 diffractometer; C2/c, $Z = 4$, $a = 14.812(8)$, $b = 9.266(6)$, $c = 26.397(12)$ Å, $\beta = 94.75(2)°$, $3 \le \theta \le 28°$, 3873 independent reflections, 2574 with $I \ge 3\sigma(I)$, $Mo_{K\alpha}$ radiation, $R = 0.050$, $R_w = 0.068$. Further details of the crystal structure investigation are available on request from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2, on quoting the depository number CSD 51490, the names of the authors, and the full citation of the journal.
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[12] IR (Nujol): ν = 2067 (m), 2010 (vs), 1984 (s), 1973 (s), 1967 (sh), 1925 (m), 1905 (s), 1855 (m), 1813 (m), 1790 (s) cm^{-1}; UV (CH_2Cl_2) λ_{max} = 505, 643 nm.

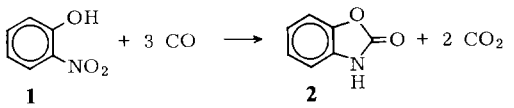
Reductive Carbonylation of *o*-Nitrophenol with a Fe-Pd Cluster-Derived Heterogeneous Catalyst; CO Migration in $[FePdPt(CO)_4(Ph_2PCH_2PPh_2)_2]$**

By *Pierre Braunstein,* Jacques Kervennal,* and *Jean-Luc Richert*

Mixed-metal cluster-derived (MMCD) heterogeneous bimetallic catalysts are of great interest at present because of their improved catalytic properties over those of conventionally prepared catalysts.[1,2] We have recently reported the selective carbonylation of nitrobenzene to phenyl isocyanate,[2] using a catalyst obtained from $[Pd_2Mo_2(\eta\text{-}C_5H_5)_2(CO)_6(PPh_3)_2]$.[3] We have subsequently become interested in Fe-Pd catalysts for the carbonylation of *o*-nitrophenol **1** to benzoxazol-2-one **2**, which is a structural element of herbicides[4] and has a high synthetic potential.

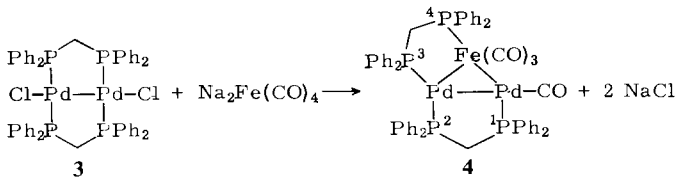
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1 2

For reasons detailed previously,[2] we therefore attempted to synthesize neutral, low-valent mixed Fe-Pd carbonyl clusters stabilized by bridging ligands such as $Ph_2PCH_2PPh_2$(dppm). This stabilization should prevent cluster fragmentation during the impregnation of the inorganic support (catalyst preparation); even with thermodynamically stable clusters, modifications of the metal core can occur under very mild impregnation conditions.[5]

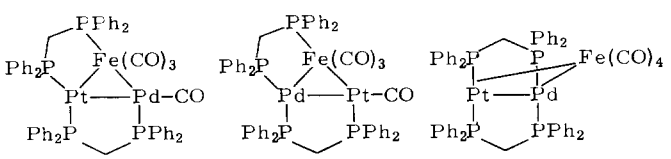


3 4

The reaction of the Pd_2 complex **3** with $Na_2Fe(CO)_4$ afforded the $FePd_2$ cluster **4**,[6] the structure of which was established on the basis of analytical and spectroscopic data[6] and by comparison with related systems.[8]

The catalyst derived from cluster **4** effects the reductive carbonylation of *o*-nitrophenol **1** to the benzoxazolone **2** better (i.e., with higher conversion and higher selectivity) than the conventional catalyst (prepared by mixing iron oxalate and palladium acetate) (Table 1). Addition of pyridine is found beneficial and the main properties of the MMCD catalyst are retained on repeated use. To our knowledge, this is, together with a patent,[9] the first reported use of heterogeneous catalysts for this reaction.

By analogy to the reaction **3**→**4**, the mixed-metal complex $[PdPtCl_2(dppm)_2]$ afforded a mixture of the two isomers **5a** and **5b**.[6] We and *Seddon* et al.[10] have independently found that **5a** and **5b** cannot be separated by either column chromatography or fractional crystallization. This could be due either to the very similar physico-chemical properties or to the rapid interconversion of the two isomers.



5a 5b 5c

However, if excess $Na_2Fe(CO)_4$ is used and the work-up is carried out at low temperatures,[6] **5a** can be obtained as the *only* isomer in 98% yield. In tetrahydrofuran (THF) at room temperature, **5a** immediately isomerizes to **5b**; a 1 : 1 mixture is obtained at equilibrium (18 h at 17 °C). This process can be followed using ^{31}P-NMR spectroscopy or IR spectroscopy (increase in intensity of the band at 2000 cm^{-1} due to the CO bonded to Pt in **5b**). The transformation **5a**→**5b** cannot be reversed by decreasing the temperature. Therefore, **5a** is the kinetically formed isomer and the thermodynamic preference for **5b** is only very small in view of the position of the **5a** ⇌ **5b** equilibrium.

This unique isomerization under very mild conditions may contribute to a better understanding of the chemistry of bi- and polynuclear as well as A-frame complexes. A possible (solvent-stabilized) intermediate could be the symmetrical complex **5c** in which the $Fe(CO)_4$ fragment would occupy the position of the isolobal CH_2 group in the known methylene-bridged A-frame complexes. Facile metal-phosphorus bond breaking and carbonyl migration appear to occur, allowing insertion of the $Fe(CO)_3$ group into the Pd–P (**5a**) or Pt–P bond (**5b**). The net result of this process is a very facile CO migration between two different adjacent metal centers, which is of relevance to the activation of bimetallic catalysts and CO chemistry.

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1, 88-75-5; **2**, 59-49-4; **3**, 64345-29-5; **4**, 97467-21-5; **5a**, 87564-92-9; **5b**, 87564-91-8; **7**, 82307-36-6; $Fe_2(C_2O_4)_3$, 2944-66-3; $Pd(OAc)_2$, 3375-31-3; $Na_2Fe(CO)_4$, 14878-31-0.

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[6] Experimental procedure: All reactions and operations, including the distillation of the solvents, were carried out under argon. **4**: $Na_2Fe(CO)_4$ (0.180 g, 0.84 mmol) and **3** (0.770 g, 0.73 mmol) were cooled to −78 °C and 125 mL of THF (−78 °C) was added. The suspension was stirred and the temperature allowed to rise slowly to 0 °C. After concentration of the green solution to ca. 10 mL and addition of pentane (150 mL, −78 °C) with stirring, the solution was filtered. The solid was washed with pentane, distilled water, ethanol, and again pentane, and dried in vacuo, affording **4** as a green powder (0.590 g, 70%); m.p. 160 °C (decomp.). Correct elemental analysis (C, H, Fe, P, Pd). IR (THF): ν(CO) = 2024 s, 1964 w, 1939 w, 1916 s, 1868 w, 1826 s. ^{31}P{^{1}H}-NMR (81 MHz, THF/C_6D_6): $\delta = -9.7$ (P^1), -7.1 (P^2), -5.3 (P^3), 52.7 (P^4), $J(P^1P^2) = 33$, $J(P^1P^3) = -2$, $J(P^1P^4) = 42$, $J(P^2P^3) = 64$, $J(P^2P^4) = 26$, $J(P^3P^4) = 26$ Hz. Detailed assignments resulted from spectral simulation. Starting from $[PdPtCl_2(dppm)_2]$ [7], under similar conditions, a mixture of **5a** and **5b** was obtained. When $Na_2Fe(CO)_4$ was used in 50% excess, the reaction mixture maintained at

Table 1. Catalytic reductive carbonylation of *o*-nitrophenol **1** to benzoxazol-2-one **2**.

Experiment	Catalyst [a]	**1** [g]	Catalyst [g]			Mole ratio		Reaction conditions [b]		Conversion [%]	Selectivity [c] [%]
			total	Fe	Pd	**1**/Fe	**1**/Pd	T [°C]	t [h]		
1	$Pd(OAc)_2 + Fe_2(C_2O_4)_3/SiO_2$	6.95	3.7	0.019	0.056	151	96	200	5	40	90
2	**4**/SiO_2	6.95	2.75	0.014	0.055	203	97	200	4	98.5	95
3	catalyst recovered from experiment 2	6.5	2.6	0.013	0.052	201	96	200	5	80	94.5

[a] The impregnation was carried out by the spray method [2]. Catalyst for expt. 1: $Pd(OAc)_2$ (0.442 g, 1.88 mmol) and $Fe_2(C_2O_4)_3$ (0.416 g, 1.11 mmol) were mixed at 50 °C in AcOH (600 mL) and H_2O (150 mL). This mixture was used to impregnate 10 g of SiO_2 (Shell), which was then dried at 350 °C for 16 h. Catalyst for expt. 2: **4** (1 g) in THF (100 mL) was used to impregnate 7 g of SiO_2, which was then dried at 450 °C for 16 h. [b] Solvent: *o*-dichlorobenzene (expt. 1), chlorobenzene (expts. 2 and 3). Total volumes: 100 mL. Pyridine (1 g) was added in all experiments. Initial CO pressure: 200 atm. 500-mL Hastelloy C reactor with magnetic stirring. [c] The selectivity is defined as the ratio **2** produced to **1** reacted.

−20°C for 24 h, and the work-up carried out below −40°C, only **5a** was formed (98% yield). Complexes **5a** and **5b** have spectroscopic features similar to **4**; the isomers can be easily distinguished by their ^{31}P-^{195}Pt coupling patterns in the $^{31}P\{^1H\}$-NMR spectrum. Correct elemental analyses were obtained.

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New Donor-Substituted Vinyl- and Alkynylcyclopropanes as Synthetic Building Blocks**

By *Schahab Keyaniyan, Michael Apel, Joe Pierce Richmond,* and *Armin de Meijere**

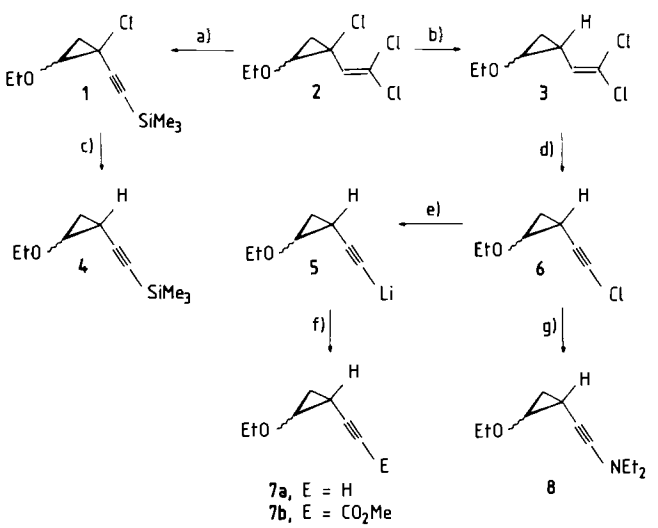
Dedicated to Professor Wolfgang Lüttke on the occasion of his 65th birthday

The vinylcyclopropane–cyclopentene rearrangement is one of the most versatile methods for the annelation of five-membered rings.[1] Enhancement of the rate of this reaction by electron-donating substituents in the 1-[2] and especially in the 2-position[3] of the cyclopropane ring is in the extreme case of 2-vinylcyclopropanolates so pronounced that cyclization occurs at room temperature. In order to extend the usefulness of the (halovinyl)-[4] and alkynylcyclopropanes[5] developed by us, we have sought access to the corresponding donor-substituted building blocks, examples of which include compounds **3**, **11** and **7**.

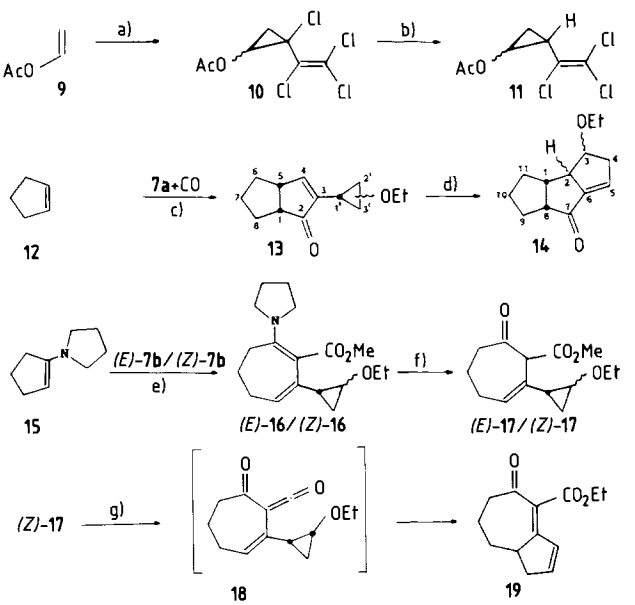
Ethyl vinyl ether and other enol ethers polymerize upon heating with tetrachlorocyclopropene. On the other hand, α-elimination of 1,1,3,3-tetrachloropropene produced the carbene 1,3,3-trichloro-2-propenylidene, which added to ethyl vinyl ether to give 1-chloro-1-(2,2-dichlorovinyl)-2-ethoxycyclopropane **2** (46%, $E/Z = 2.0$)[4c] (Scheme 1). As in the case of 1-chloro-1-(trichlorovinyl)cyclopropanes,[5] reaction of **2** with MeLi followed by quenching with electrophiles affords substituted alkynylcyclopropanes such as **1** (57%, with Me_3SiCl).[6] However, the yield upon reduction of **1** to **4** was disappointing (30%).

A substantial improvement was achieved by the newly developed sequence in which the ring chlorine in **2** is selectively removed by ultrasonication[7] with zinc/copper to yield **3** (82%, $E/Z = 1.0$) without retention of configuration.[8] The dehydrochlorination of **3** to give the chloroacetylene **6** was best achieved[9] (77%, $E/Z = 1.5$) with potassium hydroxide in CH_2Cl_2/dibenzo-[18]crown-6.[10] Reaction of **6** with lithium dialkylamides affords ynamines[11] such as **8** (38%, not optimized, $E/Z = 1.0$). Halogen-metal exchange followed by substitution with electrophiles converted **6** *via* **5** into synthetically interesting building blocks, the 1-alkynyl-2-ethoxycyclopropanes **7** (**7a**, 59%, $E/Z = 0.5$; **7b**, 78%, $E/Z = 0.83$).[6] The diastereomers of **7b** could be separated by chromatography on silica gel.

Surprisingly, the addition of thermally ring-opened tetrachlorocyclopropene[4a,b] to vinyl acetate was achieved *without* polymerization and afforded **10** (85%, $E/Z = 0.61$), which could be selectively reduced to 2-(trichlorovinyl)cyclopropyl acetate **11**, a potential precursor to building blocks analogous to **7** and **8** (Scheme 2).



Scheme 1. a) 1) MeLi, tetrahydrofurane (THF), −35°C; a) Me_3SiCl, −35°C→RT. b) Zn/Cu, THF/H_2O (8/1), ultrasonication, 65°C, 20 h. c) $LiAlH_4$, THF, Δ, 10 h. d) KOH, CH_2Cl_2, dibenzo-[18]crown-6, 24 h. e) *n*BuLi, THF/*n*-hexane, −78°C. f) MeOH (→**7a**); $ClCO_2Me$ (→**7b**). g) $LiNEt_2$, Et_2O, −20°C.



Scheme 2. a) Tetrachlorocyclopropene, 155°C, 36 h. b) Zn/Cu, THF/H_2O (8/1), ultrasonication, 65°C, 20 h. c) $Co_2(CO)_8$, CO, 120°C, 48 h. d) 600°C, 0.1 torr, 0.09 s. e) (*E*): 125°C, (*Z*): 135°C. f) Et_2O, 2 N HCl, RT. g) 250°C, 0.02 torr, 0.8 s.

Cycloadditions to the triple bond of such alkynylcyclopropanes afford vinylcyclopropanes[12] in which the vinyl group is incorporated into a ring and whose rearrangement to a cyclopentene should be facilitated by the 2-ethoxy or the 2-acetoxy function.

Thus reaction of (*E*/*Z*)-**7a** with cyclopentene **12** and $Co_2(CO)_8$ under CO (cf. [13]) followed by chromatographic separation gave a 1 : 1.6 mixture (30%) of both diastereomers of 3-(2-ethoxycyclopropyl)-*cis*-bicyclo[3.3.0]oct-3-en-2-

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one, (*E*)-**13**[6] with (*E*) configuration on the 3-membered ring and a 1:1 mixture (4%) of both diastereomers of (*Z*)-**13**. Reaction of pure (*E*)-**7b** with 1-cyclopentenylpyrrolidine **15** at 125°C furnished the cycloheptadiene derivative (*E*)-**16** (55%); (*Z*)-**7b** was converted at 135°C into (*Z*)-**16** (47%). The enamines **16** can be hydrolyzed to the methyl 7-oxo-2-cycloheptene-1-carboxylates (*E*)-**17** (16%) and (*Z*)-**17** (37%),[6] respectively.

Upon flash vacuum pyrolysis, **13** is smoothly converted into the linearly annelated triquinane **14**[6] (39% after chromatography on SiO_2).[13] Product **14** consisted of three stereoisomers in a ratio of 4:2:1, whose separation thus far has been achieved only by capillary gas chromatography. According to ^{1}H-, ^{1}H,H-COSY- and ^{1}H,^{13}C-correlation-NMR spectra, the ratio of *anti*- and *syn*-configurated isomers is 5:2 or 3:4. The cycloheptene derivative, (*Z*)-**17**, rearranges especially easily; evidently the main reason for this is that the β-ketoester splits off methanol above 250°C, forming the ketoketene **18**,[14, 15] which, due to favorable stereochemistry, can cyclize with ethoxy-group migration to give ethyl 3-oxobicyclo[5.3.0]deca-1,9-diene-2-carboxylate **19**.

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[6] All new compounds were unequivocally characterized by their IR, ^{1}H-NMR, and where necessary, ^{13}C-NMR spectra; in most cases satisfactory elemental analyses were obtained. Examples: **13**: IR (film): ν=3030–2850 (C–H), 1700 (C=O), 1630 (C=C), 1200–1020 (C–O) cm^{-1}; ^{1}H-NMR (270 MHz, $CDCl_3$): δ=0.90–1.00 (m, 1H, 3′-H$_a$), 1.10–1.20 (m, 1H, 3′-H$_b$), 1.20 (t, ^3J=7.0 Hz, 3H, 2″-H), 1.50–1.95 (m, 7H, 6,7,8,1′-H), 2.70–2.80 (m, 1H, 1-H), 3.10–3.20 (m, 1H, 5-H), 3.25–3.35 (m, 1H, 2′-H), 3.48+3.59 (q+mc, 2H, int. ratio 1:1.6, 1″-H), 6.74+6.77 (2d, 1H, ^3J=3.5 Hz, int. ratio 1.6:1, 4-H); MS (70 eV): *m/z* 206 (M^+). – **14**: IR (film): ν=3030–2850 (C–H), 1700 (C=O), 1620 (C=C), 1150–1020 (C–O) cm^{-1}; ^{1}H-NMR (400 MHz, C_6D_6): δ=0.83–2.00 (m, 6H, 9,10,11-H), 1.04, 1.10, 1.13 (3t, ^3J=7.0 Hz, 3H, int. ratio 1:2:4, 2′-H), 2.00–2.40 (m, 1H, 8-H), 2.40–2.70 (m, 3H, 1,4-H), 2.64–3.32 (m, 3H, 2,1′-H), 3.66, 3.72, 3.88 (3 mc, 1H, int. ratio 1:2:4, 3-H), 6.01, 6.08, 6.17 (3mc, 1H, int. ratio 2:4:1, 5-H); MS (70 eV): *m/z* 206 (M^+)–(*Z*)-**17**: IR (film): ν=3400 (O–H), 3030–2850 (C–H), 1640 (C=O), 1590 (C=C), 1240, 1030 (C–O) cm^{-1}; ^{1}H-NMR (270 MHz, C_6D_6): δ=0.61 (ddd, ^2J=5.8 Hz, ^3J(1′,3′*E*)=9.6 Hz, ^3J(2′,3′*E*)=6.2 Hz, 1H, 3′-H(*E*)), 0.70 (ddd, ^3J(1′,3′*Z*)=7.0 Hz, ^3J(2′,3′*Z*)=3.6 Hz, 1H, 3′-H(*Z*)), 1.02 (X component of an ABX$_3$ system, ^3J(AX)=^3J(BX)=7.0 Hz, 3H, OCH$_2$CH_3), 1.75–2.03 (m, 5H, 5,6,1′-H), 2.25–2.58 (m, 2H, 4-H), 3.04 (ddd, ^3J(1′,2′)=6.4 Hz, 1H, 2′-H), 3.30 (AB component of an ABX$_3$ system, 2H, OCH_2CH$_3$), 3.36 (s, rel. int. 0.5, 1-H), 3.37 (s, 3H), 5.93 (mc, 1H, 3-H), 7.44 (bs, rel. int. 0.5, enol-H). – **19**: IR (film): ν=3030–2830 (C–H), 1710, 1640 (C=O), 1600 (C=C), 1220, 1180, 1020 (C–O) cm^{-1}; ^{1}H-NMR (270 MHz, C_6D_6): δ=0.84 (mc, 1H, 6-H$_a$), 0.96 (X component of an ABX$_3$ system, ^3J(AX)=^3J(BX)=7.0 Hz, 3H, 3′-H), 1.08–1.20 (m, 2H, 5-H$_a$, 6-H$_b$), 1.35 (mc, 1H, 5-H$_b$), 1.50 (dddd, ^2J=–19.2 Hz, ^3J(8a,7)=1.8 Hz, ^3J(8a,9)=2.2 Hz, ^3J(8a,10)=2.8 Hz, 1H, 8-H$_a$), 2.03–2.18 (m, 2H, 4-H$_a$, 8-H$_b$), 2.27 (mc, ^2J=–15.2 Hz, 1H, 4-H$_b$), 4.11 (AB component of an ABX$_3$ system, 2H, 2′-H), 5.96 (ddd, ^3J(*cis*)=5.5 Hz, ^4J(10,8a)=^4J(10,8b)=2.8 Hz, 1H, 10-H), 6.81 (ddd, ^3J(9,8a)=^3J(9,8b)=2.2 Hz, 9-H); MS (70 eV): *m/z* 220 (M^+), 151 ($M-C_2H_5$)$^+$.

[7] Simple heating of **2** with Zn/Cu couple in THF/H_2O did not lead to reduction as described for 7,7-dibromonorcarane (R. M. Blankenship, K. A. Burdett, J. S. Swenton, *J. Org. Chem. 39* (1974) 230). The selective reduction of **2** with Zn/Cu in a laboratory cleaning bath (Bandelin, Mod. RK 225) is a further example of the utilization of ultrasound-activated zinc in organic synthesis (cf. B.-H. Han, P. Boudjouk, *J. Org. Chem. 47* (1982) 751, 5030).

[8] Similar reduction of (*Z*)-**2** gave a 1:1 mixture of (*E*)- and (*Z*)-**3**.

[9] With the method described for other chloroacetylenes (LiNEt$_2$, Et$_2$O, –78°C: J. Villieras, P. Perriot, J. F. Normant, *Synthesis* 1975, 458) the maximum yield of **6** was 56%.

[10] Based on the method of: E. V. Dehmlow, M. Lissel, *Liebigs Ann. Chem. 1980*, 1; *Tetrahedron 37* (1981) 1653.

[11] Cf. L. Brandsma: *Preparative Acetylenic Chemistry*, Elsevier, Amsterdam 1971, p. 85; S. Y. Delavarenne, H. G. Viehe in H. G. Viehe (Ed.): *Chemistry of Acetylenes*, Marcel Dekker, New York 1969.

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[13] Analogously synthesized compounds of type **13** without electron-donating substituents required up to 150°C higher pyrolysis temperatures under otherwise identical conditions; J. P. Richmond, T. Liese, A. de Meijere, unpublished results.

[14] Cf. C. Wentrup, K.-P. Netsch, *Angew. Chem. 96* (1984) 792; *Angew. Chem. Int. Ed. Engl. 23* (1984) 802.

[15] α-Ketoketenes of type **18** were detected in the pyrolysis of **17**-analogues without the ethoxy substituent (cf. [12]).

Heterogeneous Redox Catalysis on Ti/TiO_2 Cathodes—Reduction of Nitrobenzene**

By *Fritz Beck** and *Wolfgang Gabriel*

Reductions with low valency titanium compounds are well known in organic chemistry. Typical examples are, inter alia, the reduction of nitro compounds with Ti^{II}[1][2] and the reductive dimerization of ketones to olefins with Ti^{II}.[3] Stoichiometric quantities of reducing agent were used in these reactions. The selectivity of the processes is explained in terms of a complexation of the reactants with the titanium species. Since large amounts of reagents such as $TiCl_3$ are not easy to handle, it was suggested that the reduction be carried out on an inert cathode in the presence of a dissolved redox mediator such as $(TiO)SO_4$[4a] or $TiCl_4$.[4b] We report herein on a further simplification, namely the oxidic Ti-redox system fixed to the surface of a Ti cathode.

The Ti/TiO_2 electrode was fabricated using a method employed in the production of ceramics.[13] As shown by the cyclic voltammograms 1a, b in Figure 1, reduction of the surface layer starts at ca. $U_H = -0.1$ V with respect to a standard hydrogen electrode. This corresponds to the equilibrium potential for Reaction (a):[5]

$$Ti(OH)_4 + e^{\ominus} + H^{\oplus} \longrightarrow Ti(OH)_3 + H_2O \qquad (a)$$

At more negative potentials, further reduction processes come into operation, with a current maximum at $U_H = -0.73$ V and a shoulder at $U_H = -0.65$ V. Whether $Ti^{IV/III}$ transitions, e.g. Reaction (b),

$$TiO_2 + H_2O + H^{\oplus} + e^{\ominus} \longrightarrow Ti(OH)_3,\ U_{H,O} = -0.79\ V \qquad (b)$$

or $Ti^{III/II}$ redox processes operate,[6] both of which are possible in this voltage range, cannot be decided with certainty. At still more negative potentials, cathodic evolution of hydrogen begins to take place (Fig. 1, g). The corresponding re-oxidation processes are detected cyclovoltammetrically. The TiO_2 layer is converted up to 2–20%, a relatively high value for a solid-state reaction, the conversion decreasing with increasing voltage scan rate. The redox processes can be repeated as often as desired. At higher pH val-

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ues all potentials shift to more negative values. Slopes of 47 to 56 mV/pH are indicative of the presence of protonated oxidized species on the electrode surface.[7]

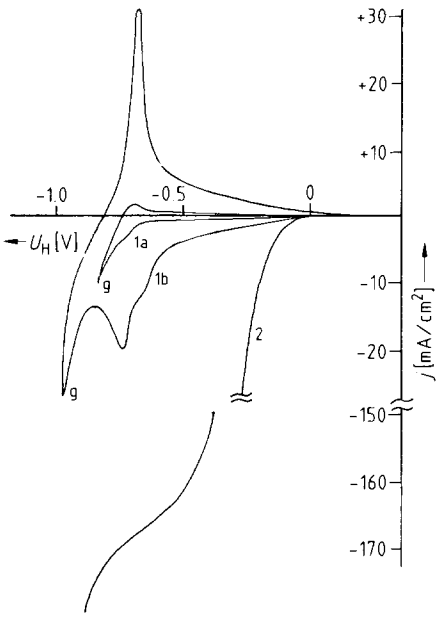


Fig. 1. Current/voltage curves at Ti/TiO_2 ceramic electrodes. 1a, b) In 1 M H_2SO_4, $v_s = 2$ and 50 mV s^{-1}, respectively. 2) 0.2 M nitrobenzene, 1 M H_2SO_4 in 70% (v/v) MeOH, $v_s = 5$ mV s^{-1}. 20 °C, stirring. v_s = voltage scan rate. H_2-evolution occurs at g.

Ti/TiO_2 electrodes prepared thermally by firing Ti metal sheet (10 min, 400–600 °C) in air do not exhibit these reversible redox processes before the evolution of hydrogen; in the same voltage range, only ca. 1% of the current density is reached, the cathode current significantly predominating.

Redox processes on Ti/TiO_2 electrodes prepared by anodization have been described in the literature;[8–11] they resemble those of the electrodes prepared by firing in air. The unusual behavior of our ceramic electrodes, particularly the much higher current densities, cannot be explained alone by a higher surface factor but rather in terms of an activation. Figure 1 also shows the current-voltage curve for the reduction of nitrobenzene on these electrodes (curve 2). The curve rises steeply at the point of reduction to $Ti(OH)_3$. It may therefore be assumed that we have here a further example of a heterogeneous redox catalysis.[7, 12] In the electrochemical step [Reaction (a)], Ti^{III} species are generated. These react in a chemical follow-up step with the organic depolarizer nitrobenzene to give aniline; $Ti(OH)_4$ is thereby recovered [Reaction (c)].

$$6\,Ti(OH)_3 + C_6H_5NO_2 + 4\,H_2O \xrightarrow{k} 6\,Ti(OH)_4 + C_6H_5NH_2 \qquad (c)$$

The limiting current in Figure 1 is a pure diffusion limiting current, so that the chemical step [Reaction (c)] is not rate-determining. The electrodes should have a long lifetime, since TiO_2 and Ti_2O_3 are insoluble in acids.

Hitherto, primarily anodic oxidations via surface fixed oxides in various redox states have been described: $Ru^{III/IV}$,[13, 14] $Pb^{II/IV}$,[15] $Ni^{II/III}$,[16, 17] and $Cr^{III/VI}$.[7, 12]

Should the redox peak immediately before the start of cathodic H_2-evolution correspond to a change in valency $Ti^{III/II}$, then this electrode process (in acidic solution) should also proceed via heterogeneous redox catalysis. The chemical step

$$2\,TiO + H_2O \xrightarrow{k_1} Ti_2O_3 + H_2 \qquad (d)$$

is very rapid.[6] $Ti^{2\oplus}$ ions are extremely unstable in aqueous media.[6] In a more recent work[18] on the mechanism of the Ti/H_2 cathode, the acid-base interaction of the species involved with surface-bound TiO is taken into consideration, not however the redox behavior.

Experimental

Preparation of the electrodes: A 1 mm-thick titanium sheet (Contimet 35, Thyssen Edelstahlwerke, Krefeld) is treated for 1 h at 95 °C with 20% hydrochloric acid. This roughening or etching is a prerequisite for obtaining a sufficiently adhering TiO_2 layer. After rinsing with water and drying, a solution of titanium acetylacetonate (2.189 g) (titanium butoxide gives similar results) in conc. HNO_3 (5 mL) and H_2O (3 mL) (made up to 50 mL with isopropanol) is transferred onto the titanium sheet (with a painting brush in the case of large surface areas) in amounts of 10 μL/cm^2. After drying at 80 °C (10 min) the sheet is baked in air in a muffle furnace at 450 °C. After a total of three activation cycles a TiO_2 concentration of 5 μmol/cm^2 is present on the electrode. According to scanning electron microscope photographs the greyish layer has a rippled structure. The layer thickness is ca. 1 μm. A porous structure results from the electrochemical behavior of the layer. According to X-ray diffraction diagrams the TiO_2 is present in the anatase form. Reduction of nitrobenzene: A stirred solution of 0.2 M nitrobenzene and 1 M H_2SO_4 in 70% v/v methanol (2 L) was electrolyzed at 20 °C for 4 h at a current density of 5 A/dm^2, corresponding to a theoretical Faradayic conversion (6 F/mol) of 33%, using an activated Ti/TiO_2 cathode (Contimet 35, expanded metal with ten mashes per cm^2 (f = 1) and a total surface area of 107 cm^2). The lead anode was separated from the cathode by a alundum diaphragm. Cathode potential: $U_H = -0.23$ V. The yellow solution was neutralized with Na_2CO_3, extracted continuously with chloroform, and dried with Na_2SO_4. Aniline was detected by gas chromatography. Current yield: 70%. Nitrobenzene conversion: 65%. Since no evolution of H_2 was observed, other products must also have been formed.

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$C_6H_5NO_2$, 98-95-3; TiO_2, 13463-67-7; H_2, 1333-74-0; Ti, 7440-32-6.

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[18] E. J. Kelly, H. R. Bronstein, *J. Electrochem. Soc. 131* (1984) 2232.

Decabenzylgermanocene: Synthesis and Structure of a Monomeric, Air-Stable Germanocene**

By *Herbert Schumann,* Christoph Janiak, Ekkehardt Hahn, Jörg Loebel,* and *Jerold J. Zuckerman**

Decaphenylstannocene[1] has S_{10} symmetry with two parallel, staggered cyclopentadienyl rings and a stereochemically inert electron pair at Sn^{II}. It has not yet been determined whether the corresponding compounds of Ge^{II}[2] or Pb^{II}[2] have similar structures. In the germanocenes studied up to now, $(\eta^5\text{-}C_5H_5)_2Ge$,[3] $(\eta^5\text{-}CH_3C_5H_4)_2Ge$,[4] and $(\eta^5\text{-}C_5Me_5)_2Ge$,[5] on the other hand, the planes of the two cyclopentadienyl rings intersect at an angle of 34 to 50°; the compounds are very reactive.

We have now obtained decabenzylgermanocene, **1**, the first germanocene that, despite nonparallel cyclopentadienyl ring planes, is stable toward air. **1** is formed as large, pale yellow crystals by addition of germanium diiodide to a freshly prepared solution of pentabenzylcyclopentadienyllithium in tetrahydrofuran (THF).[6]

$$2\,C_5Bn_5H + 2\,LiC_4H_9 + GeI_2 \xrightarrow{THF} \underset{\mathbf{1}}{(C_5Bn_5)_2Ge} + 2\,LiI + 2\,C_4H_{10}$$

Bn: $C_6H_5CH_2$

The X-ray structure determination[7] shows that **1** (Fig. 1) is monomeric, and that the two cyclopentadienyl rings are bonded in η^5-fashion to Ge^{II}. The planes of the two cyclopentadienyl rings form an angle of 31°.

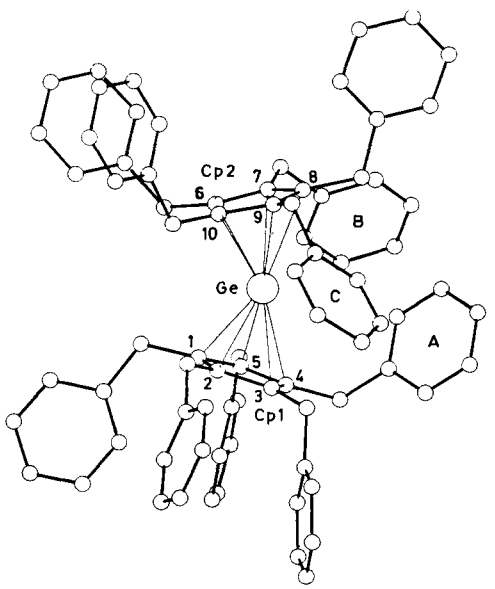


Fig. 1. Crystal structure of **1**. Selected bond lengths [Å] and bond angles [°]: Ge-Cp1 2.240(4), Ge-Cp2 2.288(4), Ge-C1 2.444(4), Ge-C2 2.429(3), Ge-C3 2.623(4), Ge-C4 2.636(4), Ge-C5 2.528(4), Ge-C6 2.489(4), Ge-C7 2.661(4), Ge-C8 2.723(4), Ge-C9 2.613(4), Ge-C10 2.441(4); Cp1-Ge-Cp2 163.1(1) (Cp: centroids of the cyclopentadienyl groups).

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Of the ten benzyl (Bn) groups, seven are directed away from and three toward the central atom. The phenyl ring plane of Bn group A (distances: Ge-C_{Ph} 3.635 to 5.509 Å) is thereby intersected by the assumed vector of the lone pair of electrons on the germanium atom. The two Bn groups B and C (distances: Ge-C_{Ph} 4.107 to 5.847 and 3.739 to 5.554 Å, respectively) flank the space occupied by the lone pair electrons.

This arrangement of ligands explains the unexpected stability of **1** toward atmospheric oxygen. The Bn groups form a protective shield not only for the reactive positions of the cyclopentadienyl rings, but also, particularly, for the central germanium atom. A comparable interaction between the lone pair of electrons of a divalent element of the fourth main group and a phenyl group has been found in $[\{(PhO)_2PS_2\}_2Sn]_2$.[8] In that case, too, a phenyl group is nearly perpendicular to the postulated vector of the lone pair electrons on tin, resulting also in unusual air-stability of the compound.

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[6] Experimental procedure: A solution of LiC_5Bn_5 (2.90 mmol, freshly prepared from C_5Bn_5H [9] and LiC_4H_9) in 15 mL of THF at 0°C was added to a suspension of GeI_2 (0.47 g, 1.45 mmol) in 5 mL of THF. After stirring for 2 h, the THF was removed in vacuo, the oily brown residue was dissolved in 20 mL of benzene, the solution was decanted from insoluble matter, and the clear yellow-orange solution was concentrated until a precipitate began to appear. By addition of a layer of pentane, pale-yellow crystals were obtained. Total yield: 0.42 g **1** (26%). M.p. = 105°C (decomp.). Characterized by complete elemental analysis, IR, Raman, and mass spectra. ^{1}H-NMR (C_6D_6, 25°C): δ = 4.02 (s, 20H, CH_2), 7.08 (m, 50H, C_6H_5).
[7] **1**: $P2_1/n$ (non-standard arrangement of $P2_1/c$), a = 17.539(5), b = 23.329(4), c = 14.890(2) Å, β = 106.90(2)°, V = 5829.4 Å^3, Z = 4, ρ_{calcd} = 1.258 g/cm^3; $Mo_{K\alpha}$ radiation, −105(3)°C, 1° ω-scans. Data reduction with Lorentz and polarization correction, no absorption correction (μ = 5.28 cm^{-1}). Solution with Patterson techniques and refinement with Fourier techniques, 7602 independent reflections, 5456 reflections ($I \geq 2\sigma(I)$) for calculation, R = 0.0438, R_w = 0.0432. Further details of the crystal structure investigation are available on request from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2, by quoting the depository number CSD 51372, the names of the authors, and the journal citation.
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Synthesis of the Immunologically Essential Saccharide Sequence of the "Enterobacterial Common Antigen"

By *Hans Paulsen,** and *Jens Peter Lorentzen*

Most bacterial surface antigens contain specific saccharide sequences as immunodeterminants, which permit the serological differentiation of the different species of a genus. In contrast, the "enterobacterial common antigen"

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(ECA) is wide-spread; it is a family-specific antigen of all Enterobacteriaceae, to which a large number of pathogenic bacteria belong.[1] For this reason, the detection of ECA and of ECA antibodies has become of importance for the taxonomy of bacteria and for the diagnosis of enterobacterial infections.[1,2] The oligomeric saccharide that is responsible for the immunological reactions is composed of the following repeating trisaccharide chain:[3]

[→4)-β-D-Man*p*NAcA-(1→4)-α-D-Glc*p*NAc-(1→3)-α-D-Fuc*p*4NAc-(1→]$_n$

Cyclic structures[3] and L-*glycero*-phosphatide units[2] may play a role in the anchoring of the carbohydrate chain to the outer cell membrane of gram-negative bacteria. We have now synthesized a derivative of the trisaccharide unit, which should make possible the synthesis of a corresponding synthetic antigen.

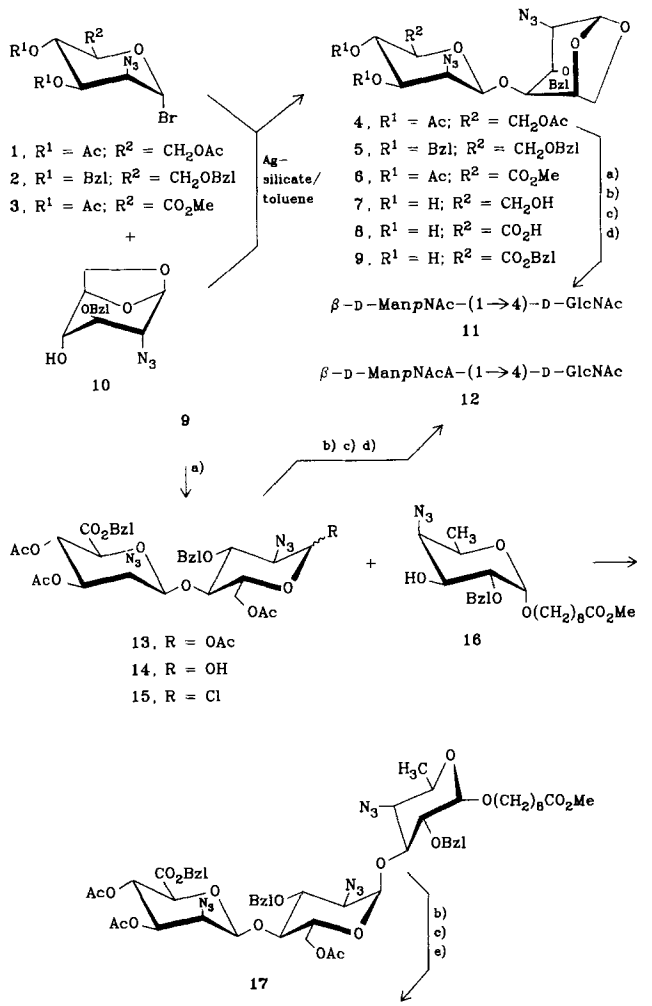
Recently, we were able to couple 2-acetamido-2-deoxy-D-mannopyranose and 2-acetamido-2-deoxy-D-mannopyranuronic acid with the poorly reactive 4-OH group of 2-acetamido-2-deoxy-D-glucose, forming a β-glycosidic linkage.[4] On reaction of the glycosyl bromides **1**, **2**, and **3**[5] with the glycosyl acceptor **10** using heterogeneous silver silicate catalysis,[6] the β-linked disaccharides **4** (48%), **5** (79%), and **6** (29%) are obtained.[4] As we expected,[7] the reactive benzyl compound **2** reacts more selectively than the less reactive triacetate **1**, while the uronic acid **3** appears to be relatively unsuitable for glycoside syntheses. It is therefore better to carry out the oxidation to the uronic acid after the glycosidation. Deblocking of **4** in four steps affords the disaccharide **11** (56%, $[\alpha]_D^{20}$ −30.0), which, in many gram-positive bacteria, is the site at which peptidoglycan and teichonic acid are linked.[8]

After deacylation of **4** to give **7**, it was possible to oxidize **7** to the uronic acid disaccharide **8** by selective catalytic oxidation with O_2/Pt[9] (turbo stirrer). **8** reacts with phenyldiazomethane to give the benzyl ester **9**, which can be functionalized again after acetylation by acetolysis with trifluoroacetic acid/acetic anhydride to form the derivative **13**. The three-step deblocking of **13** permits the synthesis of the disaccharide **12** (potassium salt; 73%, $[\alpha]_D^{20}$ −35.5); **12** is found in the capsular polysaccharide of *Haemophilus influenzae* type d.[10]

The derivative **16**, containing a spacer linked through an α-glycosidic bond, is used as the glycosyl acceptor for the trisaccharide synthesis. **16** can be synthesized via a multistep, but efficient route from selectively blocked derivatives of 4-azido-4-deoxy-D-fucose.[11] The acetate **13** cannot be transformed directly into the halide because of the acid lability of the 3-*O*-benzyl ether group. It is initially selectively deacetylated to **14** with piperidine;[12] **14** is then converted into the glycosyl donor **15** using the Vilsmeier reagent chloro-*N*,*N*-dimethylformamidinium chloride. Reaction of **15** with **16** under the conditions of the in-situ anomerization in the α-glycoside synthesis[7] ($AgClO_4$, Ag_2CO_3) affords the trisaccharide **17** (40%, $[\alpha]_D^{20}$ +7.6, $J_{1,2}$ = 3.7, $J_{1',2'}$ = 3.5 Hz).

Stepwise deblocking of **17** is achieved by reduction of the azide groups with H_2S, *N*-acetylation, cleavage of the benzyl groups by hydrogenolysis, and deacetylation. In this sequence of reactions, the ester groups of the molecule are cleaved selectively.

18 (sodium salt; 51%, $[\alpha]_D^{20}$ +83.6) is the first oligosaccharide containing an aminouronic acid moiety to be synthesized. It can be reacted, via the spacer, with proteins, e.g., with serum albumin or polylysine, to give the synthetic antigen using known methods.[13]



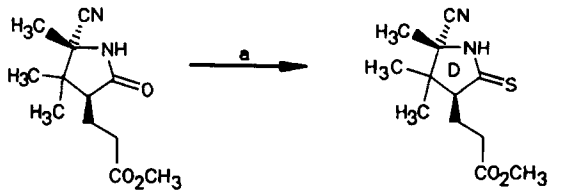
Scheme 1. a) Ac_2O, CF_3COOH (10:1, v/v), 3 h, 20°C. b) C_5H_5N, H_2O (2:1, v/v), H_2S, 24 h, 20°C; C_5H_5N, Ac_2O (2:1, v/v), 6 h, 20°C. c) MeOH, Pd-C, 1 h, 20 bar H_2. d) MeOH, K_2CO_3 (1:2.5, v[mL]/w[mg]), 24 h, 0°C. e) MeOH, MeONa (500:1, v[mL]/w[g]), 2 h, 20°C.—Ac = acetyl, Bzl = benzyl, Me = methyl.

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4, 97783-74-9; **7**, 95451-83-5; **8**, 95451-86-8; **9**, 97783-75-0; **11**, 85734-86-7; **12** (K salt), 97783-77-2; **13**, 97783-76-1; **14**, 97783-78-3; **15**, 97783-79-4; **16**, 97783-80-7; **17**, 97783-81-8; **18** (Na salt), 97783-82-9.

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3 4

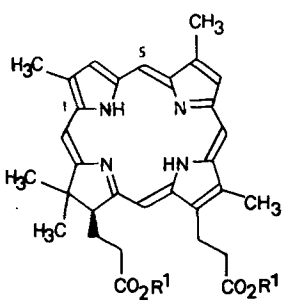
Scheme 1. a) 1.1 equiv. 2,4-bis(4-methoxyphenyl)-1,3-,2λ⁵,4λ⁵-dithiadiphosphetane-2,4-dithione ("Lawesson reagent"), tetrahydrofuran (THF), reflux (rfl.), 30 min (87% crystalline **4**).

Total Synthesis of (±)-Bonellin Dimethyl Ester**

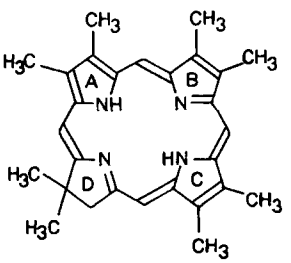
By *Franz-Peter Montforts** and *Ulrich M. Schwartz*

Dedicated to Professor Albert Eschenmoser on the occasion of his 60th birthday

Bonellin **1a** or ent-**1a**[1] is the green sex-differentiating pigment of *Bonellia viridis*, a marine animal widely distributed in the Mediterranean.[2] Initially sex-indifferent larvae which come into contact with the body wall of the female, which contains the green bonellin, develop into males of 1–3 mm in length. The larger females (15 cm) evolve from those larvae having no contact with bonellin. The unusual biological activity and antitumor properties of bonellin in vitro[3] certify it as an attractive synthetic target. During the course of our investigations, racemic bonellin dimethyl ester *rac*-**1b** was recently synthesized in another laboratory via a photochemical route.[4]



1a, $R^1 = H$
1b, $R^1 = CH_3$

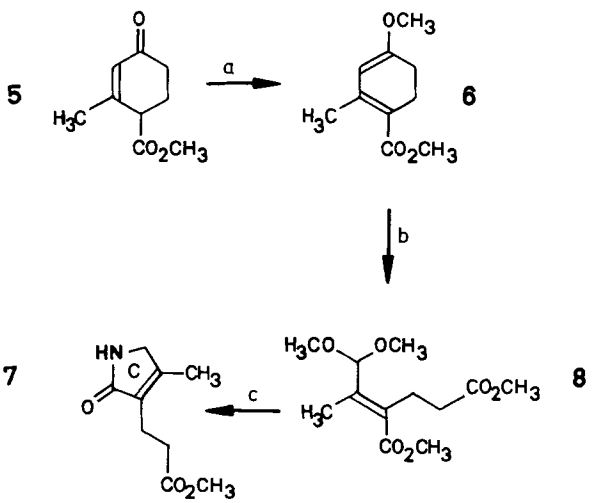


2

Following a model synthesis[5] of chlorin **2**, we were able to synthesize bonellin dimethyl ester *rac*-**1b** from four monocyclic building blocks—**4**, **7**, **9**, and **10**—and the selectively cleavable malonic ester **13**.

Since ring D of bonellin **1a** or ent-**1a** is constitutionally identical with ring C of vitamin B_{12} it was decided to start from the lactam **3**[6]—a building block used in the syntheses of vitamin B_{12} by *Woodward*[7] and *Eschenmoser*.[8] **3** is converted into its thia analogue **4** (Scheme 1).

A novel entry to the ring-C dihydropyrrolone **7**[9] was opened up by the use of the Hagemann ester **5** as starting material. Selective ozonolysis of the enol ether **6** produced the desired propionic acid side chain and a (protected) aldehyde function. The aldehyde group and the ester group at the double bond in **8** enabled the incorporation of nitrogen, and formation of the five-membered heterocycle **7** (Scheme 2).



5 6 7 8

Scheme 2. a) 5 equiv. $HC(OCH_3)_3$, *p*-toluenesulfonic acid (TsOH), catalytic amount, benzene, rfl., 2.5 h (71% **6**).—b) 1) O_3/O_2, CH_2Cl_2, 1.5 equiv. CH_3OH, −80°C; 1.5 equiv. CH_3SCH_3, room temperature (RT), 3 h. 2) 2 equiv. $HC(OCH_3)_3$, TsOH, catalytic amount, RT, 12 h (73% **8**).—c) 1) Raney nickel, H_2, CH_3OH, RT, 4.5 h. 2) 60% $HClO_4$, catalytic amount, CH_3CN, H_2O, RT, 2.5 h, crude producted reacted further. 3) NH_3, CH_3OH (saturated), 2 equiv. NH_4Cl, RT, 4.5 h, crude producted reacted further. 4) CH_3COOH, rfl., 5.5 h (37% crystalline **7**).

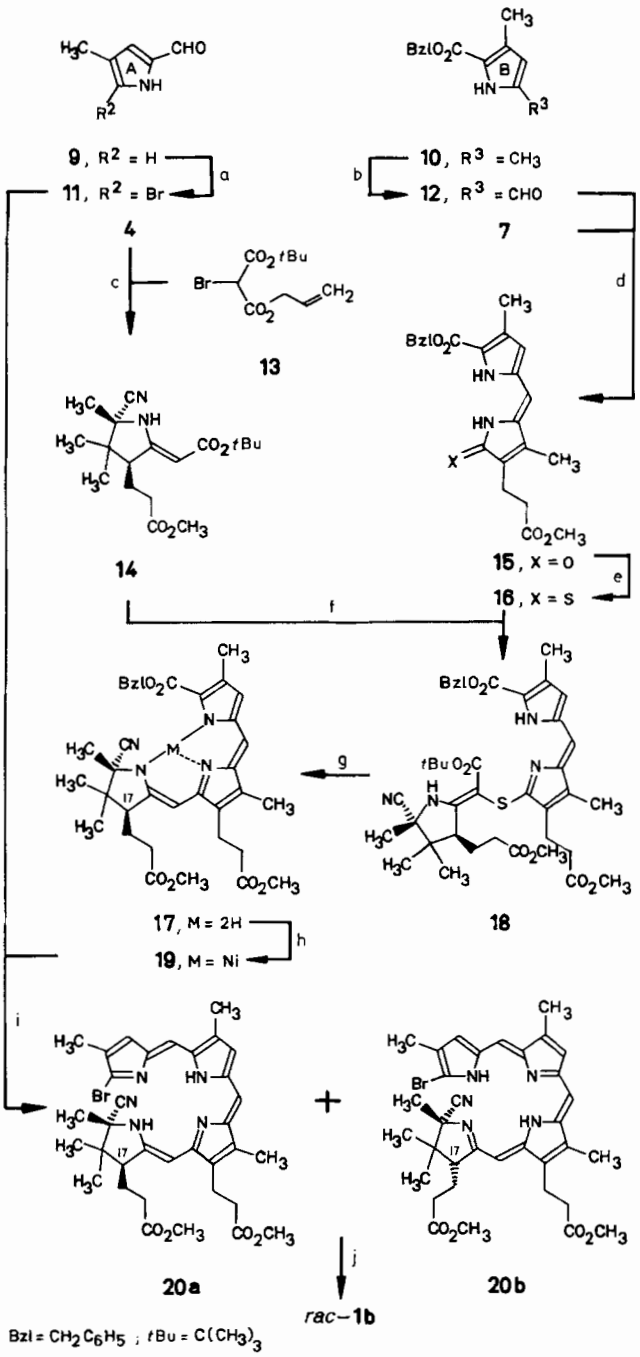
Lead tetraacetate, in the preparatively decisive solvent chloroform, oxidizes the methylpyrrole **10**[10] to the ring-B pyrrolecarbaldehyde **12**. The ring-A building block **11** is obtained by selective bromination of the α-unsubstituted pyrrolecarbaldehyde **9**.[11]

The thiolactam **4** and the malonic ester **13**[13] are converted, free of epimerization, into the vinylogous urethane **14** by sulfide contraction and subsequent Pd-catalyzed ester cleavage.[12] The dihydropyrrolone **7** and the ring-B aldehyde **12** undergo base-catalyzed reaction[14] to give the B–C bicycle **15**, which is then converted into the thiolactam **16**. Coupling **14** and **16** via a brominating agent affords the sulfur-bridged A–B–C tricycle **18**, which is converted by acid-induced sulfide contraction according to the method of *Rasetti* et al.[15] into the C–C coupled product **17**.

The complexation of **17** with nickel to give **19** stabilizes the chromophore towards atmospheric oxidation and enables the ready separation of the C-17 epimers, whose formation is unavoidable under strongly acidic conditions. For preparative purposes, however, the separation is not

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Scheme 3. a) 1.1 equiv. Br_2, 2 equiv. pyridine, CH_2Cl_2, −45°C (77% crystalline **11**).—b) 1) 2.5 equiv. lead tetraacetate, $CHCl_3$, rfl., 210 h. 2) 2.5 N aq. HCl, RT, 6 h (71% crystalline **12**).—c) 1) 1 equiv. **4** + 1.1 equiv. **13**, 1.2 equiv. diazabicycloundecene (DBU), CH_3CN, 0°C, 20 min (coupling). 2) $P(OC_2H_5)_3$, 80°C, 2 h (desulfurization). 3) 5.1 equiv. piperidine, $[(C_6H_5)_3P]_4Pd$, catalytic amount, THF, argon, RT, 2 h (76% crystalline **14**).—d) 1.1 equiv. base [14], benzene, rfl., 10 h (88% crystalline **15**).—e) 1.1 equiv. "Lawesson reagent", THF, rfl., 30 min (90% crystalline **16**).—f) **14** + 1.1 equiv. *N*-bromosuccinimide, CH_2Cl_2, RT, 20 min; +0.92 equiv. **16**, 4 equiv. DBU, CH_3CN, RT, 40 min (product **18** reacted further, after chromatographic purification).—g) 7.6 equiv. $P(CH_2CH_2CN)_3$, CF_3CO_2H, benzene, rfl., 25 min (crude product **17** reacted further).—h) 20 equiv. $Ni(CH_3CO_2)_2 \cdot 4H_2O$, 70 equiv. sodium acetate, CH_2Cl_2, CH_3OH, RT, 1 h (yields referred to **16**: 57% epimeric mixture, crystalline; 21% **19** and 18% C-17 epimer of **19**, crystalline).—i) **19** + C-17 epimer, Pd/C, hydrogen, MeOH, RT, 1 h; +2.5 equiv. **11**, 15 equiv. TsOH, $CHCl_3$, rfl., 15 min (product **20a** + **20b** reacted further after chromatographic purification).—j) 1) 2.5 equiv. $Zn(CH_3CO_2)_2$, potassium *tert*-butoxide, *tert*-butyl alcohol, rfl., 1 h; 2) CH_2N_2, ether, RT (yield referred to **19** + C-17 epimer: 42% crystalline *rac*-**1b**).

necessary: The acid-catalyzed condensation of **11** (ring A) after hydrogenolysis of the benzyl ester in **19** likewise effects epimerization at C-17.

The mixture of secochlorin **20a** and its C-17 epimer **20b** undergoes base catalyzed cyclization in the presence of zinc(II), which exercises a template effect and can be readily removed from the chlorin system acidolytically, to give the racemic bonellin dimethyl ester *rac*-**1b**.

The formation of enantiomerically pure **1b** or ent-**1b** from the *pure* secochlorins **20a** or **20b**, whose separation has not yet been accomplished, should be possible under cyclization conditions that avoid epimerization.

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(±)-**1b**, 89254-54-6; (±)-**3**, 98015-33-9; (±)-**4**, 98015-34-0; **5**, 35490-07-4; **6**, 98015-35-1; **7**, 774-16-3; **8**, 98015-36-2; **9**, 24014-19-5; **10**, 40236-19-9; **11**, 98015-37-3; **12**, 94781-44-9; **13**, 98015-38-4; (±)-**14**, 98015-39-5; **15**, 98015-40-8; **16**, 98015-41-9; (±)-**17**, 98015-43-1; (±)-**18**, 98015-42-0; (±)-**19** (epimer 1), 98050-02-3; (±)-**19** (epimer 2), 98103-42-5; **20a**, 98015-44-2; **20b**, 98102-31-9; 2-(*tert*-butylimino)-2-(diethylamino)-1,3-dimethyl-1,3-diaza-2-phosphocyclohexane, 98015-45-3.

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[13] Prepared by esterification of malonic acid mono-*tert*-butyl ester with allyl alcohol and subsequent bromination of the anion.
[14] The best results are achieved with 2-*tert*-butylimino-2-diethylamino-1,3-dimethyl-1,3-diaza-2λ⁵-phosphacyclohexane as base. We thank Dr. *R. Schwesinger* (Freiburg) for a sample of the base before publication of his results.
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Distortional Isomers of $[LWOCl_2]^+$ in the Solid State and in Solution; Crystal Structures of the Blue and Green Forms of $[LWOCl_2]PF_6$**

By *Karl Wieghardt,* Gabriele Backes-Dahmann, Bernhard Nuber,* and *Johannes Weiss*

The blue and green crystals of the diamagnetic neutral complex *cis-mer*-$[MoOCl_2(PMe_2Ph)_3]$[1] exhibit so-called distortional isomerism. In each case, the Mo^{IV} center is surrounded octahedrally by the monodentate ligands in identical spatial arrangement *(cis-mer)*; in the solid state, the two forms differ only in the lengths of the Mo=O bond and the Mo–Cl bond *trans* to the oxo group (Mo=O: 167.6(7) (blue), 180.3(11) pm (green); Mo–Cl 255.1(3) and 242.6(6) pm, respectively). In solution, the green form is transformed irreversibly into the blue form. *Wilkinson* et al. have described analogous blue and green crystals of $[MoOCl_2(PMe_3)_3]$, but did not characterize these as distortional isomers.[2] Recently, we were able to confirm the existence of this type of isomerism in the complex anions $[PPh_4]_2[MoO(CN)_4(H_2O)]\cdot 4H_2O$ (green) and $[AsPh_4]_2[MoO(CN)_4(H_2O)]\cdot 4H_2O$ (blue) by X-ray analysis. In this case, too, the blue form exhibits a shorter Mo=O bond than the green form. Salts of $[MoO(CN)_5]^{3-}$ ions also exist in blue and green forms.[3] Common to all of these compounds is a Mo^{IV}=O group, their diamagnetism, and the fact that, in solution, only *one* form prevails.

This type of distortional isomerism is not well understood as yet due to the limited number of firmly established examples. Is it restricted to diamagnetic Mo^{IV}=O complexes or is it a solid-state effect (packing effect, etc.)? We report here the characterization of distortional isomers, both in the solid, state *and* in solution, of the *paramagnetic* cation $[LWOCl_2]^+$ (L = *N,N',N''*-trimethyl-1,4,7-triazacyclononane), the hexafluorophosphate salt of which has been crystallized in a blue form **1** and a green form **2**.[4]

The infrared spectra of **1** and **2** (KBr) are very similar. Only in the region of the W=O stretching vibrations are significant differences apparent: **1** exhibits the ν(W=O) vibration at 980 cm^{-1}, whereas for **2** it is observed at 960 cm^{-1}. **1** and **2** are stable in the solid state and do not undergo a change in color over several months; even at temperatures up to 450 K, they are not transformed into each other.

The crystal structure determinations show that **1** and **2** crystallize in the same space group with very similar unit cell parameters.[5] The packing of the $[LWOCl_2]^+$ ions and of the disordered PF_6^- ions is also identical in the two salts. In both cases, the geometry of the ligands around the W^V center is identical (Fig. 1): the tridentate ligand *N,N',N''*-trimethyl-1,4,7-triazacyclononane occupies three facial coordination sites of a distorted octahedron; two chloro ligands in *cis* positions with respect to each other and an oxo group occupy the remaining three coordination sites. The only significant differences between the complex cations in **1** and **2** are the lengths of the W=O bond and probably of the W–N1 bond *trans* to it. In the blue form, a shorter W=O distance (172(2) pm) and a longer W–N1 distance (237(2) pm) are observed; in the green form, these distances are 189(2) and 232(2) pm, respectively. Because of the relatively large error limits, however, the significance of the difference in bond lengths of the two W–N1 bonds is experimentally unresolved.

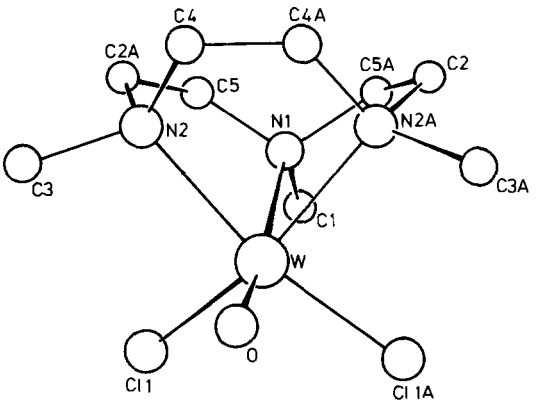


Fig. 1. Structure of the cation $[LWOCl_2]^+$ in **1** and **2**. The atoms W, C1, N1, and O lie on a crystallographic mirror plane. Selected bond lengths [pm] and bond angles [°] in **1** (corresponding values for **2** in parentheses): W-O 171.9(18) (189.3(20)), W-Cl1 232.2(5) (229.5(6)), W-N1 237.0(17) (232.1(20)), W-N2 223.9(13) (224.7(16)); Cl1-W-Cl1A 91.7(3) (93.5(4)), Cl1-W-O 102.8(8) (101.4(8)), Cl1A-W-N2 163.7(8) (164.5(8)), N2-W-N2A 78.3(6) (76.9(8)), Cl1-W-N2 93.1(5) (93.3(7)), O-W-N2 91.1(8) (90.9(8)), N1-W-N2 75.4(6) (75.8(8)).

Crystals of **1** and **2** dissolve in dry acetonitrile, affording blue and green solutions, respectively. Such solutions are stable for several days; in no case is a color change from green to blue or vice versa observed.

The electronic absorption spectra of **1** and **2** in CH_3CN (Fig. 2) show a weak-intensity d-d transition in the visible range (**1**: $\lambda = 712$ nm, $\varepsilon = 20$ cm^{-1} mol^{-1} L; **2**: 693 (40)), which is typical for oxo complexes of W^V. Interestingly, the spectrum of **2** shows a relatively strong charge transfer band (probably of the W=O group) at 419 nm ($\varepsilon = 890$ cm mol^{-1} L), which is responsible for the green color of **2** and

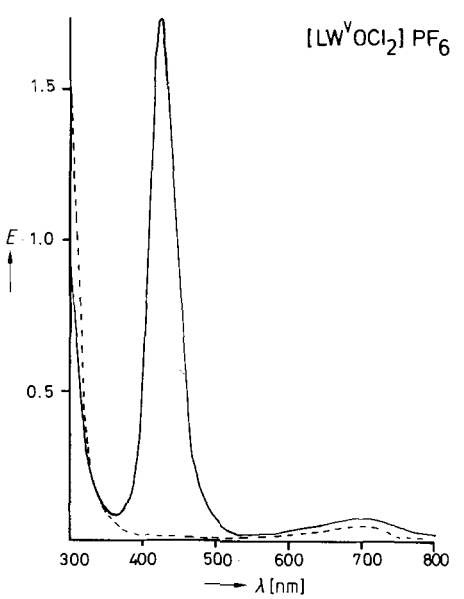


Fig. 2. Electronic absorption spectrum of **1** (----) (3.5×10^{-3} M) and **2** (—) (2.0×10^{-3} M) in dry acetonitrile (1-cm cuvette).

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which, for **1**, is shifted to appreciably shorter wavelengths (286 nm). From the ESR measurements on these solutions at 293 K, g values of 1.775(3) for **1** and 1.790(3) for **2** were derived.

Both methods show that two species of the cation $[LW^{V}OCl_2]^+$ also exist *in solution*. When small amounts of water are added to the green solution of **2**, an immediate color change to blue is observed. Blue **1** can be crystallized nearly quantitatively from this solution by addition of solid $NaPF_6$. Electrochemically, **1** and **2** can be reversibly reduced to $[LW^{IV}OCl_2]$ in dry CH_3CN with 0.1 M tBu_4NPF_6 as electrolyte ($E^f = -1.14$ V vs. ferrocenium/ferrocene for **1** and **2**).[4a]

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CAS Registry number:
1, 97879-02-2.

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[4] a) G. Backes-Dahmann, W. Wieghardt, *Inorg. Chem.*, in press; b) **1**, **2**: Air oxidation of an aqueous solution of red $[LW^{IV}Cl_3]Cl$ (313 K, 20 min) resulted in a blue solution, from which *blue*, hydrolytically stable $[LWOCl_2]PF_6$ **1** crystallized after addition of solid $NaPF_6$. If, on the other hand, $[LW(CO)_3]$ in 10 M HCl is refluxed for 2 d in the presence of air and then solid $NaPF_6$ is added to the cooled, green solution, green $[LWOCl_2]PF_6$ **2** crystallizes. Elemental analyses of the two salts (C, H, N, Cl, W) gave nearly identical values [4a] and are in very good accord with the composition $[LWOCl_2]PF_6$. Both salts are paramagnetic; the effective magnetic moments of the two forms are temperature independent from 98 to 293 K and correspond to the spin-only value of the d^1 electronic configuration of a W^{V} center (**1**: $\mu_{eff}(293\,K) = 1.90\mu_B$, **2**: $\mu_{eff}(293\,K) = 1.89\mu_B$).

[5] X-ray structure analysis of blue **1** and green **2** (values for **2** in parentheses): Pbcm (Pbcm); $a = 722.3(4)$ (726.7(5)), $b = 1489.8(6)$ (1495(1)), $c = 1653.5(8)$ (1649(1)) pm; $Z = 4$ (4); $\rho_{calcd} = 2.19$ (2.17) g cm^{-3}; $R = 0.062$ (0.073) for 1608 (1378) independent reflections ($I > 2\sigma(I)$); $Mo_{K\alpha}$ radiation, AED-Siemens II. Further details of the crystal structure investigation are available on request from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2, by quoting the depository number CSD 51404, the names of the authors, and the journal citation.

$[L_2Fe^{II}_2(\mu\text{-}OH)(\mu\text{-}CH_3CO_2)_2](ClO_4)\cdot H_2O$, a Model Compound for the Diiron Centers in Deoxyhemerythrin**

By *Phalguni Chaudhuri, Karl Wieghardt,* Bernhard Nuber,* and *Johannes Weiss*

In the oxidized forms of the oxygen-transporting protein hemerythrin containing dinuclear (μ-oxo)bis(μ-carboxylato)diiron(III) structural units,[1] the two Fe^{III} centers are strongly antiferromagnetically coupled ($J = -134$ cm^{-1} in metazidohemerythrin).[2] Some low-molecular, dinuclear Fe^{III} complexes of this type have recently been synthesized and characterized.[3] The agreement between the spectroscopic properties (electronic, resonance Raman, and Mössbauer spectra) and the magnetic susceptibilities of methemerythrin on the one hand, and those of the inorganic model compounds on the other, is remarkable. This underscores the value and relevance of studies on low-molecular model complexes for an understanding of metal-containing proteins.[4]

The active form of the protein, deoxyhemerythrin, contains dinuclear Fe^{II} complexes with high-spin electron configuration. The electronic spectrum and the magnetic properties of deoxyhemerythrin have been well documented,[5] but give very little information about its structure; a crystal structure analysis has so far not been reported.

MCD-ESR measurements on deoxyhemerythrin indicate a bis(μ-carboxylato)(μ-hydroxo)-bridging for the diiron(II) centers;[6] the same structure was proposed by *Stenkamp* et al.[12] The coupling constant J was estimated to be -13 ± 5 cm^{-1}. We report here on the first low-molecular model compound for the active protein.

Reaction of $Fe(ClO_4)_2\cdot 6H_2O$ in anhydrous methanol with the cyclic triamine *N,N',N''*-trimethyl-1,4,7-triazacyclononane (L) in the presence of anhydrous sodium acetate and in strict absence of oxygen led to pale greenish-yellow crystals of $[L_2Fe^{II}_2(\mu\text{-}OH)(\mu\text{-}CH_3CO_2)_2](ClO_4)\cdot H_2O$, **1**.[7]

The structure of **1** (Fig. 1)[8] consists of a μ-hydroxo-bridged diiron(II) unit containing two further acetate bridges and non-coordinatively bound, statistically disordered perchlorate ions. Two facially coordinated, tridentate amine ligands complete the distorted octahedral coordination sphere of the two Fe^{II} centers. The structure of **1** thus corresponds to the structure proposed[6] for deoxyhemerythrin. The Fe-O and Fe-N bonds in **1** are significantly longer than in **2**, the oxidation product of **1**; they are consistent with a d^6 high-spin electron configuration of the Fe^{II} centers.

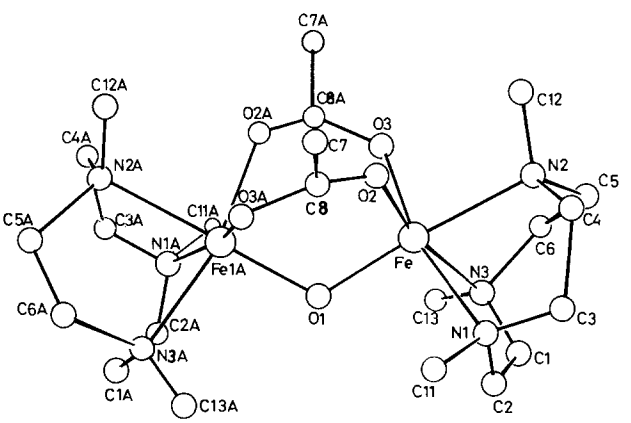


Fig. 1. Structure of the $[L_2Fe^{II}_2(OH)(CH_3CO_2)_2]^+$ cation in the crystal of **1**. Important bond lengths [pm] and angles [°]: Fe-O1 198.7(8), Fe-O2 214.2(9), Fe-O3 212.3(9), Fe-N1 225.7(10), Fe-N2 230(1), Fe-N3 231(1), C8-O2 120(2), C8-O3A 134(2), C7-C8 155(2), Fe-Fe1A 332(1); Fe-O1-Fe1A 113.2(2), O1-Fe-O2 98.2(4), O1-Fe-O3 95.6(5), O2-Fe-O3 92.6(5).

The electronic spectrum of **1** in methanol (Fig. 2, left) [$\lambda = 928$ nm ($\varepsilon = 10$ cm^{-1} mol^{-1} L); 1100 (sh) (7)] is very similar to that of deoxyhemerythrin.[5] The magnetic susceptibility data (Faraday method) for crystalline **1** in the

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temperature range 100–298 K were readily fitted using an isotropic Heisenberg model, $H' = 2JS_1 \cdot S_2$ ($S_1 = S_2 = 2$) and $g = 2.24$. The spin exchange coupling constant J of $-14(2)$ cm^{-1},[11] which is in excellent agreement with the value derived for deoxyhemerythrin,[6] indicates weak antiferromagnetic behavior. **1** is thus a very good model for the bonding of the Fe^{II} centers in deoxyhemerythrin and confirms the structure proposed by *Solomon* et al.[6] and Stenkamp et al.[12]

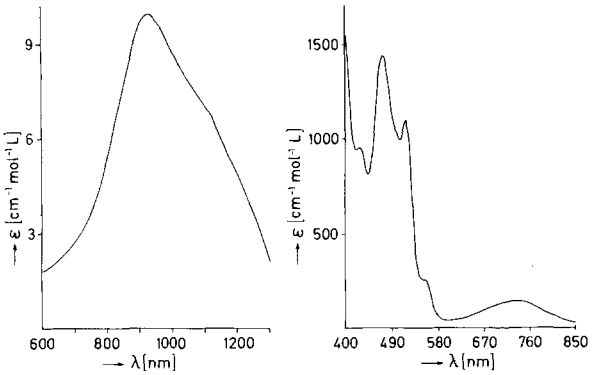


Fig. 2. Left: Electronic spectrum of **1** in methanol at 293 K; right: electronic spectrum of **2** in methanol at 293 K (a further absorption was observed at 1031 nm ($\varepsilon = 7$ cm^{-1} mol^{-1} L).

Oxidation of **1** by air yields $[L_2Fe_2(\mu\text{-}O)(\mu\text{-}CH_3CO_2)_2](ClO_4)_2$ **2**, which has already been prepared previously via an alternative route.[9] The two Fe^{III} centers are linked via a μ_2-oxo bridge and two acetato bridges (Fig. 3). The Fe–N and Fe–O bond lengths correspond to those of other model compounds for the diiron(III) centers in metazidohemerythrin.[3] The electronic spectrum of **2** in methanol (Fig. 2, right) resembles that of metazidohemerythrin. The magnetic susceptibility data for **2** (100–298 K) yielded a J value of -115 cm^{-1}, which is very similar to the value of -134 cm^{-1} for metazidohemerythrin, and indicates strong antiferromagnetic coupling.

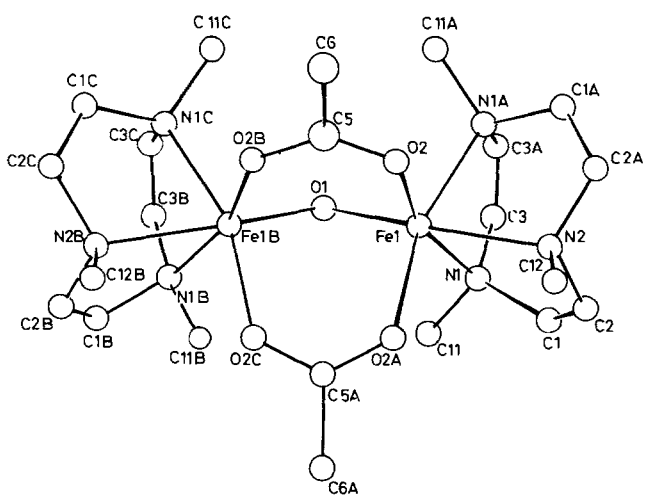


Fig. 3. Structure of the cation $[L_2Fe^{III}_2(O)(CH_3CO_2)_2]^{2+}$ in the crystal of **2**. Important bond lengths [pm] and angles [°]: Fe-O1 180.0(3), Fe-O2 203.4(3), Fe-N1 219.8(4), Fe-N2 226.8(6), C5-O2 124.6(4), C5-C6 146(1), Fe-Fe1B 312(1); O1-Fe-O2 97.2(2), O1-Fe-O2A 97.2(3), O2-Fe-O2A 96.5(2), Fe-O1-Fe1B 119.7(1).

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[7] Procedure: **1**: All operations were carried out under argon. A stirred solution of *N,N',N''*-trimethyl-1,4,7-triazacyclononane (L) [10] (0.51 g, 3 mmol) in anhydrous methanol (40 mL) was treated with 0.36 g (1 mmol) of $Fe(ClO_4)_2 \cdot 6H_2O$. After 2.5 hours' stirring at room temperature, anhydrous sodium acetate (0.2 g, 2.4 mmol) was added to the solution and stirring was continued for a further 30 min. After addition of 0.4 g $NaClO_4 \cdot H_2O$ and reduction of the volume of the reaction mixture to 15 mL, 150 mg of green-yellow crystals of **1** precipitated, which were filtered off and dried in an argon atmosphere.—**2**: When air was passed through the above reaction solution, the color changed from greenish-yellow to reddish-brown, and, after allowing to stand for 48 h in the presence of air, 470 mg of reddish-brown dichroic crystals of **2** precipitated out.

[8] X-ray structure analysis of **1** and **2** (data for **2** in brackets): $P4_12_12$ (Amam); $a = 1092(1)$ (1307.8(2)), $b = 1092(1)$ (1773.2(3)), $c = 2785(3)$ (1529.0(3)) pm; $Z = 4(4)$; $\rho_{calc} = 1.416$ (1.513) g cm^{-3}; $R = 0.082$ (0.079) for 1264 (2980) independent reflections ($I > 1.5\sigma(I)$); $Mo_{K\alpha}$ radiation; Siemens AED II diffractometer. Further details of the crystal structure investigations are available on request from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2, on quoting the depository number CSD 51466, the names of the authors, and full citation of the journal.

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Cleavage of an Ether Bond via β-Elimination of Ethanol from $[(H_2O)_5CrCH_2CH_2OC_2H_5]^{2+}$ in Aqueous Solutions; A Pulse Radiolysis Study**

By *Haim Cohen* and *Dan Meyerstein**

Dedicated to Professor Schulte-Frohlinde on the occasion of his 60th birthday

Recently it has been shown that pentaaqua(β-hydroxyalkyl)chromium(III) complexes decompose via β-elimination of the hydroxy radical to yield $[Cr(H_2O)_6]^{3\oplus}$ and the corresponding alkene.[1–4] The β-hydroxyalkylchromium(III) complexes therefore have a considerably shorter lifetime

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than the analogous alkyl- or α-hydroxyalkylchromium(III) complexes.[1,7] The β-elimination reaction has been shown to be a relatively fast acid-catalyzed process,[1-4] resulting in the formation of an unstable alkenechromium(III) complex.[3,4] The products of the reaction between $[Cr(H_2O)_6]^{2\oplus}$ and α,β-dihaloalkanes are also alkenes, indicating that pentaaqua(β-haloalkyl)chromium(III) complexes decompose via β-elimination of halides.[5] It seemed of interest to check whether ether bonds, which are considered to be kinetically considerably more stable, also decompose via β-elimination. We report here that the complex **1** (with $ClO_4^{\ominus}$ as counterion) indeed decomposes in an acid-catalyzed process to yield $[Cr(H_2O)_6]^{3\oplus}$, ethylene, and ethanol.

$[(H_2O)_5CrCH_2CH_2OC_2H_5]^{2\oplus}$ **1**

The relatively stable complex **2**[6,7] is usually prepared via Reactions (a)–(c).

$$[Cr(H_2O)_6]^{2\oplus} + H_2O_2 + H_3O^{\ominus} \longrightarrow [Cr(H_2O)_6]^{3\oplus} + {}^{\circ}OH + 2H_2O \quad (a)$$
$k(a) = 7.1 \times 10^4\ M^{-1}\ s^{-1}$ [8]

$$^{\circ}OH + (C_2H_5)_2O \longrightarrow H_2O + {}^{\circ}CH(CH_3)OC_2H_5 \quad (b)$$
$k(b) = 1.4 \times 10^9\ M^{-1}\ s^{-1}$ [9]

$$[Cr(H_2O)_6]^{2\oplus} + {}^{\circ}CH(CH_3)OC_2H_5 \longrightarrow [(H_2O)_5CrCH(CH_3)OC_2H_5]^{2\oplus} \quad (c)$$
2
$k(c) = 3.4 \times 10^7\ M^{-1}\ s^{-1}$ [1]

This synthetic route is based on the observation that the major product of reaction of hydroxy radicals with diethyl ether is the α-radical [Reaction (b)].[6] However, from the relative rates of hydrogen abstraction at the α- and β-carbons of diethyl ether by hydroxy radicals,[9] one would expect that ca. 20% of the free radicals should be formed via Reaction (d). Thus one would expect that ca. 20% of the product should be **1** [Reaction (e)].

$$^{\circ}OH + (C_2H_5)_2O \longrightarrow {}^{\circ}CH_2CH_2OC_2H_5 + H_2O \quad (d)$$

$$[Cr(H_2O)_6]^{2\oplus} + {}^{\circ}CH_2CH_2OC_2H_5 \longrightarrow [(H_2O)_5CrCH_2CH_2OC_2H_5]^{2\oplus} \quad (e)$$
1

However, the decomposition of **2** obeys a purely first-order rate law[6] suggesting that only one species is decomposing. Accordingly, **1** decomposes prior to the start of the measurement of the kinetics of decomposition of **2**. Since the hydrolysis of $[(H_2O)_5CrCH_3]^{2\oplus}$ is not fast, a plausible mechanism for the fast decomposition of **1** could be β-elimination [Reaction (f)].

$$[(H_2O)_5CrCH_2CH_2OC_2H_5]^{2\oplus} + H_3O^{\ominus} \longrightarrow [Cr(H_2O)_6]^{3\oplus} + C_2H_4 + C_2H_5OH \quad (f)$$

In order to check this mechanism, the complex **2** was prepared via two routes. In the first procedure, solutions containing 0.5 M $(C_2H_5)_2O$ and 0.05 M $[Cr(H_2O)_6]^{2\oplus}$ at pH 1.0 or 3.5 were mixed with aqueous H_2O_2 so that the final amount of H_2O_2 was 1.0×10^{-2} M. In the second procedure, He-saturated solutions at pH 1.0 or N_2O-saturated solutions at pH 3.5 containing 0.5 M $(C_2H_5)_2O$ and 5×10^{-3} M $[Cr(H_2O)_6]^{2\oplus}$ were irradiated using a ^{60}Co γ-source (4500 rad/min, total dose 67500 rad, i.e., ca. 4×10^{-4} mol free radicals formed). The reaction mixtures were analyzed by FT-IR spectroscopy (Nicolet MXs) and gas chromatography (T.C.D. Varian 1440) for possible formation of ethylene within 20 min from the start of the reaction (i.e., long before **2** had decomposed). In all the reaction mixtures ethylene was detected; the yield of ethylene was ≥ 10% of the total yield of free radicals. Since the relative rates of Reactions (b) and (d) (formation of α- and β-radicals, respectively) are not known exactly, no effort was made to determine exactly the yield of ethylene.

The formation of ethylene in these systems clearly proves that Reaction (f) indeed occurs. In order to measure the rate of Reaction (f), we used the pulse radiolysis technique. The experimental setup was identical to that described earlier.[10] N_2O-saturated solutions containing 0.5 to 0.8 M $(C_2H_5)_2O$ and 1×10^{-4} to 1×10^{-5} M $[Cr(H_2O)_6]^{2\oplus}$ in the pH range 1.0 to 4.0 were irradiated. Under these conditions the following processes occur in addition to Reactions (b) and (d):

$$H_2O \xrightarrow{e^{\ominus}} e_{aq}^{\ominus},\ {}^{\circ}OH,\ H,\ H_2,\ H_2O_2 \quad (g)$$
(the relative yields of the primary products are 2.65, 2.65, 0.60, 0.45, and 0.75, respectively [11])

$$e_{aq}^{\ominus} + N_2O + H_3O^{\oplus} \longrightarrow N_2 + {}^{\circ}OH + H_2O \quad (h)$$
$k(h) = 8.7 \times 10^9\ M^{-1}\ s^{-1}$ [12]

$$e_{aq}^{\ominus} + H_3O^{\oplus} \longrightarrow H + H_2O \quad (i)$$
$k(i) = 2.3 \times 10^{10}\ M^{-1}\ s^{-1}$ [12]
(the relative yields of Reactions (h) and (i) depend on the pH)

$$H + (C_2H_5)_2O \longrightarrow {}^{\circ}CH(CH_3)OC_2H_5 + H_2$$
$$H + (C_2H_5)_2O \longrightarrow {}^{\circ}CH_2CH_2OC_2H_5 + H_2 \quad (j)$$
$k(j) = 4.7 \times 10^7\ M^{-1}\ s^{-1}$ [13]
(the relative yields of α- and β-abstraction by H atoms are larger than those by OH radicals since the latter are more reactive)

Under the experimental conditions, Reactions (g) to (j) as well as (b) and (d) are over within the time duration of the pulse (ca. 1 μs).

These reactions are followed by Reactions (c), (e), (a), (k), (l), and probably (f).

$$[Cr(H_2O)_6]^{2\oplus} + H \longrightarrow [(H_2O)_5Cr{-}H]^{2\oplus} + H_2O \quad (k)$$
$k(k) = 1.5 \times 10^9\ M^{-1}\ s^{-1}$ [14]

$$[(H_2O)_5CrH]^{2\oplus} + H_3O^{\oplus} \longrightarrow [Cr(H_2O)_6]^{3\oplus} + H_2 \quad (l)$$
$k(l) = 1.8 \times 10^4\ M^{-1}\ s^{-1}$ [14]

We have observed three kinetic processes (Fig. 1). The first process is attributed to Reactions (c) and (e), which are expected to have similar rate constants and might hide a small contribution from Reaction (k), which is considerably faster.[14] The second process is attributed to Reaction (a) followed by reactions (b) to (e), since in this process the absorption increases somewhat due to the alkylchromium complex and since the rate is pseudo first order in $[Cr(H_2O)_6]^{2\oplus}$ and agrees with the reported rate constant of Reaction (a).[8]

The third process can be due either to Reaction (l) or to Reaction (f). We attribute it to the latter for the following reasons. First, the process obeys a pseudo-first-order rate law in $H_3O^{\oplus}$. The pH dependence of the reaction is plotted in Figure 2, from which $k(f) = (4.6 \pm 0.8) \times 10^3\ M^{-1}\ s^{-1}$ is calculated. This rate constant differs significantly from $k(l)$. Second, the percentage of decrease in the absorption caused by this process at pH 3 to 4 is nearly independent of the ratio of the concentration of $(C_2H_5)_2O$ to that of $[Cr(H_2O)_6]^{2\oplus}$ although the relative yields of Reactions (j) and (k) are linearly dependent on this ratio. Third, the percentage of decrease in the absorption caused by this pro-

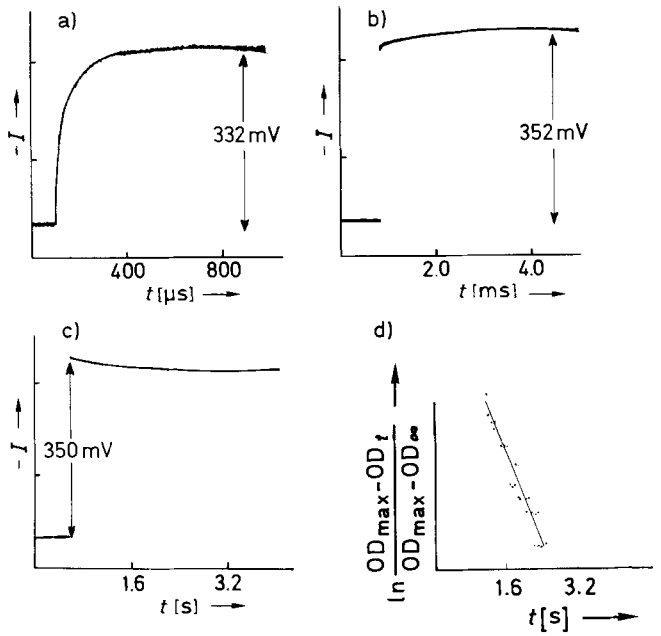


Fig. 1. Kinetic traces of absorption changes upon irradiation at 310 nm of N_2O-saturated aqueous solutions containing 0.5 M $(C_2H_5)_2O$ and 0.05 M $[Cr(H_2O)_6]^{2\oplus}$ at pH 3.5. a) Formation of **2** and **1**. b) Formation of Cr–C compounds by the reaction of H_2O_2 with $(C_2H_5)_2O$ and $[Cr(H_2O)_6]^{2\oplus}$. c) Decomposition of **1**. d) First-order decrease in the concentration of **1**. $-I_0 = 755$ mV.

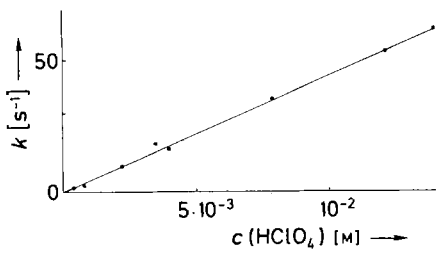


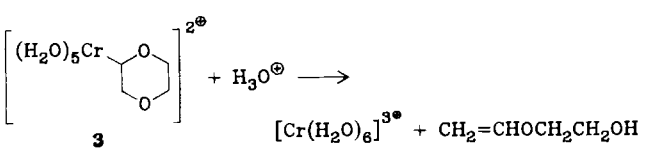
Fig. 2. Dependence of the rate of decomposition of **1** on pH, measured in N_2O-saturated aqueous solutions containing 0.5 M $(C_2H_5)_2O$ and 1×10^{-3} to 1×10^{-2} M $[Cr(H_2O)_6]^{2\oplus}$ at 315 nm. Ionic strength was not taken into consideration.

cess is nearly pH independent in the pH range 2 to 4 although the relative yields of Reactions (b) and (h) depend linearly on the pH.

The large residual absorbance remaining after the third process is that due to complex **2**.

We thus conclude that the third process responds to concentration variables as expected and, since ethylene is detected as a product, this process is indeed the β-elimination of ethanol [Reaction (f)] and $k(f) = (4.6 \pm 0.8) \times 10^3$ $M^{-1} s^{-1}$.

This is the first reported rate constant for the cleavage of an ether bond via β-elimination. The rate constant is similar to that reported for β-eliminations of the hydroxyl group from $[(H_2O)_5CrCH_2C(CH_3)_2OH]^{2\oplus}$ and related compounds,[3,4] thus suggesting a similar transition state for the two processes. It is tempting to speculate that the fast decomposition of complex **3** is not a hydrolysis reaction as suggested[1] but rather a β-elimination reaction [Reaction (m)].



3 (m)

$k(m) = 0.48$ $M^{-1} s^{-1}$ [1]

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Selectivity and Mechanism of Diene Cyclodimerization on Iron(0) Complexes**

By *Heindirk tom Dieck** and *Jörg Dietrich*

Dedicated to Professor Günther Wilke on the occasion of his 60th birthday

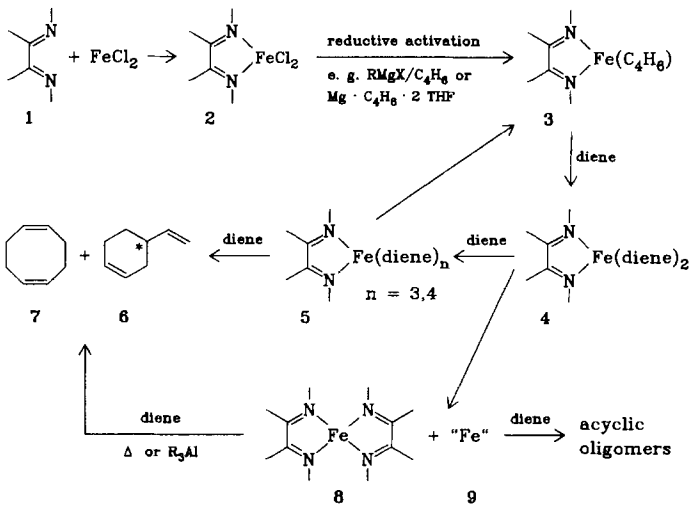
The cyclodimerization of 1,3-dienes on "nickel-ligand" catalysts[2] is one of the most investigated homogeneous catalytic reactions, but the mechanism of the product release is still unknown. To clarify this we have carried out investigations on the diazadiene-iron system.[3]

Reaction of 1,4-diaza-1,3-dienes (dad), **1**, and iron(II) chloride leads to formation of the complexes **2**, which, for the butadiene cyclodimerization, can be reductively activated by Grignard compounds or butadienemagnesium (with $Mg \cdot C_4H_6 \cdot 2THF$ to give **3**, or with $Mg \cdot 2C_4H_6 \cdot 2THF$[4] to give **4**, stabilized by solvent). In the presence of an excess of butadiene, the reducing agent has no influence on the ratio **6** : **7** (Table 1). On complete conversion, up to 98% of **7** is formed (with **1a**) and up to 80% **6** (with **10a**). When dad is too bulky (**1c**, **1d**), the catalytic reaction is suppressed at room temperature, or (e.g. with **1e**) a disproportionation to $Fe(dad)_2$, **8**, and "Fe", **9**, is observed. Diene-stabilized iron atoms **9** (without diene, iron particles are formed!) appear to be responsible for the comparatively slow formation of linear dimers (see Table 1) and higher oligomers; **8** is only catalytically active at higher temperatures.[5]

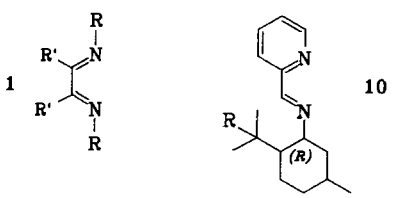
Ligands, which—due to steric requirements—do not form $(dad)_2M$ complexes or, if so, only slowly, such as **1f**

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[**] Diazadienes as Control Ligands in Homogeneous Catalysis, Part 11. This work was supported by the Deutsche Forschungsgemeinschaft, the Fonds der Chemischen Industrie, and Hoechst AG. – Part 10: [1].



with nickel(0),[6] yield long-lived and rapid catalysts with Fe^0.[7] The *N*-substituent in **1g** is particularly small, and, according to an X-ray structure analysis, in **1h** the phenyl ring is turned out by ca. 70° from the dad plane and thus also counts among the sterically less demanding ligands.[8] Nevertheless, catalysts **3g** and **3h** do not convert any butadiene at room temperature, though both catalysts smoothly convert isoprene and *trans*-1,3-pentadiene into methylated cyclodimers analogous to **6** and **7**. In the case of most of the other catalysts with ligands **1** and **10** (Table 1), isoprene and 1,3-pentadiene are converted less rapidly than butadiene—similarly as in the L–Ni system.[9] If, however, isoprene (10 or 100 moles/mole Fe) is added to an "inert" butadiene/**3h** mixture (100 : 1), the cyclodimerization of *butadiene* proceeds rapidly at room temperature. Up to more than 50% conversion, codimers and isoprene dimers are not observed. On the other hand, if **2h** is activated with 1.5 equivalents of $Mg \cdot C_4H_6 \cdot 2THF$ in the presence of 100 equivalents of isoprene, 2.5% of butadiene-isoprene codimers are obtained, and, on activation of an isoprene run with bis(butadiene)magnesium, traces of **6** and **7** are also formed.



10

From these observations it must be assumed that an equilibrium is set up between butadiene and isoprene ligands on iron. Moreover, as the necessity of the isoprene as a "releaser" shows, at least three diene units must be bound to iron in **5**.

Very active catalysts such as **3f** also show a constant reaction rate (dilatometry) up to almost complete conversion of butadiene; consequently the product release (e.g. from **5**) is rate determining. In the case of the isoprene-induced butadiene dimerization on **3h** the change of the isoprene equivalents from 1 to 10 and to 100 mol per mol Fe surprisingly effects a marked change in the ratio **6** : **7**. This finding can be hardly explained in terms of an intermediate of the type **5** with n = 3, but rather in terms of a (dad)Fe^0 system containing four diene units on iron immediately before the product release. With different amounts of isoprene, different amounts of (dad)Fe"$(C_4H_6)_3$"(C_5H_8) or (dad)Fe"$(C_4H_6)_2$""$(C_5H_8)_2$" can be expected. It is virtually impossible to make any statements about the coupling of the dienes. In a (dad)Fe"$(diene)_4$" species two dienes ought to be η^2-bound, the two others already form a coupled σ,σ bound unit, so that the complex satisfies the noble gas rule and concomitantly is a meaningful precursor for the product.

3f is a slow catalyst for the dimerization of isoprene or 1,3-pentadiene, but shows a remarkable selectivity with 1 : 1 mixtures of the two dienes. Besides 3.3% of isoprene dimers 96.7% of codimers are formed, 9.5% of which being 2-methyl-4-*trans*-propenylcyclohexane and 91.5% 1,7-dimethyl-1,5-cyclooctadiene, which is thus readily accessible in an overall yield of over 88%.

The influence of the diazadienes on the course of the catalytic reaction is possibly even better demonstrated by chirality transfer. Of the numerous chiral dad and dad-like

Table 1. Influence of control ligands **1** and **10** on catalytic butadiene dimerization.

Cpd.	R	R'	Product distribution [%] [a] VCH = **6**	COD = **7**	MHT	OT	Dimer [%]	*T* [°C]	
1a	2,6-$Me_2C_6H_3$	Me	2	98	—	—	100	25	
1b	2,6-$iPr_2C_6H_3$	Me	6	93	—	1	96	25	
exo-**1c**	2-Bornyl	H	—	—	—	—	—	25	
			—	—	—	—	—	50	
endo-**1c**	2-Bornyl	H	7	86	7	—	13	25	
1d	3-*p*-Menthanyl	Me	—	—	—	—	—	25	
			48	41	11	—	19	50	
1e	*t*Bu	H	9	76	—	15	20	25	
1f	iPr_2CH	H	6	93	—	1	96	25	EtMgBr [b]
			7.5	91	—	1.5	93	25	*i*PrMgBr
			8	90.5	—	1.5	95	25	*t*BuMgBr
1g	*i*Pr	H	—	—	—	—	—	25	
			21	79	—	—	66	50	
1h	Ph	Me	—	—	—	—	—	25	
			20	80	—	—	88	50	
10a	H	—	80	20	—	—	100	5	(*ee* = 47 [c])
			69	31	—	—	100	25	(*ee* = 23.8)
10b	Me	—	49	51	—	—	100	25	(*ee* = 56)
10c	Ph	—	33	67	—	—	100	25	(*ee* = 62)

[a] VCH = 4-vinylcyclohexene, COD = 1,5-cyclooctadiene, MHT = methylheptatriene, OT = 1,3,6-octatriene. [b] Activator. [c] Enantiomeric excess *ee* [%] of (*S*)-4-vinylcyclohexene with $[\alpha]_D = -113$ (W. von E. Doering, M. Frank-Neumann, D. Hasselmann, R. L. Kaye, *J. Am. Chem. Soc. 94* (1972) 3833).

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ligands, (1*R*)-menthylimine **10a** and the 8-substituted menthylimines **10b** with 55% *ee* and **10c** with 62% *ee* of **6** have so far proven the best. This chiral induction was hitherto not achieved with chiral "Ni–P" systems[10] and is certainly an exceptionally good result for a catalytic reaction of unpolar substrates with exclusive σ/π reorganization.

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[7] In a typical butadiene catalysis ca. 5 g (ca. 100 mmol) of dry butadiene and 12 17 mL of dry ether are condensed into a flask at −80°C and treated successively with 0.2–0.4 mmol of precatalyst **2** and then with the activator R–MgX (up to a fourfold molar amount, referred to Fe) or with MgC_4H_6 (up to a 1.7-fold molar amount). The thoroughly mixed reaction solution is then kept at room temperature in a graduated, thin Schlenk tube (NORMAG) up to the calculated maximum contraction (0.5–50 h); at higher temperatures, sealed ampules are used. The reaction solution is then treated with dilute H_2SO_4, washed with water, dried over Na_2SO_4, and distilled. Product characterization by GC, GC/MS, and preparative GC/NMR.
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Novel Retro-Ene Reactions of β-Hydroxyacetylenes**

By *Henning Hopf** and *Reinhard Kirsch*

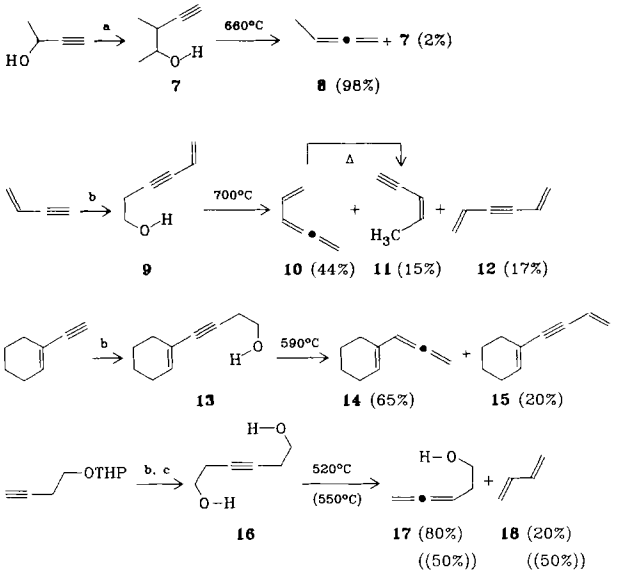
Dedicated to Professor Hans Musso on the occasion of his 60th birthday

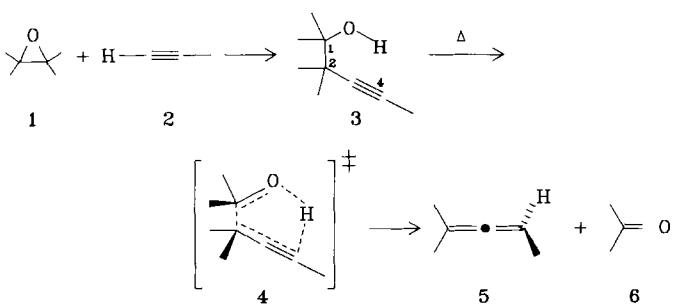
On gas-phase pyrolysis, 3-butyn-1-ols **3** decompose into allenes **5** and a carbonyl component **6**.[1]

As demonstrated by *Viola* et al. in comprehensive mechanistic investigations **5** and **6** are formed via **4** in a retro-ene type 1,5-sigmatropic rearrangement.[2] Since the alcohols **3** can be prepared, inter alia, from oxiranes **1** and 1-alkynes **2**, the two-step process **2**→**3**→**5** effects a conversion of terminal alkynes into terminal allenes with lengthening of the chain by one carbon atom.[3] In view of the growing importance of allenes in preparative chemistry[4,5] and the simplicity of the above synthesis it appeared desirable to widen its scope of application: hitherto, exclusively acyclic butynols **3** containing alkyl and phenyl substituents in the 1- and 4-position were pyrolyzed.[2,3,6] For an intended allene synthesis, however, substituents in the 1-position of *acyclic* reactants **3** are of no account, since this carbon atom is lost during thermolysis. In the pyrolysis of *cyclic* β-hydroxyalkynes, on the other hand, α,ω-allene-aldehydes or -ketones would have to result, since the fragments **5** and **6** remain connected to each other.

To supplement the acyclic series,[1] the alkynols **7**, **9**, and **13** and the diol **16** were prepared by conventional methods[7] and pyrolyzed (Table 1).

Table 1 [7]. Preparation of β-hydroxyalkynes of type **3** and their pyrolysis in a flow tube at 10^{-3} torr.—a) 1) PBr_3, 2) CH_3CHO, Al.—b) 1) $LiNH_2$, liquid NH_3, 2) oxirane.—c) H⊕.—THP = tetrahydropyranyl.—Yields, apart from those of **8** (NMR analysis), determined by GC analysis.





Whereas the expected 1,2-butadiene **8** is formed exclusively from **7**, in the case of **9** and **13** not only 1,2,4-pentatriene (vinylallene) **10** and 1-propadienylcyclohexene **14** are formed but also the dehydration products **12** and **15**. Moreover, at the temperature given, **10** isomerizes stereoselectively by a 1,5-hydrogen shift to give *cis*-3-penten-1-yne **11**.[8] In the case of the diol **16** the cleavage of a formaldehyde molecule not only generates the desired retro-ene product **17** but also concomitantly creates the prerequisite for a repetition of this fragmentation step: Indeed, 1,3-butadiene **18** is obtained as second pyrolysis product.

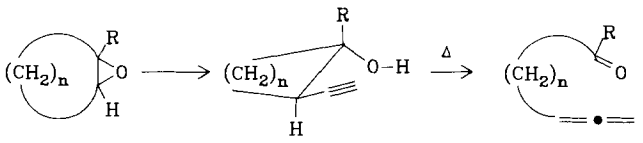
In the series of cyclic β-hydroxyalkynes, the *trans*-alcohols **20** were prepared from the epoxides **19**[9] and pyrolyzed (Table 2) as above (Table 1).

The allene-aldehydes **21b** and **21c** and the allene-ketone **21d** are formed as major products of the isomerization reactions from **20b–d**. Varying amounts of unsaturated hydrocarbons are also formed, which, according to GC/MS analysis, are dehydration products of the respective alkynols. The five-membered ring alcohol **20a** affords the al-

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[**] Thermal Rearrangements, Part 16. This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie. - Part 15: H. Hopf, R. Kirsch, *Tetrahedron Lett. 26* (1985) 3327.

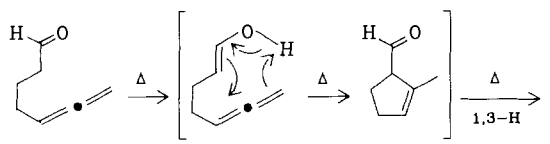
Table 2 [7]. Preparation of β-hydroxyalkynes **20** by reaction of the bicyclic epoxides **19** with lithium acetylide in dimethyl sulfoxide and pyrolysis of **20** to allene-aldehydes and -ketones **21** under the conditions given in Table 1.—Yields determined by GC analysis.



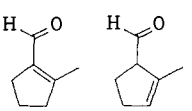
19 **20** **21**

	R	n	T [°C] **20**→**21**	Yield [%]
a	H	3	515	22
b	H	4	600	71
c	H	5	575	72
d	CH_3	4	590	50

lene derivative **21a** at 515°C, but only in moderate yield, yet widening the product pattern: possibly **21a** is unstable under the conditions of pyrolysis and rearranges into the (actually isolated) cyclopentane carbaldehydes **24** and **25**



21a **22** **23**



24 (10%) **25** (6%)

(yield determined by GC analysis). In analogy to the findings of *Conia* et al. on the thermolysis of 7-octyn-2-one, **22** and **23** can be postulated as intermediates of this cyclization.[10] The good yields obtained in the rearrangements of **20b–d** are surprising in so far as *trans*-2-(1-heptynyl)cyclohexanol resists thermal ring-opening.[1,2,11]

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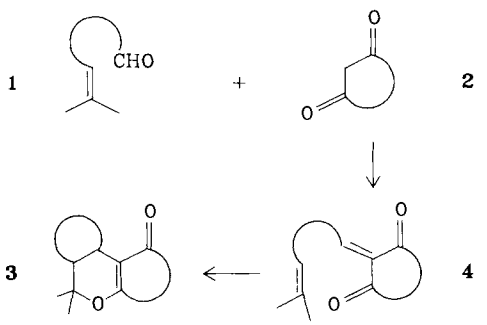
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[3] In contrast to the already well-known preparation of terminal allenes from terminal alkynes with retention of the number of carbons (review: H. Hopf in S. Patai (ed.): *The Chemistry of Ketenes, Allenes, and Related Compounds*, Wiley, Chichester 1980, p. 779 ff) the above type of reaction is little known: cf. P. Crabbé, B. Nassim, M.-T. Robert-Lopes, *Org. Synth. 63* (1984) 203, and references cited therein.
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[5] H. F. Schuster, G. M. Coppola: *Allenes in Organic Synthesis*, Wiley-Interscience, New York 1984.
[6] If the 2- and 4-position of **3** are suitably substituted, the **3**→**5** fragmentation also provides for the preparation of chiral allenes.
[7] All new reactants and products were characterized by the usual spectroscopic methods and elemental analysis.
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Highly Enantioselective Intramolecular Hetero Diels-Alder Reactions for the Synthesis of Enantiomerically Pure Tricyclic Lactones**

By *Lutz-F. Tietze,* Siegbert Brand,* and *Thomas Pfeiffer*

Dedicated to Professor Hans Musso on the occasion of his 60th birthday

Diels-Alder reactions can be used not only for the construction of carbocycles but also for the synthesis of heterocycles ("hetero Diels-Alder reactions").[1] For example, pyran derivatives may be prepared by reaction of α,β-unsaturated carbonyl compounds with enol ethers or alkenes. The reaction is particularly valuable because the educts **4** can be prepared in an easy way by condensation of aldehydes **1** with cyclic 1,3-dicarbonyl compounds **2**. The cycloaddition leads intramolecularly to *cis*- or *trans*-annelated polycyclic compounds of the type *rac*-**3** with *de* values ≥98%.[2] This method can be employed for the synthesis of such diverse natural products as cannabinoids,[3a] iridoids,[3b] and indole alkaloids.[3c]

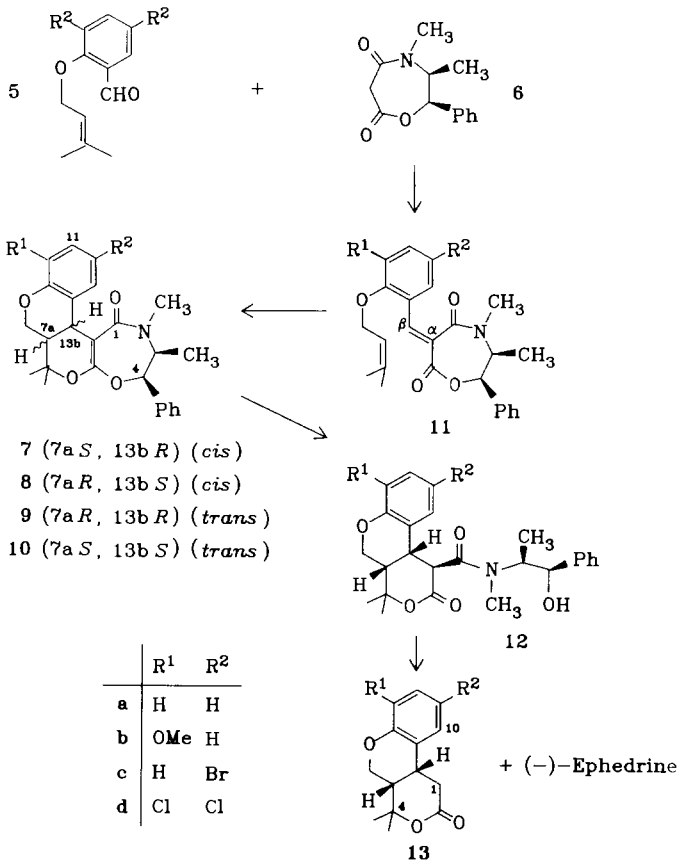


Here we describe the asymmetric induction[4] using the oxazepandione **6** as a chiral 1,3-dicarbonyl compound, which was prepared from methyl hydrogen malonate and (−)-ephedrine in 40% yield[6] according to the method of *Mukaiyama*.[5] The benzaldehyde derivations **5** are catalytically condensed with **6** to give the benzylidene-1,3-dicarbonyl compounds **11** (see Table 1). In the intramolecular hetero Diels-Alder reaction of **11**, the *cis*-annelated cycloadduct **7**[7–9] is obtained as the main product with often excellent *de* values (≥98%); the compounds **7** can be purified by crystallization or by chromatography on silica gel (Table 1).

A priori, eight cycloadducts can be formed in the reaction of **11**, since the educt contains two heterodiene moieties; each of them should give both *trans*- and *cis*-annelated products. The *trans*-annelated products **9** are formed in <1 to 4% yield; the *cis*-fused cycloadducts **8**,[7,8] which are diastereomeric to **7**, can be detected in amounts of <1 to 3%. The *trans* products **10** were not isolated; likewise, compounds whose formation may be explained by reaction of the amide carbonyl groups were not found. Without a catalyst, the selectivity of the reaction decreases dramatically. Thus, the reaction of **11a** in *o*-dichlorobenzene (100°C, 18 h) affords 45% **7a**, 21% **8a**, and 24% **9a** after

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[**] Intramolecular Hetero Diels-Alder Reactions, Part 7. This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie. We thank Dr. *H. Stegelmeier*, Bayer AG, for providing the halogenated benzaldehyde derivatives. Part 6: [2c].



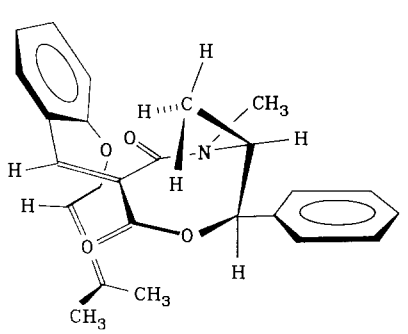
	R^1	R^2
a	H	H
b	OMe	H
c	H	Br
d	Cl	Cl

Table 1. Yields and selectivities of the Knoevenagel condensation (**5** + **6** → **11**; catalytically in acetonitrile, 20°C, 14 h, molecular sieves) and of the hetero Diels-Alder reaction (**11** → **7** + **8** + **9**; in the presence of diethylaluminum chloride in 1,2-dichloroethane, 83°C). Pure (*E*)-**11a**–**c** was used for the hetero Diels-Alder reactions; **11d** was used as a 9/1-(*E*/*Z*) mixture.

	11 Yield [%]	*E*/*Z*	**7**	**8** Yield [%] [a]		**9**	*t*
a	93	99/1 [b]	78	1		1	2 h
	99	15/1 [c]					
			45	21		24	18 h [d]
b	88	40/1 [c]	52	2		3	3 h
c	94	13/1 [c]	62		(1)		2 h
d	76	9/1 [c]	21 [e]		(6)		5.5 d

[a] Yields after chromatography. [b] Ethylenediammoniumdiacetate as catalyst; L. F. Tietze, T. Eicher: *Reaktionen und Synthesen im organisch-chemischen Praktikum*, Thieme, Stuttgart 1981. [c] Piperidine/glacial acetic acid (1:2) as catalyst. [d] In *o*-dichlorobenzene at 100°C without catalyst. [e] In refluxing $CHCl_3$ without catalyst; 39% of the educt was recovered.

purification by column chromatography. Steric interactions such as in **11d** also lower the selectivity and especially the reaction rate (Table 1).



14

We assume that the conformation of the transition state **14** of the intramolecular cycloaddition of **11a** to give **7a** is an *endo*-(*E*)-*syn* arrangement with a folded oxazepandione moiety in which the C_β *si* face is sterically shielded so that the dienophile attacks almost exclusively from the C_β *re* face. The Lewis acid catalyst may cause a lowering of the LUMO energy of the heterodiene and a fixation of the conformation in the transition state. The lower reactivity of **11** in comparison with the corresponding derivatives of dimethylbarbituric acid and Meldrum's acid[2] is presumably due to the fact that the carbonyl group on C_α of the heterodiene is twisted, to a certain extent, out of the plane of the π-system. This raises the energy of the LUMO of the heterodiene and thus decreases the rate of this Diels-Alder reaction with inverse electron demand.

The cycloadducts **7** are surprisingly stable toward alkali. With methanolic HCl (3 N HCl/MeOH = 1:1, 20°C, 14 h), however, up to 89% of the amide **12a**[7] is obtained from **7a**. Compound **12a** is cleaved in the presence of 6 N NaOH (100°C, 3.5 h), undergoing decarboxylation to give the lactone **13a**[7,8] in 80% yield. In addition to **13a**, 87% (with respect to **12a**) of the (−)-ephedrine used could be recovered. By use of (+)-ephedrine, which is also commercially available, *ent*-**13a** can be prepared analogously.

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[1] a) J. Sauer, *Angew. Chem. 78* (1966) 233; *Angew. Chem. Int. Ed. Engl. 5* (1966) 211; b) G. Desimoni, G. Tacconi, *Chem. Rev. 75* (1975) 651; c) D. F. Taber: *Intramolecular Diels-Alder and Alder Ene Reactions*, Springer, Berlin 1984; d) S. M. Weinreb, R. R. Staib, *Tetrahedron 38* (1982) 3087; e) S. Danishefsky, *Acc. Chem. Res. 14* (1981) 400; f) D. L. Boger, *Tetrahedron 39* (1983) 2869; g) M. Ohno, T. Sasaki, *Yuki Gosei Kagaku Kyokaishi (J. Synth. Org. Chem. Jpn.) 42* (1984) 125; h) E. Ciganek, *Org. React. 32* (1984) 1.

[2] a) L. F. Tietze, G. van Kiedrowski, B. Berger, *Tetrahedron Lett. 23* (1982) 51; b) L. F. Tietze, H. Stegelmeier, K. Harms, T. Brumby, *Angew. Chem. 94* (1982) 868; *Angew. Chem. Int. Ed. Engl. 21* (1982) 863; c) L. F. Tietze in W. Bartmann, B. M. Trost (Eds.): *Selectivity—a Goal for Synthetic Efficiency*, Verlag Chemie, Weinheim 1984; d) S. Takano, S. Satoh, K. Ogasawara, *Heterocycles 23* (1985) 41.

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[5] T. Mukaiyama, Y. Hirako, T. Takeda, *Chem. Lett. 1978*, 461; T. Mukaiyama, T. Takeda, K. Fujimoto, *Bull. Chem. Soc. Jpn. 51* (1978) 3368.

[6] A simplified procedure [5] involves heating dimethyl malonate and (−)-ephedrine at 80°C (1:1 without solvent, 12 h) to give the intermediary monoamide in 54–70% yield.

[7] Elemental analyses and ^1H, ^{13}C-NMR, and mass spectra are in accord with the structure given. M.p.: **7a** 190°C; **8a** 230°C; **12a** 98–104°C; **13a** 148°C.—$[\alpha]_D^{20}$ ($CHCl_3$, $c = 1$): **7a** +88.1; **8a** +69.4; **12a** +18.6; **13a** −36.3.—R_F (silica gel, ether/petroleum ether 4:1): **7a** 0.36; **8a** 0.22; **12a** 0.34; **13a** 0.46.

[8] ^{1}H-NMR ($CDCl_3$/TMS int., 200 MHz): **7a**: $\delta = 1.05$ (d, $J = 7$ Hz, 3H, 3-CH_3), 1.42 (s, 3H, 7-CH_3(ax)), 1.52 (s, 3H, 7-CH_3(eq)), 2.20 (ddd, $J(7a,8ax) = 8.5$, $J(7a,13b) = 6$, $J(7a,8eq) = 4$ Hz, 1H, 7a-H), 2.67 (s, 3H, N-CH_3), 4.15 (dd, $J_{gem} = 11.5$, $J = 8.5$ Hz, 1H, 8-H(ax)), 4.38 (dq, $J = 7$, $J = 3.5$ Hz, 1H, 3-H), 4.43 (dd, br, $J = 6$ Hz, 1H, 13b-H), 4.49 (ddd, $J_{gem} = 11.5$, $J = 4$, $J(8eq,13b) = 1$ Hz, 1H, 8-H(eq)), 5.28 (d, $J = 3.5$ Hz, 1H, 4-H), 6.78 (dd, $J = 8$, $J = 1.5$ Hz, 1H, 10-H), 6.85 (ddd, $J = 8$, $J = 1.5$ Hz, 1H, 12-H), 7.11 (dd, $J = 8$, $J = 1.5$ Hz, 1H, 11-H), 7.26–7.42 (m, 5H, phenyl), 7.57 (dd, Br, $J = 8$ Hz, 1H, 13-H).—**8a**: $\delta = 1.19$ (d, $J = 7$ Hz, 3H, 3-CH_3), 1.49 (s, 3H, 7-CH_3(ax)), 1.55 (s, 3H, 7-CH_3(eq)), 2.31 (dd, $J(7a,13b) = 6.5$, $J(7a,8ax) = 2.8$, $J(7a,8eq) = 1.8$ Hz, 1H, 7a-H), 3.05 (s, 3H, N-CH_3), 3.64 (q, $J = 7$ Hz, 1H, 3-H), 4.30 (dd, $J_{gem} = 12$, $J = 2.8$ Hz, 1H, 8-H(ax)), 4.43 (dd, $J_{gem} = 12$, $J = 1.8$ Hz, 1H, 8-H(eq)), 4.57 (d, br, $J = 6.5$ Hz, 1H, 13b-H), 5.43 (s, 1H, 4-H), 6.76 (d, br, $J = 7.5$ Hz, 1H, 10-H), 6.86 (ddd, $J = 7.5$, $J = 1$ Hz, 1H, 12-H), 7.08 (dd, Br, $J = 7.5$ Hz; 1H, 11-H), 7.18–7.58 (m, 6H, phenyl, 13-H).—**13a**: $\delta = 1.49$ (s, 3H, 4-CH_3(ax)), 1.58 (s, 3H, 4-CH_3(eq)), 2.29 (ddd, $J(4a,5ax) = 11.3$, $J(4a,10b) = 5.5$, $J(4a,5eq) = 4$ Hz, 1H, 4a-H), 2.58 (dd, $J_{gem} = 19$, $J(1ax,10b) = 10$ Hz, 1H, 1-H(ax)), 3.05 (dd, $J_{gem} = 19$, $J(1eq,10b) = 8$ Hz, 1H, 1-H(eq)), 3.52 (m, 1H, 10b-H), 4.02 (dd, $J_{gem} = 11.3$, $J(5ax,4a) = 11.3$ Hz, 1H, 5-H(ax)), 4.46 (ddd, $J_{gem} = 11.3$, $J(5eq,4a) = 4$, $J(5eq,10b) = 1.5$ Hz, 1H, 5-H(eq)), 6.87 (dd, $J = 8$, $J = 1.5$ Hz, 1H, 7-H), 6.93 (ddd, $J = 8$, $J = 1.5$ Hz, 1H, 9-H), 7.08 (dd, $J = 8$, $J = 1.5$ Hz, 1H, 10-H), 7.19 (ddd, $J = 8$, $J = 1.5$ Hz, 1H, 8-H).

[9] An X-ray structure analysis has been carried out for **7a**: G. Sheldrick, J. Antel, S. Brand, T. Pfeiffer, L. F. Tietze, unpublished.

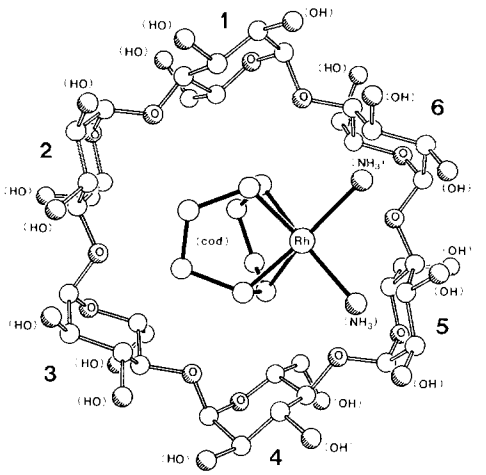


Fig. 1. A plan view of the skeletal representation of $[Rh(cod)(NH_3)_2 \cdot \alpha\text{-CD}]^{\oplus}$ in the crystal of $1 \cdot 6H_2O$. Note that the α-D-glucopyranosidic units are numbered from 1 to 6 in an anticlockwise direction.

Cyclodextrins as Second Sphere Ligands for Transition Metal Complexes—The X-Ray Crystal Structure of $[Rh(cod)(NH_3)_2 \cdot \alpha\text{-cyclodextrin}][PF_6] \cdot 6H_2O$**

By *David R. Alston, Alexandra M. Z. Slawin, J. Fraser Stoddart,** and *David J. Williams*

Transition metal complexes can be coordinated[1] in the second sphere by macrocyclic crown ethers in apolar solvents. This finding prompted us to study the potential of cyclodextrins[2] to act[3] as second-sphere ligands for organometallic compounds in aqueous media. We have discovered that cyclodextrins do indeed form stable adducts with a range[4] of transition metal complexes in H_2O. We report here on ^{1}H-NMR spectroscopic investigations of the 1 : 1 adducts **1** and **2** between α-cyclodextrin (α-CD) and $[Rh(cod)L_2][PF_6]$ (cod = 1,5-cyclooctadiene and $L_2 = (NH_3)_2$ or $H_2NCH_2CH_2NH_2$ = en), and on the structure of the crystalline hydrate of **1**

$[Rh(cod)(NH_3)_2 \cdot \alpha\text{-CD}][PF_6]$ **1**
$[Rh(cod)(en) \cdot \alpha\text{-CD}][PF_6]$ **2**

Initially, we noted that both α- and β-CDs solubilize $[Rh(cod)(NH_3)_2][PF_6]$ in water. Addition of 1 mol. equiv. of the Rh complex to a solution of α-CD in D_2O resulted in significant shifts (i) of the ^{1}H-NMR signal for H3 in α-CD to higher frequency (e.g. 20.8 Hz at 250 MHz for a concentration of 0.021 mol kg^{-1}) and (ii) of the ^{1}H-NMR signal for H5 in α-CD to lower frequency. These twelve protons are oriented inside the cavity of α-CD. The association constant K_a for 1 : 1 adduct formation could not be determined since the Rh complex slowly hydrolyzed.[5] Despite the instability of the 1 : 1 adduct, it did prove possible to obtain single crystals of the hexahydrate of **1**.[6]

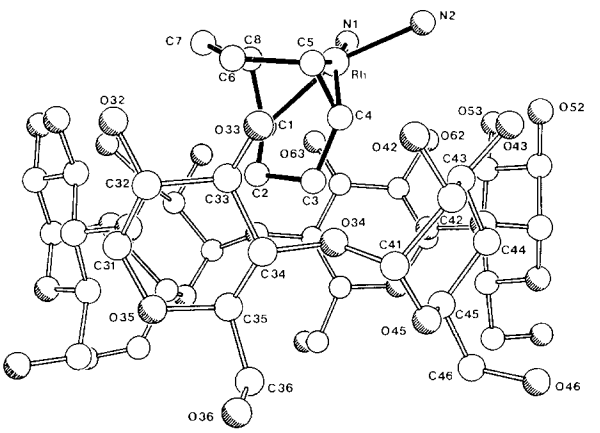


Fig. 2. A side-on view of the skeletal representation of $[Rh(cod)(NH_3)_2 \cdot \alpha\text{-CD}]^{\oplus}$ in the crystal of $1 \cdot 6H_2O$. The cod-numbering is not that recommended by the IUPAC.

An X-ray structure analysis of $1 \cdot 6H_2O$[7] (Figs. 1 and 2) showed that the cod ligand is positioned almost exactly over the center of the torus in α-CD, which adopts a characteristic tub-shaped conformation with local pseudo C_6 symmetry. One of the two ethylene groups is inserted (Fig. 2) into the α-CD cavity with C2 and C3 lying 0.88 and 1.08 Å respectively below the mean plane of the O atoms associated with the 12 secondary OH groups. Although two (C1 and C4) of the olefinic C atoms on the cod ligand lie 0.22 and 0.21 Å respectively above this plane, they clearly reside below the rim defined by the H atoms of these OH groups. The two NH_3 ligands on Rh are tilted slightly upwards and are positioned over the two α-D-glucopyranosidic units 5 and 6 (Fig. 1). There are four intra-adduct N···O contacts[8] of <3.5 Å: two are between N1 and O62 and O63 (3.46 and 3.25 Å, respectively), and the other two are between N2 and O52 and O53 (3.31 and 3.24 Å, respectively).[9]

Replacement of the two ammine ligands in $[Rh(cod)(NH_3)_2][PF_6]$ by a bidentate ethylenediamine (en) ligand afforded a stable Rh complex, **2**, in aqueous solution in the presence of α-CD. The ^{1}H-NMR spectrum of **2**

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in D_2O revealed shifts[10] to higher frequencies of the signals for H2, H3 (e.g. 21.1 Hz at 250 MHz for a concentration of 0.017 mol kg^{-1}),[11] and H4 and a shift to lower frequency of the signal for H5. A K_a value of 520 ± 80 mol^{-1} kg was obtained[12] from a quantitative ^{1}H-NMR spectroscopic analysis of the 1:1 adduct in the concentration range (0.002–0.017 mol kg^{-1}) using H3 as the probe proton.

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1, 97920-83-7; **1**·6 H_2O, 97920-84-8; **2**, 97920-86-0; α-CD, 10016-20-3; β-CD, 7585-39-9; [Rh(cod)$(NH_3)_2$][PF_6], 88995-93-1; [Rh(cod)(en)][PF_6], 97920-85-9; [Rh(cod)(en)·β-CD][PF_6], 97920-87-1; [FeCp$(CO)_2NH_3$][PF_6], 52225-44-2; [FeCp$(CO)_2C_5H_5N$][PF_6], 12088-86-7.

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[2] a) J. L. Atwood, J. E. D. Davies, D. D. MacNicol (eds.): *Inclusion Compounds*. Academic Press, London 1984; b) reviews: W. Saenger in [2a], *Vol. 2*, p. 231; *Angew. Chem. 92* (1980) 343; *Angew. Chem. Int. Ed. Engl. 19* (1980) 344; J. Szejtli in [2a], *Vol. 3*, p. 331; R. J. Bergeron in [2a], *Vol. 3*, p. 391; I. Tabushi in [2a], *Vol. 3*, p. 445; R. Breslow in [2a], *Vol. 3*, p. 473.

[3] For a discussion of the strong binding of ferrocene and some of its derivatives by β-CD in Me_2NCHO, Me_2SO, and Me_2SO/H_2O and the implications of this adduct formation, see B. Siegel, R. Breslow, *J. Am. Chem. Soc. 97* (1975) 6869; M. F. Czarniecki, R. Breslow, *ibid. 100* (1978) 7771; R. Breslow, M. F. Czarniecki, J. Emert, H. Hamaguchi, *ibid. 102* (1980) 762; R. Breslow, G. Trainor, A. Ueno, *ibid. 105* (1983) 2739; A. Ueno, F. Moriwaki, T. Osa, F. Hamada, K. Murai, *Tetrahedron Lett. 26* (1985) 899. See A. Harada, S. Takahashi (*J. Chem. Soc. Chem. Commun. 1984*, 645, for the preparation of crystalline α-, β-, and γ-CD-ferrocene adducts and a discussion of their properties. For a description of rotaxane adducts of α- and β-CD with μ-(α,ω-diaminoalkane)-bis[chlorobis(ethylenediamine)cobalt(III)], see H. Ogino, *J. Am. Chem. Soc. 103* (1981) 1303 and H. Ogino and K. Ohata, *Inorg. Chem. 23* (1984) 3312.

[4] E.g. [Fe(Cp)$(CO)_2NH_3$][PF_6] and [Fe(Cp)$(CO)_2C_5H_5N$][PF_6] (Cp = cyclopentadiene) form 1:1 adducts with both α- and β-CD. J. F. Stoddart et al., unpublished.

[5] The pH of the D_2O solution increases slowly with time as NH_3 is released from the first coordination sphere. The lability of the NH_3 ligands in [Rh(cod)$(NH_3)_2$][PF_6] has been observed previously (H. M. Colquhoun, S. M. Doughty, A. M. Z. Slawin, J. F. Stoddart, D. J. Williams, *Angew. Chem. 97* (1985) 124; *Angew. Chem. Int. Ed. Engl. 24* (1985) 135).

[6] Experimental: **1**·6 H_2O: 80 mg (0.20 mmol) [Rh(cod)$(NH_3)_2$][PF_6] was dissolved in H_2O (1 mL) containing 240 mg (0.25 mmol) α-CD with gentle warming. On cooling, a white precipitate formed initially followed by a crop of fine yellow crystals. On gentle warming, the yellow crystals redissolved leaving behind the white precipitate which was filtered off. *Very slow cooling* during 6 h afforded a few yellow crystals (m.p. > 200 °C, decomp.), suitable for X-ray structural investigation.

[7] Crystal data for **1**·6 H_2O: $P2_12_12_1$, $a = 14.035(4)$, $b = 19.517(6)$, $c = 23.803(6)$ Å, $V = 6520$ Å^3, $Z = 4$, $\rho_{calc} = 1.5$ g cm^{-3}, $\mu(Cu_{K\alpha}) = 34$ cm^{-1}, 4015 independent observed reflections with [$|F_0| > 3\sigma(|F_0|)$, $\theta \leq 58°$], $R = 0.086$, $R_w = 0.077$. An empirical absorption correction was applied. The structure was solved by the heavy-atom method and refined anisotropically. Further details of the crystal structure investigations can be obtained from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW. Any request should be accompanied by the full literature citation for this communication.

[8] Interestingly, there is an N-H···F interaction (3.07 Å) between N1 and one of the F atoms of the PF_6^- counterion.

[9] Characteristically, there is an extensive network of H bonds, some involving the H_2O molecules and others linking symmetry-related α-CD ligands. The formula **1**·6 H_2O merely indicates the presence of 6 H_2O molecules in the asymmetric unit: there are, however, 7 discrete sites occupied by the six H_2O molecules—5 of these have 100% occupancy and the other 2 have 50% occupancy.

[10] Interestingly, the four ethylene protons in the en ligand of **2** resonate as an AA'BB' system in the range $\delta = 2.64$–2.78, indicating the anisochronous nature of the enantiotopic CH_2 protons in the chiral environment of α-CD. In contrast, a singlet for these protons is observed in the ^{1}H-NMR spectrum of [Rh(cod)(en)·β-CD][PF_6] in D_2O.

[11] In the ^{1}H-NMR spectrum of [Rh(cod)(en)·β-CD][PF_6] in D_2O, the signal for H3 is shifted to lower frequency relative to that observed in the spectrum of free β-CD.

[12] The chemical shift differences observed on changing progressively the concentration x [in mol kg^{-1} (D_2O)] of the 1:1 adduct were analyzed using the equation,

$$\Delta = \Delta_0 - (\Delta/x)^{1/2} \cdot (\Delta_0/K_a)^{1/2}$$

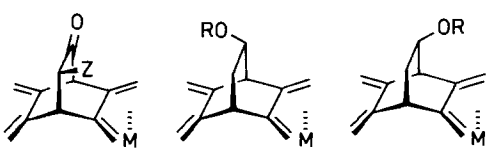
where Δ is the difference between the observed chemical shift for H3 in the solution of the 1:1 adduct (at equilibrium) and that for H3 in free α-CD, and Δ_0 is the difference between the limiting chemical shift of the 1:1 adduct (assumed fully formed) and that for H3 in the free α-CD. A plot of Δ against $(\Delta/x)^{1/2}$ gave a straight line and the K_a value was obtained from the slope, $-(\Delta_0/K_a)^{1/2}$, and the intercept, Δ_0, which equalled 29.7 Hz.

Stereoselective Nucleophilic Additions to a Bicyclic Ketone Controlled by a Remote Tricarbonyl(diene)iron Moiety**

By *Jean-Christophe Zwick* and *Pierre Vogel**

A great deal of effort has been devoted to understanding relative asymmetric induction in nucleophilic additions to chiral carbonyl compounds.[1] A variety of transition-state models based on steric factors[2] or on the interaction of the σ-orbitals of α-substituents with the π-orbital of the carbonyl group have been proposed.[3] We report on the hydride addition to the ketone **1** in which asymmetry is induced by a remote tricarbonyl(diene)iron moiety.[4]

The hydride reductions of **1** give alcohols **2** and **3**, whose ratio is dependent on the reagent, solvent, and temperature (Table 1). The hydride always prefers to attack



1, Z = H
4, Z = D
2, R = H
5, R = SO_2Me
3, R = H
6, R = SO_2Me
M = $Fe(CO)_3$

Table 1. Stereoselectivity of the hydride reductions of **1**.

Reagent	Solvent	Conc. [M] (molar ratio)	T [°C]	t [min]	**2**/**3** [a] (yield [%])
$NaBH_4$	THF [b]	0.1 (3.5)	20	1020	2:1 (90)
$NaBH_4$	THF/*i*PrOH 1:5	0.08 (35)	20	3	4:1 (93)
$NaBH_4$	THF/H_2O 1:1	0.06 (15)	20	10	4:1 (90)
$NaBH_4$	THF/*i*PrOH 1:1	0.055 (16)	−50	1800	5.2:1 (90)
Vitride [c]	THF/toluene 1:1	0.01 (24)	−78	120	6.5:1 (95)
$LiAlH_4$	THF	0.07 (12)	−78	30	11.5:1 (90)
$LiBH_4$	THF/toluene 1:1	0.03 (14)	−78	360	7.7:1 (90)
$LiBHEt_3$	THF	0.09 (12)	−78	180	20.7:1 (90)
DIBAH	THF/toluene 1:1	0.05 (13.5)	−78	90	1.5:1 (90)

[a] Determined by ^{1}H-NMR spectroscopy (360 MHz). [b] Tetrahydrofuran. [c] Sodium bis(2-methoxyethoxy)aluminum hydride.

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the CO group on its *syn* face with respect to the $Fe(CO)_3$ moiety, giving **2**, whose structure was established by 360-MHz ^{1}H-NMR spectroscopy and confirmed by lanthanide-induced shift (LIS) measurements (Table 2[5]). It is noteworthy that the base-catalyzed H/D exchange of **1** is also stereoselective, **4** being formed ca. 100 times faster than the corresponding dideuterated derivative.[6]

Table 2. Physical data for **2** [a].

m.p. 152°C

UV (EtOH): $\lambda = 215$ (sh, $\varepsilon = 19400$), 282 (sh, 2200) nm

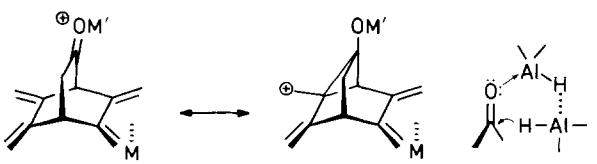
IR (KBr): $\nu = 3460$, 3010, 2970, 2940, 2900, 2870, 2050 (s), 2000 (s), 1970 (s), 1630 cm^{-1}

^{1}H-NMR ($CDCl_3$) [Eu(thd)$_3$] [b]: $\delta = 5.5$ (s, 1H [19.7]), 5.28 (s, 1H [16.1]), 4.93 (s, 1H [25]), 4.82 (s, 1H [15.2]), 4.35 (m, $J = 9.0$, 3.0, 2.5 Hz, H–C(2) [100]), 3.25 (d, $J = 3$ Hz, H–C(1) [53.8]), 3.18 (t, $J = 3$ Hz, H–C(4) [21.3]), 2.49 (m, $J = 13.0$, 9.0, 3.0 Hz, H–C(3) *anti* with respect to OH [36.2]), 1.8 (2d, $J = 2.5$ Hz, 2H [9.4] and [10.4]), 1.71 (m, $J = 13.0$, 3.0, 2.5 Hz, H–C(3) *syn* with respect to OH [68]), 0.25 and 0.20 (2d, $J = 2.5$ Hz, 2H [8.5] and [9.0])

MS (70 eV): *m/z* 314 (1), 286 (23), 258 (60), 230 (100), 212 (8), 156 (18), 141 (11)

[a] Correct elemental analysis. [b] thd = 2,2,6,6-tetramethyl-3,5-heptanedionate.

Preliminary X-ray crystallographic data on **1**[7] showed that the two faces of the ketone offer the same steric hindrance toward nucleophilic attack. Thus, the selectivities of the reactions **1**→**2** and **1**→**4** cannot be attributed to steric factors in the ground state. Unless there is a special distortion of the bicyclic skeleton of **1** in solution,[6] electronic factors must be invoked. The field effect of the $Fe(CO)_3$ group in **1** could induce a preferred *syn* attack of the nucleophile (**1**→**2**).[8] Accordingly, the transition state with the largest dipole moment should lead to the highest stereoselectivity. This is consistent with the observation that the reduction of **1** by $LiAlH_4$ or $LiBHEt_3$, which takes place via a partially ionized transition state having a high dipole moment,[9] gives better selectivity than that with diisobutylaluminum hydride (DIBAH), the transition state of which is non-ionized and has a smaller dipole moment[10] (Table 1).



7 M=Fe(CO)$_3$ **8** **9**

Alternatively, the results could be interpreted in terms of charge delocalization involving the uncomplexed diene moiety in **1** (**7**↔**8**). The stronger the charge development, the more **8** contributes and the more reaction **1**→**2** is favored, in agreement with our results. The low stereoselectivity for the reaction of **1** with DIBAH could be attributed to the smaller charge development in the transition state (see **9**[10]).[11]

The relative ability of the uncomplexed diene and tricarbonyl(diene)iron moieties to participate in the charge delocalization in **7** has been tested by comparing the rates of solvolysis of the methanesulfonates **5** and **6** (S_N1 reaction). In $(CF_3)_2CHOH/H_2O$ (2:1, 2,6-lutidine as buffer, 25°C) **6** was hydrolyzed at least 2000 times faster than **5**.

At present neither of the possible explanations discussed above to explain the observed stereoselectivities in the reduction of **1** can be dismissed. Our work, however, demonstrates that a remote tricarbonyl(diene)iron moiety can influence the stereoselectivity of nucleophilic addition to a carbonyl function and that this effect is not due to a steric factor.

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1, 87224-67-7; **2**, 97134-71-9; **3**, 87134-56-3; **5**, 97102-74-4; **6**, 97134-72-0; DIBAH, 1191-15-7; $NaBH_4$, 16940-66-2; $LiAlH_4$, 16853-85-3; $LiBH_4$, 16949-15-8; $LiBHEt_3$, 22560-16-3; vitride, 22722-98-1.

[1] H. S. Mosher, J. D. Morrison, *Science 221* (1983) 1013; P. A. Bartlett, *Tetrahedron 36* (1980) 2.

[2] D. J. Cram, D. R. Wilson, *J. Am. Chem. Soc. 85* (1963) 1245; J. W. Cornforth, R. H. Cornforth, K. K. Mathew, *J. Chem. Soc. 1959*, 112; G. J. Karabatsos, *J. Am. Chem. Soc. 89* (1967) 1367; M. Chérest, H. Felkin, N. Prudent, *Tetrahedron Lett. 1968*, 2199; O. Arjona, R. Pérez-Ossorio, A. Pérez-Rubalcaba, M. L. Quiroga, *J. Chem. Soc. Perkin Trans. 2 1981*, 597.

[3] K. Fukui: *Theory of Orientation and Stereoselection*, Springer, Heidelberg 1975; K. Fukui, H. Fujimoto, S. Inagaki, *J. Am. Chem. Soc. 98* (1976) 4054; M. N. Paddon-Row, N. G. Rondan, K. N. Houk, *ibid. 104* (1982) 7162; E. M. Burgess, C. L. Liotta, *J. Org. Chem. 46* (1981) 1703; N. T. Anh, O. Eisenstein, *Nouv. J. Chim. 1* (1977) 61; see also: H. B. Bürgi, J. M. Lehn, G. Wipff, *J. Am. Chem. Soc. 96* (1974) 1956; J. Klein, *Tetrahedron 30* (1974) 3349.

[4] For reductions of bicyclic ketones remotely perturbed, see, e.g., H. C. Brown, J. Muzzio, *J. Am. Chem. Soc. 88* (1966) 2811; see also J. Warkentin, *Can. J. Chem. 48* (1970) 1391; P. G. Gassman, J. G. Schaffhausen, P. W. Raynolds, *J. Am. Chem. Soc. 104* (1982) 6408. For acyclic ketones, see: G. Solladié, C. Greck, G. Demailly, A. Solladié-Cavallo, *Tetrahedron Lett. 23* (1982) 5047; M. Tramontini, *Synthesis 1982*, 605.

[5] Preparation and structure of **1** and **3**, see: R. Gabioud, P. Vogel, *Helv. Chim. Acta 66* (1983) 1134; see also E. Tagliaferri, P. Campiche, R. Roulet, R. Gabioud, P. Vogel, G. Chapuis, *ibid. 68* (1985) 126.

[6] R. Gabioud, P. Vogel, *Tetrahedron Lett. 24* (1983) 1983.

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Diboriranides and a 1,3-Diboraallyl System with *B*-H-*B* Bridge**

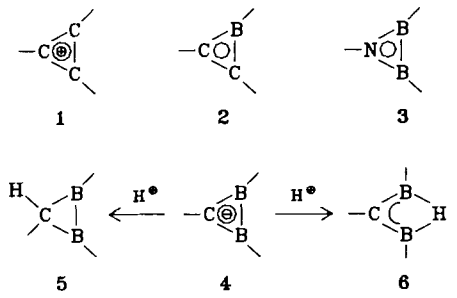
By *Rolf Wehrmann, Harald Meyer,* and *Armin Berndt**

Dedicated to Professor Karl Dimroth on the occasion of his 75th birthday

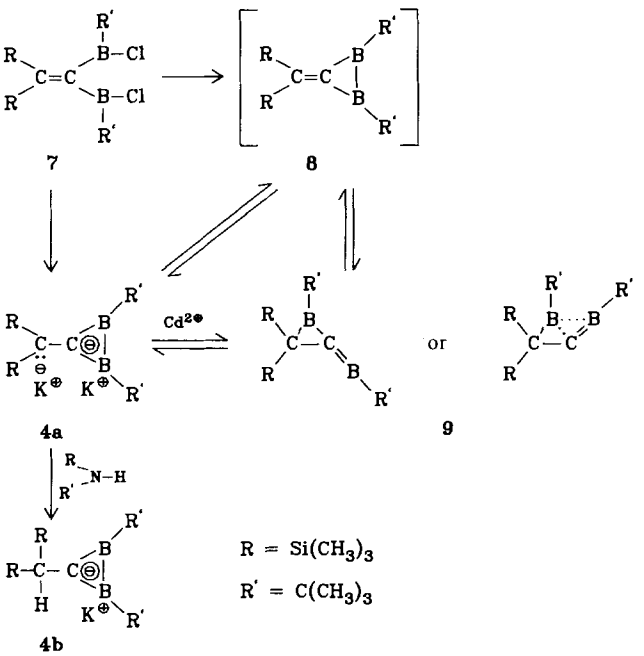
Diboriranides, **4**, are isoelectronic with the 2π-arenes **1**–**3**;[1] protonation of **4** could lead to diboriranes **5** or to 1,3-diboraallyl systems containing a *B*-H-*B* bridge, **6**.[2] According to molecular orbital calculations unsubstituted **5** has planar geometry at the ring C atom, while the corresponding species **6** was found to be considerably lower in energy (31.7 kcal/mol) than **5**.[3] We report here on the synthesis of the first derivatives of **4** and **6**.

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[**] This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.



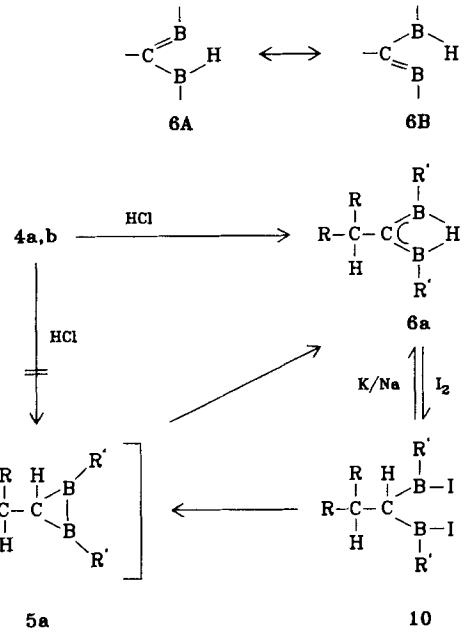
Reaction of the dichloride **7**[4] with four equivalents of potassium or K/Na alloy in tetrahydrofuran (THF) leads to formation of the diboriranide **4a**. Oxidation of **4a** with $CdCl_2$ leads to the boranediylborirane **9**,[5,6] which is also accessible by reaction of **7** with two equivalents of K/Na alloy in pentane. Reduction of **9** with K/Na alloy in pentane affords **4a** in ca. 20% yield.[7] These reactions can easily be explained in terms of the methylenediborirane **8** as common intermediate.



Reaction of **4a** with the very weak acid *tert*-butyl(trimethylsilyl)amine leads to formation of the diboriranide **4b**.

The structures **4a** and **4b** follow from ^{1}H-, ^{13}C-, ^{11}B-, and ^{29}Si-NMR spectra;[8] they are consistent with the formation and reactions of these compounds. The chemical shift of the boron atoms ($\delta(^{11}B) = 39$ and 45, respectively) is similar to that in borirenes **2** (36-49).[9] The ring C atoms ($\delta(^{13}C) = 162$ and 148, respectively) are shielded compared to those in borirenes with partial positive charge on these atoms ($\delta(^{13}C) = 180$-195).[9] **4a** is remarkably thermostable in the absence of solvents which can function as proton-donators (THF): heating the solid salt to 150°C for five hours does not lead to any NMR spectroscopically measurable changes.

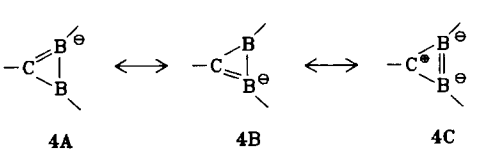
Further protonation of **4b** with bis(trimethylsilyl)amine or reaction of **4a** or **4b** with gaseous HCl does not lead to diborirane **5a**, but to the isomeric **6a**.[8] In the undecoupled ^{13}C-NMR spectrum, the signal of the C atom bearing the two boron atoms is not a doublet but a singlet. Also its position ($\delta = 128$) is not reconcilable with **5a**, but is so with



6a. The H-bridge between the boron atoms of **6a** follows from the characteristic[10] broad IR band at 1580 cm^{-1}, which, in deuterated **6a** (reaction of **4b** with $(Me_3Si)_2N$-D), is shifted to 1185 cm^{-1}. We ascribe the appearance of two signals for the *tert*-butyl groups on cooling **6a** to hindered rotation of the $(Me_3Si)_2CH$ group[11] ($\Delta G^{+} = 13.4$ kcal/mol). An explanation in terms of a rapidly established equilibrium between **6A** and **6B** can be ruled out because of the absence of an IR or Raman band in the region for B=C double bonds.[5,6b] **6A** and **6B** are merely resonance formulas of **6a** in which two π electrons are delocalized over the three centers B-C-B; thus a 1,3-diboraallyl system is realized. The *B*-H-*B* bridge in **6a** is the first 3-center 2-electron bond with only *tri*coordinated boron atoms. The NMR signal of the proton of the *B*-H-*B* bridge appears in the region for vinyl protons at $\delta = 4.9$ (verified by ^{2}H-NMR spectroscopy of the deuterated compound). Signals of the protons of BH_2B bridges with *tetra*coordinated boron atoms appear at $\delta = 0.5$ to 1.5.[11]

6a neither reacts with the strong base **4a** nor with K/Na alloy or with strong mineral acids (HCl, HBF_4 in ether). It reacts smoothly with iodine to give **10**,[8] whereupon the hydrogen migrates from the boron to the carbon (doublet in the undecoupled ^{13}C-NMR spectrum at $\delta = 47.7$). Dehalogenation of **10** with K/Na alloy does not lead to the primarily expected diborirane **5a**, but back to **6a**. Apparently, **5a** rapidly rearranges into **6a**.

The formation of **6a** instead of **5a** via two independent routes confirms the results of the calculations,[3] according to which the unsubstituted diboraallyl compound **6** with a *B*-H-*B* bridge is considerably more stable than the corresponding diborirane **5**.



Despite the negative charge of the diboriranides **4a** and **4b**, their ring C atom (with $\delta = 162$ and 148, respectively) is deshielded compared to that of **6a** (128). This points to ap-

preciable participation of the resonance structure **4C**, and thus to considerable double-bond character of the B-B bond, which is also found from calculations.[2]

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[2] In reference [3] **6** is formulated with additional σ-bonding between the boron atoms and cyclic delocalization of the π-electrons. The NMR data of **6a** are not consistent with a structure with tetracoordinated boron. In the meantime Prof. *Schleyer* has informed us that further ab initio calculations (6-31G*) have given a three-center *B*-H-*B* bridge with only weak B-B bonding (distance 1.736 Å) and a short C-B distance of 1.432 Å for unsubstituted **6**. For unsubstituted **4**, bond lengths of 1.463 Å (C-B) and 1.600 Å (B-B) have been calculated, which indicate considerable double bond character and thus cyclic delocalization (aromaticity).
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[4] H. Klusik, C. Pues, A. Berndt, *Z. Naturforsch. B 39* (1984) 1042.
[5] H. Klusik, A. Berndt, *Angew. Chem. 95* (1983) 895; *Angew. Chem. Int. Ed. Engl. 22* (1983) 877.
[6] a) P. H. M. Budzelaar, P. von R. Schleyer, K. Krogh-Jespersen, *Angew. Chem. 96* (1984) 809; *Angew. Chem. Int. Ed. Engl. 23* (1984) 825; b) G. Frenking, H. F. Schaefer III, *Chem. Phys. Lett. 109* (1984) 521.
[7] The structures of the other products could not yet be determined.
[8] Spectra of **4a** and **4b** in [D$_8$]THF, and of **6a** and **10** in $CDCl_3$; δ values. **4a**: yellow-orange crystals, m.p. (decomp.) >200°C, yield 82%; ^{1}H-NMR: 1.07 (s, 18H, *t*Bu), 0.01 (s, 18H, $SiMe_3$); ^{13}C-NMR (−35°C): 161.7 (br. s, 1C, BCB), 36.4 (s, 1C, CSi_2), 35.1 (q, 6C, $C(CH_3)_3$), 23.4 (br. s, 2C, CMe_3), 4.7 (q, 6C, $SiMe_3$); ^{11}B-NMR: 39; ^{29}Si-NMR: −18.3.—**4b**: yield >90% (^{13}C-NMR spectroscopically); ^{1}H-NMR: 1.4 (s, 1H, $HCSi_2$), 0.91 (s, 18H, *t*Bu), −0.09 (s, 18H, $SiMe_3$); ^{13}C-NMR (−30°C): 147.8 (br. s, 1C, BCB), 33.7 (q, 6C, $C(CH_3)_3$), 26.8 (d, 1C, $HCSi_2$, $^1J(CH)=94$ Hz), 22.6 (br. s, 2C, CMe_3), 1.2 (q, 6C, $SiMe_3$); ^{11}B-NMR: 45; ^{29}Si-NMR: −0.6.—**6a**: colorless liquid, b.p. 68°C/10^{-2} torr, yield >85% (^{13}C-NMR spectroscopically); ^{1}H-NMR: 4.9 (br., 1H, B-H-B), 1.75 (s, 1H, $HCSi_2$), 1.09 (s, 18H, *t*Bu), 0.00 (s, 18H, $SiMe_3$); ^{13}C-NMR (−38°C): 128 (br. s, 1C, BCB), 30.1, 29.7 (q, each 3C, $C(CH_3)_3$), 19.9, 18.9 (br. s, each 1C, CMe_3), 18.4 (dd, 1C, $HCSi_2$, $^1J(CH)=110.4$ Hz, long-range coupling 13 Hz), −0.3 (q, 6C, $SiMe_3$); ^{11}B-NMR: 27; ^{29}Si-NMR: −0.9; MS (28 eV): *m/z* 308 ($M^{\oplus}$, 95%), 251 ($M^{\oplus}-57$, 51%).—**10**: colorless crystals, decomp. at RT ($\tau_{1/2}\approx 1$ h), yield quantitative (^{13}C-NMR spectroscopically); ^{1}H-NMR: 3.43 (d, 1H, HCB, $^3J(HH)=2$ Hz), 1.13 (s, 18H, *t*Bu), 0.93 (d, 1H, $HCSi_2$, $^3J(HH)=2$ Hz), 0.24 (s, 18H, $SiMe_3$); ^{13}C-NMR (−35°C): 47.7 (br. d, 1C, HCB, $^1J(CH)=102$ Hz), 33.7 (br. s, 2C, CMe_3), 29.2 (q, 6C, $C(CH_3)_3$), 17.2 (d, 1C, $HCSi_2$, $^1J(VH)=103$ Hz), 3.7 (q, 6C, $SiMe_3$); ^{11}B-NMR: 83.
[9] C. Pues, A. Berndt, *Angew. Chem. 96* (1984) 306; *Angew. Chem. Int. Ed. Engl. 23* (1984) 313; C. Habben, A. Meller, *Chem. Ber. 117* (1984) 2531.
[10] B. Wrackmeyer, R. Köster in Houben-Weyl: *Handbuch der Organischen Chemie*, 4th Ed., Vol. XIII/3c, Thieme, Stuttgart 1984, p. 440, 444.
[11] In 1,1,2,2-tetrakis(trimethylsilyl)ethane the barrier to rotation is $\Delta G^{\ddagger}_{353}\approx 18.8$ kcal/mol: S. Brownstein, J. Donogues, D. Lindsay, K. U. Ingold, *J. Am. Chem. Soc. 99* (1977) 2073.

Chemoselective Multicomponent Synthesis of α,β-Unsaturated Esters and Lactones and of Their Diels-Alder Adducts

By *Hans Jürgen Bestmann** and *Rainer Schobert*

Dedicated to Professor Hans Musso on the occasion of his 60th birthday

Chemoselective multicomponent syntheses, which do not require the isolation of intermediates or the use of protecting groups, are increasingly attracting the attention of preparative organic chemists. We have found that α,β-unsaturated esters **5** are obtainable in good to very good yields via a three-component reaction between an alcohol **1**, an aldehyde **2**, and the easily accessible ketenylidenetriphenylphosphorane **3**.[1] Presumably, **1** and **3** initially react to give **4**,[2] which then undergoes an *E*-stereospecific Wittig reaction[3] to give **5**.

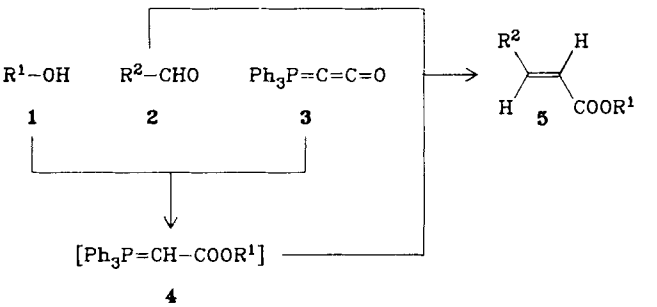
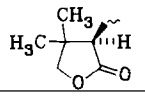


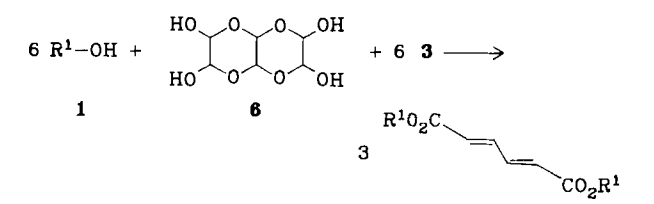
Table 1. α,β-Unsaturated esters **5** via three-component synthesis [a].

	R^1	R^2	Yield [%]	B.p. [°C/torr]	$[\alpha]_D^{25}$ [b] (EtOH)
5a	n-C_6H_{13}	n-C_4H_9	94	70/0.01	–
5b	n-C_4H_9	n-C_4H_9	92	60/0.01	–
5c	(*S*)-MeEtCHCH$_2$	n-C_4H_9	90	61/0.01	+5.2 ($c=1$)
5d	(−)-Menthyl	n-C_3H_7	81	92/0.01	−66.8 ($c=1$)
5e		n-C_3H_7	55	110/0.01	+10.6 ($c=0.2$)

[a] A solution of **1** (10 mmol), **2** (10 mmol), and **3** (3.02 g, 10 mmol) in 100 mL of dry toluene was refluxed for 12 h under inert atmosphere. After evaporation of the solvent, the residue was filtered through 20 g of silica gel with ca. 200 mL of hexane/ether (1:1), the eluate was evaporated, and the final residue was distilled in vacuum. [b] By saponification of the esters **5**, the optically active alcohols **1** are obtained, which have the same rotation as at the start of the reaction sequence.

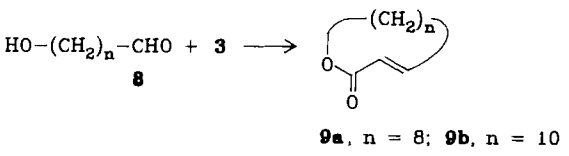
Table 1 shows that the chiral esters **5**, which are important for enantioselective diene syntheses,[4] are very easily accessible from the optically active alcohols **1**; as expected, the reaction takes place without racemization (as shown by saponification of the esters to the optically pure alcohols).

Similarly, the (*E,E*)-muconic ester **7** is formed from **1**, trimeric glyoxal hydrate **6**, and **3** in a molar ratio of 6:1:6. In this case, too, chiral compounds such as **7b**, which may be of interest for enantioselective [2+4] cycloadditions involving inverse electron demand, are easily obtainable (Table 2).



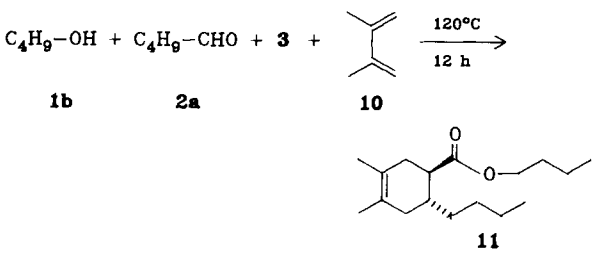
When ca. 0.1 M solutions of long-chained ω-hydroxy aldehydes **8** are added slowly to a refluxing solution of **3** in xylene (high-dilution conditions), the macrocyclic lactones **9** are formed (Table 2). The yields are similar to or better than those obtained in the lactone synthesis we described earlier,[5] in which the aldehyde group had to be protected first as the acetal.

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9a, n = 8; **9b**, n = 10

Diels-Alder adducts of α,β-unsaturated esters **5** may be obtained directly via a four-component reaction in a reaction bomb at 120°C. Examples include the syntheses with 2,3-dimethylbutadiene **10** and cyclopentadiene **12** as diene components (Table 2).



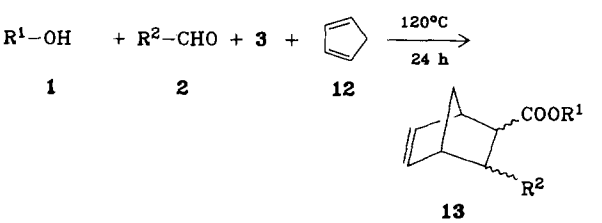


Table 2. Muconic esters **7** and unsaturated macrocyclic lactones **9** via three-component synthesis; cycloadducts **11** and **13** via four-component synthesis.

	R^1	R^2	Yield [%]	B.p.[°C/torr] (m.p.[°C])	$[\alpha]_D^{25}$ ($CHCl_3$)
7a	n-C_4H_9	—	80	73–75/0.01 [a] (34–35)[b]	—
7b	(−)-Menthyl	—	80	(166)[b]	−83 (c = 0.5)
9a	—	—	60–65	58/0.01	—
9b	—	—	60–65	78.5/0.02	—
11	—	—	51	101/0.01	—
13a	(n-C_3H_7)$_2$CH	n-C_3H_7	55	90/0.01	—
13b	(−)-Menthyl	C_2H_5	58	110/0.01	−53.8 (c = 1.16)

[a] Kugelrohr, air-bath heating. [b] From hexane.

A stereochemically pure cycloadduct **11** is formed from butanol **1b**, pentanal **2a**, **3**, and **10**. The bicyclo[2.2.1]heptene derivatives **13** are obtained as diastereomeric mixtures (**13a**, 77 : 23; **13b**, 80 : 20). A definite *endo-exo* assignment has not yet been possible.

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Oxidation of α,β-Unsaturated Esters and Lactones with Selenium Dioxide to γ-Oxo or γ-Hydroxy Derivatives; Synthesis of (±)-A 26771 B and Norpyrenophorin

By *Hans Jürgen Bestmann** and *Rainer Schobert*

Dedicated to Professor Hans Musso on the occasion of his 60th birthday

γ-Oxo-α,β-unsaturated esters **2** are interesting synthetic building blocks, for example, for [2+4] cycloadditions. We have found that these compounds are easily accessible via oxidation of α,β-unsaturated esters[1] with SeO_2 in anhydrous dioxane.[2] Chiral esters such as **2c** are of particular interest for enantioselective cycloadditions.[3]

When the reaction is carried out in dioxane containing 3% water, the γ-hydroxy-α,β-unsaturated esters **3**[4] are obtained. Table 1 gives several examples.

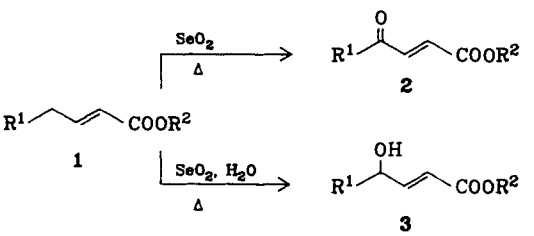


Table 1. Esters **2** [a] and **3** [b] via oxidation of α,β-unsaturated esters **1** with selenium dioxide.

	R^1	R^2	Yield[%]	B.p.[°C/torr]
2a	n-C_3H_7	n-C_6H_{13}	89	92/0.01
2b	n-C_3H_7	n-C_4H_9	90	76/0.01
2c	C_2H_5	(−)-Menthyl	78	99/0.02 [c]
3a	n-C_3H_7	n-C_6H_{13}	52	[d]
3b	C_2H_5	CH(n-C_3H_7)$_2$	61	105/0.01
3c	CH_3	(−)-Menthyl	60	132/0.01 [e]

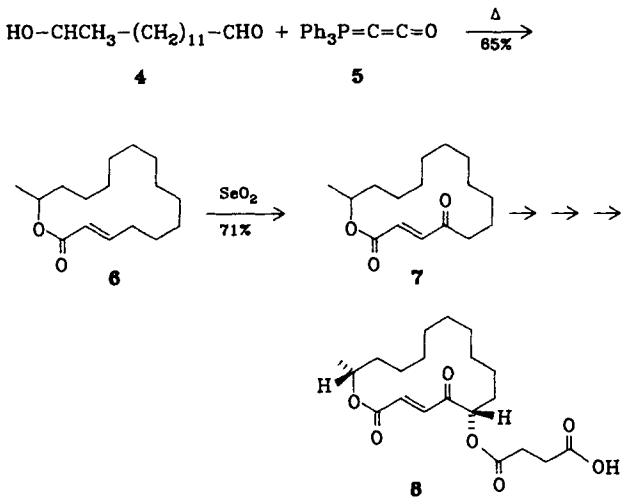
[a] SeO_2 (14 mmol) is added to a solution of **1** (10 mmol) in ca. 100 mL of dry dioxane, and the mixture is heated under inert atmosphere for 48 h. The selenium is filtered off, the filtrate is concentrated, and the residue is purified by distillation or chromatography. [b] The same procedure is used as in [a] except that ca. 3 mL of water is added to the reaction mixture. [c] $[\alpha]_D^{25}$ −59.6 (c = 1.0; EtOH). [d] Chromatographic purification on silica gel 60; R_f = 0.44 (hexane/ether 3 : 1). [e] $[\alpha]_D^{25}$ −77.8 (c = 1.11, $CHCl_3$).

A number of macrolide antibiotics are γ-oxo or γ-hydroxy-α,β-unsaturated lactones, e.g., cytochalasins,[5] pyrenophorins,[6] the macrocycle A26771B,[7] and brefeldin A.[8] The use of selenium dioxide oxidation in the synthesis of such compounds is illustrated by the following examples.

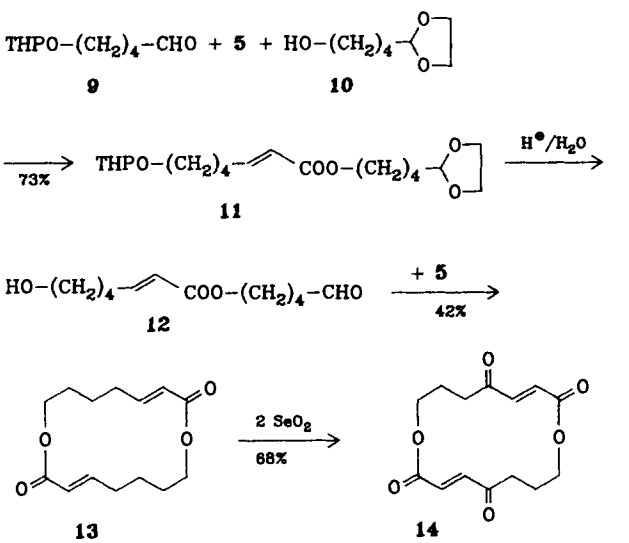
(±)-A26771B **8**: The hydroxy aldehyde **4** undergoes cyclization with ketenylidenetriphenylphosphorane **5** to give the α,β-unsaturated lactone **6**.[1] Oxidation of **6** with selenium dioxide gives the γ-oxo compound **7**, whose transformation into the antibiotic **8** has already been described.[9, 10] (**6**: b.p. = 100°C/0.05 torr; **7**: b.p. = 93°C/0.05 torr (kugelrohr, air-bath heating); **8**: m.p. = 131°C.)

Norpyrenophorin **14**: The α,β-unsaturated ester **11** is obtained by three-component reaction[1] of the tetrahydropyranyl ether **9** and the acetal **10** of ω-hydroxypentanal with **5** in benzene and its protecting groups are then

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cleaved in acid. The ω-hydroxy aldehyde **12** so formed is not isolated but rather cyclized to the diolide **13** by addition of a ca. 0.1 M solution of **12** in xylene to the molar equivalent amount of **5** in refluxing xylene (high-dilution conditions).[1] The subsequent oxidation of **13** with two



equivalents of selenium dioxide affords norpyrenophorin **14**[1] (**11**: b.p. = 125–128 °C/0.05 torr (kugelrohr, air-bath heating); **13**: m.p. = 55 °C (hexane), b.p. = 127 °C/0.01 torr; **14**: m.p. = 131 °C).

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CAS Registry numbers:
1 (R^1 = *n*-C_3H_7, R^2 = *n*-C_6H_{13}), 97827-33-3; **1** (R^1 = *n*-C_3H_7, R^2 = *n*-C_4H_9), 97827-34-4; **1** ($R^1 = C_2H_5$, R^2 = (−)-menthyl), 97827-35-5; **1** ($R^1 = C_2H_5$, $R^2 = CH(n\text{-}C_3H_7)_2$, 97827-36-6; **1** ($R^1 = CH_3$, R^2 = (−)-menthyl), 57564-56-4; **2a**, 97827-37-7; **2b**, 97827-38-8; **2c**, 97827-39-9; **3a**, 97827-40-2; **3b**, 97827-41-3; **3c**, 97827-42-4; (±)-**4**, 97827-43-5; **5**, 15596-07-3; (±)-**6**, 97827-44-6; (±)-**7**, 77413-26-4; (±)-**8**, 56448-20-5; **9**, 14194-86-6; **10**, 83516-55-6; **11**, 97827-45-7; **12**, 97827-46-8; **13**, 97827-47-9; **14**, 69604-23-5.

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Chiral Poly(9,9′-spirobifluorene) Crown Ethers

By *Max Dobler, Miljenko Dumić, Martin Egli,* and *Vladimir Prelog**

The first two members of the poly(9,9′-spirobifluorene) crown ether series, bis(9,9′-spirobifluorene)-[26]crown-4 **4** and bis(9,9′-spirobifluorene)-[32]crown-6 **5**, were initially obtained as side products in the preparation of the corresponding mono(9,9′-spirobifluorene) crown ethers from 2,2′-bis(bromomethyl)-9,9′-spirobifluorene **1** and the alkoxides of ethylene glycol and diethylene glycol, respectively.[1] Direct synthesis via condensation of **1** with alkoxides of the two dihydroxy ethers **2** and **3** in the presence of potassium *tert*-butoxide affords the cyclic products only in moderate, nonreproducible yields.

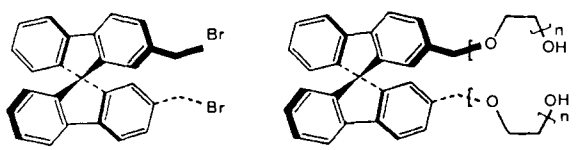
In the meantime, it has been found that the two bis(9,9′-spirobifluorene) crown ethers **4** and **5** exhibit, as ionophores, high enantioselectivity for salts of biologically active α-amino alcohols (e.g., ephedrine),[2] thus enhancing their interest. We have attempted to improve the second procedure of preparation of the compounds **4** and **5** by modifying the reaction conditions. It was finally possible to obtain **4** and **5** reproducibly in 40–50% yield by reaction of **1** with the dihydroxy ethers **2** and **3**, which may be prepared quantitatively, under the conditions of phase-transfer catalysis.[3]

Upon investigation of the crude products by thin layer chromatography, the two bis(9,9′-spirobifluorene) crown ethers **4** and **5** were found to be accompanied by several closely related compounds, which could be separated by chromatography on silica gel. These compounds were identified as poly(9,9′-spirobifluorene) crown ethers **6** to **9** on the basis of their UV, CD, NMR, and, in particular, mass spectra[4] and are summarized in Table 1.

The crown ethers **6** to **9**[5] are striking in several respects. They are well-defined cyclic compounds with a large number of ring members (52 to 104). They belong to the class of chiral yet highly symmetrical compounds (point group symmetry C_n, n = 4, 6, 8), for which only a few examples are known.[6] As crown ethers, they are potential host molecules. On account of their chirality, they are expected to be enantioselective, like the compounds **4** and **5**.[2] It is therefore advantageous that their sense of chirality, or absolute configuration, is known.

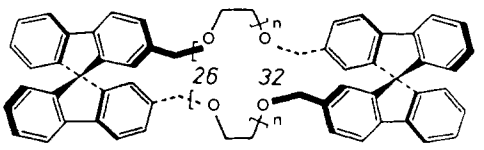
Characteristic of the poly(9,9′-spirobifluorene) crown ethers is the strong binding of solvent and crystallization

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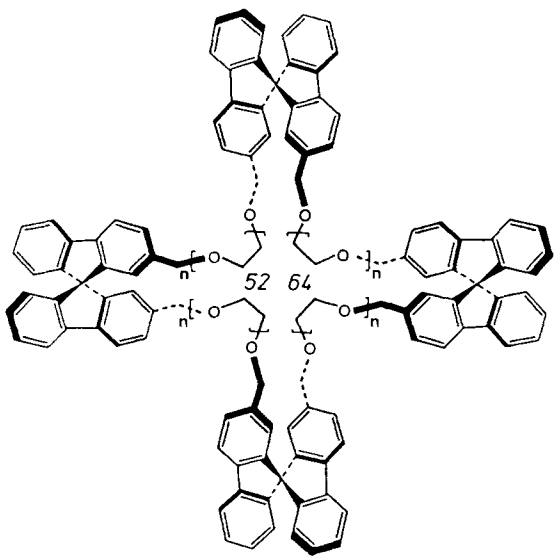


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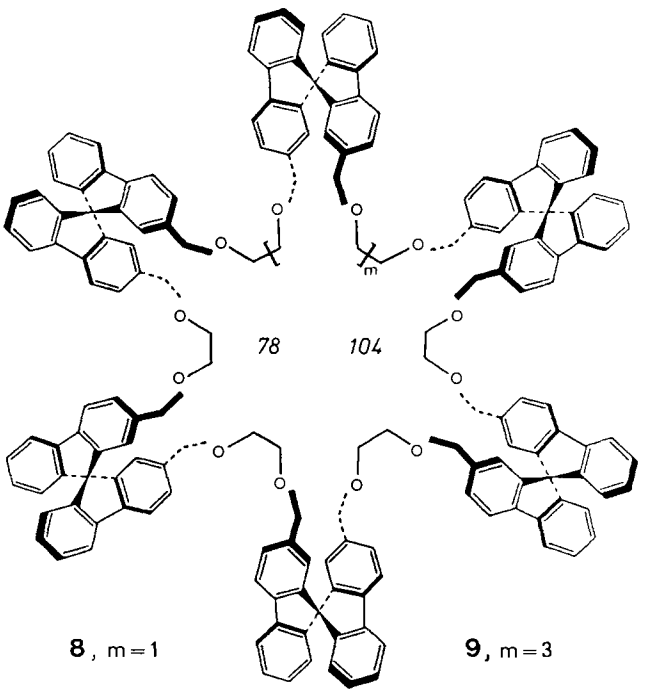
2, n=1 ; 3, n=2



4, n=1 ; 5, n=2



6, n=1 ; 7, n=2



8, m=1 9, m=3

Table 1. Poly(9,9′-spirobifluorene) crown ethers [4].

	Ring members	Empirical formula	M_r calcd	M_r found (MS)	Yield [%]	R_f	$[\alpha]_D$ [a] [°]
4 Bis	26	$C_{58}H_{44}O_4$	805.0 + 2 C_6H_6 961.2	M^+ 804 [b]	42	0.48 [c]	+138
6 Tetra	52	$C_{116}H_{88}O_8$	1610.0	$[M+Na]^+$ 1631 [d]	10.5	0.37 [c]	−12
8 Hexa	78	$C_{174}H_{132}O_{12}$	2415.0	$[M+K]^+$ 2451 [d]	2	0.28 [c]	−41
9 Okta	104	$C_{232}H_{176}O_{16}$	3220.0	$[M+Na]^+$ 3243.4 [e]	0.1	0.20 [c]	—
5 Bis	32	$C_{62}H_{52}O_6$	893.1 + CH_2Cl_2 978.0	M^+ 892 [b]	45	0.56 [f]	+29
7 Tetra	64	$C_{124}H_{104}O_{12}$	1786.2	$[M+K]^+$ 1823 [d]	7	0.37 [f]	−13

[a] $CHCl_3$, $c \approx 1$. [b] Recorded on a Hitachi-Perkin Elmer RMU-6M; direct injection, EI, 70 eV. [c] Benzene/ethyl acetate (9 : 1). [d] Recorded on a KRATOS MS 50; FAB, matrix 3-nitrobenzyl alcohol + KI, Xe 6 kV. [e] Recorded by Dr. *F. Raschdorf*, Ciba-Geigy, Basel, on a VG Micromass ZAB with high-field magnet; FAB, matrix 3-nitrobenzyl alcohol, Xe 7 kV. [f] Benzene/ethyl acetate (7 : 3).

with solvent molecules. Thus, **4** crystallizes with two molecules of benzene (m.p. = 122–124 °C) and **5** with one molecule of dichloromethane (m.p. = 153–156 °C). The results of the X-ray analyses[7] are presented in Figures 1 and 2.

The 26-membered compound **4** has a structure similar to those of other crown ethers having the same ring size.[8] The shape and size of its chiral cavity account for its complexing abilities and the observed enantioselectivity. The structure of the 32-membered compound **5** differs: the 9,9′-spirobifluorene moieties are closer to each other (separation of the two spiro atoms in **4**, 11.09 Å; in **5**, 6.65 Å) and the two oxygen-containing chains lie to the side so that no cavity for a guest molecule is present. The host molecule must first adapt itself to the guest by a significant conformational change. Such an "induced fit" has often been observed for natural as well as for synthetic ionophores.[9]

Experimental Procedure

Poly(9,9′-spirofluorene) crown ethers **4**, **6**, **8**, and **9**: (*S*)-(−)-2,2′-bis(bromomethyl)-9,9′-spirobifluorene **1** (502 mg) in 5 mL of toluene was added over 2 h with vigorous stirring to a solution of KO*t*Bu (447 mg) and CsI (259 mg) in 25 mL of ethylene glycol at 70 °C. The reaction mixture was then heated for an additional 13 h. After dilution with water and acidification, it was extracted with 500 mL of benzene. The washed benzene extracts, containing the dihydroxy ether **2** in practically quantitative yield, were concentrated to 200 mL, treated with an additional 478 mg of **1** as well as with tetrabutylammonium hydrogen sulfate (97 mg), acetonitrile (100 mL), and 200 mL of 50% sodium hydroxide solution, and vigorously stirred for 20 h at room temperature. The reaction mixture was diluted with water and acidified. The benzene layer was separated, washed, dried with $MgSO_4$, and evaporated. The residue (840 mg) afforded **4** · 2 C_6H_6 (323 mg) after recrystallization from benzene. By flash chromatography [10] of the mother liquor on silica gel 60 (Merck) with benzene/ethyl acetate (9.5 : 0.5) and (9 : 1) and recrystallization, an additional 70 mg of **4** · 2 C_6H_6 was obtained from the first fractions. The later fractions were rechromatographed and gave **6** (82.5 mg), **8** (14.1 mg), and **9** (1.0 mg). The final fractions contained the dihydroxy ethers with five (74.5 mg; $C_{147}H_{116}O_{12}$; $[M+K]^+ = 2111$) and with three (91.5 mg; $C_{89}H_{72}O_8$;

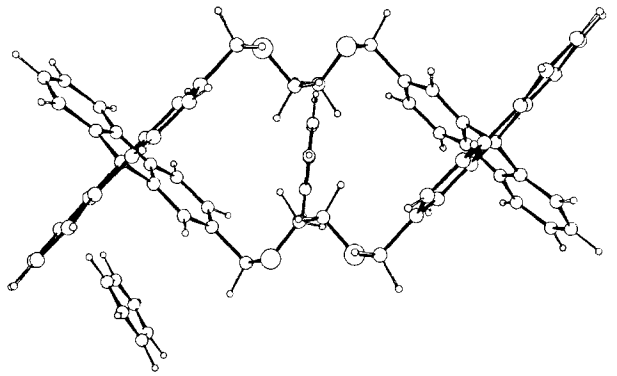


Fig. 1. Crystal structure of $4 \cdot 2C_6H_6$ along the crystallographic two-fold axis. The benzene molecule drawn in the center lies 5.7 Å below the crown ether ring. Important bond distances, bond angles, and torsion angles: spirobifluorene, six-membered ring 1.348...1.435, average 1.387 Å; 117.0...123.2°, average 120.0°. Five-membered ring, single bonds 1.443...1.556, average 1.513 Å, angles (without angles at spiro atom) 106.5...111.6°, average 109.7°, at spiro atom 100.2, 101.8°. Angle between the best planes 91.3°. 26-membered ring, values for the asymmetric moiety, beginning at the spiro atom: distances 1.542, 1.348, 1.385, 1.540, 1.443, 1.407, 1.518, 1.438, 1.425, 1.506, 1.409, 1.384, 1.509 Å; angles 113.0, 126.7, 119.4, 120.2, 111.5, 111.6, 107.8, 108.1, 111.9, 114.9, 120.4, 117.8, 126.9°; torsion angles 59.7, −172.9, 179.9, −45.6, −70.5, 176.1, 70.5, −177.7, −71.4, −32.1, −178.4, −178.3, 56.8°.

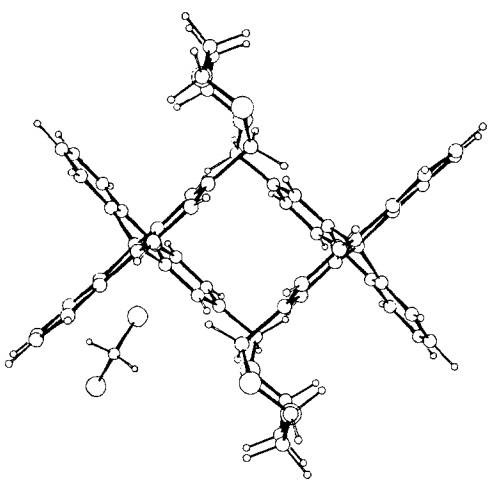


Fig. 2. Crystal structure of $5 \cdot CH_2Cl_2$ along the crystallographic two-fold axis. Important bond distances, bond angles, and torsion angles: spirobifluorene, six-membered ring 1.354...1.420, average 1.385 Å; 116.3...123.4°, average 120.0°. Five-membered ring, single bonds 1.500...1.552, average 1.522 Å, angles (without angles at spiro atom) average 109.6°, at spiro atom 101.1, 101.4°. Angle between the best planes 92.2°. 32-membered ring, values for the asymmetric moiety, beginning at the spiro atom: distances 1.552, 1.371, 1.398, 1.518, 1.402, 1.426, 1.486, 1.405, 1.443, 1.492, 1.414, 1.418, 1.569, 1.389, 1.373, 1.511 Å; angles 117.4, 128.5, 118.5, 120.2, 109.7, 110.4, 107.5, 108.7, 114.2, 107.8, 115.2, 115.8, 111.7, 118.0, 117.4, 128.3°; torsion angles 45.5, −178.8, 176.5, 36.2, 179.6, 172.3, −72.0, 174.3, −173.8, 80.7, −69.6, −64.2, 131.5, 176.7, 177.6, 59.3°.

$[M+K]^+ = 1307$) 9,9′-spirobifluorene residues as intermediate or side products along with 27 mg of unreacted **2**.

Poly(9,9′-spirobifluorene) crown ethers **5** and **7**: Analogously, $5 \cdot CH_2Cl_2$ (439 mg) and **7** (62.5 mg) were obtained from a total of 1004 mg of **1** with diethylene glycol.

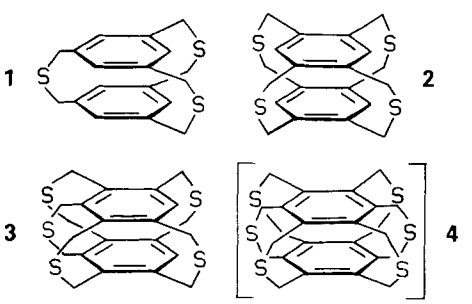
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[3] Phase-transfer catalysis has already been used for the preparation of crown ethers by P. DiCesare, B. Gross, *Synthesis 1979*, 458; G. Coudert, G. Guillaumet, M. Mpassi, *ibid. 1985*, 112.
[4] We thank Prof. *J. Seibl* for the mass spectra.
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[7] **4**: C2; $a = 15.47(1)$, $b = 11.265(9)$, $c = 15.220(4)$ Å, $\beta = 91.54(5)°$, $V = 2651.9$ Å^3, $\rho_{calcd} = 1.20$ for $Z = 2$. 2474 measured reflections (Nonius CAD4 diffractometer), 995 with $F > 3\sigma(F)$. Structure determined by direct methods (SHELX84), least-squares refinement, atoms with $U_{iso} > 0.055$ refined anisotropically. Unit weighting, $R = 0.067$.—**5**: $P4_12_12$; $a = 20.958(7)$, $c = 11.779(9)$ Å, $V = 5173.8$ Å^3, $\rho_{calcd} = 1.26$ for $Z = 4$. 2932 measured reflections (Nonius CAD4 diffractometer), 1532 with $F > 2\sigma(F)$. Structure determined by direct methods (MULTAN80), least-squares refinement, all non-H atoms anisotropic. Unit weighting, $R = 0.077$.—Details for both crystal structures: M. Dobler et al., in preparation.
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First Sixfold Bridge-Formation in One Step**

By *Wolfram Kissener* and *Fritz Vögtle**

While threefold,[1] fourfold,[2] and fivefold[2] bridging between two benzene rings in one step have all been successfully demonstrated in the past 15 years in the synthesis of the phanes **1**–**3**, the realization of a sixfold bridging, e.g. to give the ten-membered "superphane hexasulfide" **4**, in one step has not proven possible, despite numerous efforts.[1–4]

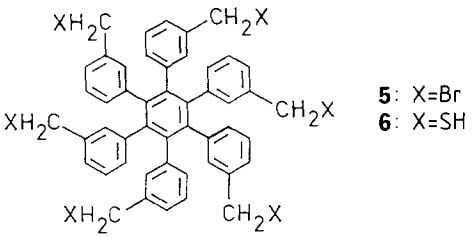


We assume that all previous attempts at achieving this aim have remained unsuccessful, not because of the number of bridges involved, but primarily because of the steric strain. Working on this basis we have now found that even six bridges can indeed be coupled intermolecularly if sterically less demanding starting materials are allowed to react with each other using the cesium effect[5] and dilution principle. An example is the reaction of hexakis[3-(bromomethyl)phenyl]benzene **5**[6] with the corresponding hexathiol **6**[7] to give **7**.

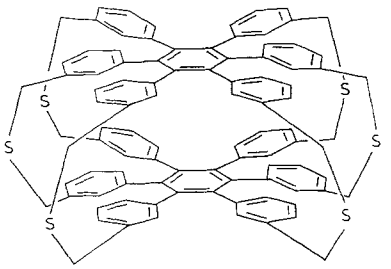
Using a general procedure previously optimized by us in earlier work,[2,5] this reaction resulted in precipitation of the 22-membered polycyclic hexasulfide **7** as pale yellow crystals (m.p. >320°C) in ca. 0.1% yield. The mass spec-

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[**] We wish to thank Prof. *F. W. Röllgen* and Dipl.-Chem. *S. S. Wong* (Bonn), Prof. *H. Egge* (Bonn), Prof. *H. Hoberg* and Dr. *D. Henneberg* (Mülheim a. d. Ruhr), and Dr. *G. Eckhardt* (Bonn) for carrying out the mass spectrometric investigations, Prof. *H. Irngartinger* (Heidelberg) for performing crystallographic studies, and Dr. *B. Steffan* and Mr. *C. Schmitt* (Bonn) for measuring the 400-MHz ^{1}H-NMR spectra.



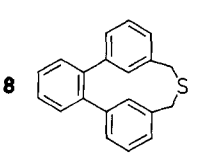
5: X=Br
6: X=SH



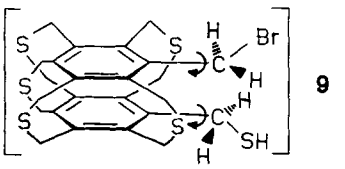
7

trum (m/z 1416 (M^+)) shows the molecular ion as an intense peak. The ^{1}H-NMR absorptions of the previously purified crystalline crude product are considerably broadened in CD_2Cl_2 as solvent. The polycondensation product[8] formed at the same time in the reaction, which is responsible for the broad signals, is removed by chromatography on silica gel with dichloromethane as eluent (R_F=0.61). The ^{1}H-NMR spectrum then shows an AB system for the CH_2 protons (δ_A=2.65, δ_B=3.2, J_{AB}=15 Hz) and sharp signals at δ=6.85–7.05 for the aromatic protons (in CD_2Cl_2). These findings are consistent with an all-*anti* conformation for **7**.[9] It is easily seen on comparison with the conformationally flexible 2-thia[3]*ortho*-terphenylophane **8**,[10] that **7** can be fixed conformationally, due to strain; according to model considerations the hexaphenylbenzene skeleton is present in a six-bladed propeller arrangement. This now raises the question whether **7** is sufficiently ridgid (and thus helical) in solution that it can be separated into enantiomers. Analytical separation on "Okamoto" resin[11] would indicate that this is indeed the case.

The successful one-step sixfold bridging realized with **7** throws light on the reasons why **4** was hitherto unobtainable: The last CH_2X groups in the intermediate **9** may no longer achieve the conformation requisite for the sixth bridging span.



8



9

With the synthesis of **7**, it has been shown for the first time that more than fivefold bridge formation is possible in one step if steric factors are carefully taken into account. Owing to the "six-coordination of the benzene ring", the sixfold bridging, particularly with longer bridges to give molecules with large cavities suitable for the encapsulation of organic guest molecules, opens up novel aspects: According to model considerations, the cavity of **7** is, as it were, tailor-made for the accommodation of a benzene molecule, whereas longer, flexible bridges are stretched after passage of the guest molecule; due to the widening of the cavity the guest becomes "trapped".

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CAS Registry numbers:
5, 95216-95-8; **6**, 97877-67-3; **7**, 97877-68-4; thiourea, 62-56-6.

[1] F. Vögtle, *Liebigs Ann. Chem. 735* (1970) 193; F. Vögtle, P. Neumann, *Chem. Commun. 1970*, 1464.
[2] B. Klieser, F. Vögtle, *Angew. Chem. 94* (1982) 632; *Angew. Chem. Int. Ed. Engl. 21* (1982) 618; *Angew. Chem. Suppl. 1982*, 1392.
[3] P. Neumann, *Dissertation*, Universität Heidelberg 1970; B. Schelcher, *Diplomarbeit*, Universität Bonn 1983; E. Koepp, *Diplomarbeit*, Universität Bonn 1985.
[4] The six bridges of the known "superphane" were coupled in a multistep synthesis: V. Boekelheide, *Top. Curr. Chem. 113* (1983) 89; V. Boekelheide in T. Lindberg (ed.): *Strategies and Tactics in Organic Synthesis*, Academic Press, New York 1984, p. 1; H. Hopf, S. El-Tamany, *Chem. Ber. 116* (1983) 1682.
[5] K. Meurer, F. Vögtle, A. Mannschreck, G. Stühler, H. Puff, A. Roloff, *J. Org. Chem. 49* (1984) 3484.
[6] W. Kissener, F. Vögtle, *Angew. Chem. 97* (1985) 227; *Angew. Chem. Int. Ed. Engl. 24* (1985) 222.
[7] Prepared from **5** by the thiourea method. ^{1}H-NMR (90 MHz), $CDCl_3$/TMS int.): δ=1.22 (t, SH), 3.3 (d, CH_2S), 6.75 (s, aryl, m-H). MS: m/z 810 (M^+).
[8] The crystallinity of this product is remarkable; the product is possibly a high-molecular-weight cyclic oligomer. Due to poor solubility, an osmometric molecular weight determination could not be carried out.
[9] Cf. K. Böckmann, F. Vögtle, *Chem. Ber. 114* (1981) 1065.
[10] Cf. E. Hammerschmidt, F. Vögtle, *Chem. Ber. 113* (1980) 1125.
[11] Cf. [6] and K. Meurer, A. Aigner, F. Vögtle, *J. Inclusion Phenom. 3* (1985) 51. Due to solubility problems (cyclohexane/1% THF), difficulties were encountered in the *preparative* separation of the enantiomers.

BOOK REVIEWS

Determination of Organic Reaction Mechanisms. By *B. K. Carpenter*. Wiley, Chichester 1984. xi, 247 pp., bound, £ 32.20.—ISBN 0-471-89369-2

This short, compactly-written, introductory textbook on the methods of investigating the reaction mechanisms of organic chemical reactions is based on a one-semester lecture course for new graduate students.

One could wish that such a lecture course were compulsory for all chemistry students at our universities after completion of their undergraduate work. It is true that the most important reaction classes and their mechanisms are treated in most general lecture courses, but additional knowledge concerning the experimental and theoretical basis of reaction mechanisms and their general limitations is needed in order to be able to understand them and their information content in a critical manner.

This book is capable of closing this gap. After a short introductory chapter, in which the scientific method of learn-

ing is generally described in brief, there are seven chapters in which the most important methods of investigating reaction mechanisms are described with brief treatments of their limitations and areas of application: isotopic labeling, chirality and stereochemistry, kinetics, isotope effects, acid-base catalysis, the interpretation of activation parameters including the elements of thermochemistry and bringing in linear free enthalpy relationships, methods of detecting reactive intermediates. Then follows a chapter which describes the combined application of these techniques with the aid of examples of investigations taken from recent literature. An appendix explains a range of mathematical techniques for the analysis of kinetics and symmetry problems; then follow tables of Benson group increments.

Almost all recent methods up to and including picosecond spectroscopy and laser methods are described briefly and in a way that is easily followed up and critically discussed upon the basis of a few chosen examples from the literature. An overemphasis on pericyclic reactions can be detected in the choice of examples, but account is also taken of classical fields, such as solvolysis and arene chemistry, while radical chemistry is dealt with too briefly. Unfortunately, little account is taken of the German literature. Topics which are omitted from the examples are steric effects including the force field method, the Curtin-Hammett principle, the interrelationships between selectivity and reactivity, and, finally, the isoselective relationship.

Is it necessary to know the treasure house of methods for studying reaction mechanisms in the era of preparative chemistry which we are now experiencing? In my opinion yes! It was the development of "physical organic chemistry" over the last 30 years that first made possible the new breakthroughs in preparative chemistry. It is only quantitative investigation methods that make possible the purposeful optimization of synthesis.

It is in this sense that the present book, which can only be criticized on the basis of a somewhat one-sided choice of examples, is thoroughly to be recommended. A German translation is to be desired.

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Sources and Applications of Ultraviolet Radiation. By *R. Phillips*. Academic Press, New York 1983, xvi, 434 pp., bound, $ 60.00.—ISBN 0-12-553880-4

Normally, a book review begins with a short description of the contents. It seems more appropriate in the case of this book to start with the story of its origins. The author candidly admits in his foreword that his original intention was to write a monograph concerning (A) "Photopolymerization of Organic Surface Coatings" with emphasis on the chemical aspects. However, it soon became clear to him that there was already sufficient review literature covering this field and he thought it more useful and original to emphasize (B) "Sources of Radiation Suitable for Photopolymerization". Then that seemed to him to be too restricted and he became fascinated by the idea of writing a book entitled (C) "Radiation Sources in Applied Photochemistry". But this was also too specialized for him (or his publisher) and thus he came to the very general and sales-promoting title (D) "Sources and Applications of Ultraviolet Radiation".

The illogical construction of this book and its repetitions, shortcomings, and errors have two basic causes. Firstly, the various texts that had already been written ought to have been rewritten on going from (A) through (B) and (C) to (D). However, the author made it easy for himself and simply added sections or subsections to what had already been written. Secondly, in the course of the transition from (A) to (D) the author concerned himself with fields in which he was no longer competent. The eleven friendly helpers who checked the parts of the original manuscript and whom the author thanks in his foreword have probably avoided the worst. This help is evident in the text because of competently and fluently written passages, which pleasantly distinguish themselves from the often clumsy, imprecise or simply false formulations of the author.

One would actually expect in a book entitled "Sources and Applications of Ultraviolet Radiation" firstly to learn something about sources of UV light and afterwards something about their applications. The first chapter (37 pp., 274 refs.), however, is concerned with "Applications of Ultraviolet Radiation". It is not surprising that the applications furthest from the interests of the author consist in practice of pure enumeration, that many concepts are employed which are only explained in later chapters and that it is very seldom mentioned which UV source was employed.

The main purpose of Chapter 2 ("The Nature of Light", 10 pp., 2 refs.) is to introduce some concepts from atomic spectroscopy, which are required later for the discussion of gas discharge lamps.

Chapter 3 ("Photochemistry and Photopolymerization", 50 pp., 205 refs.) corresponds to the originally planned monograph (A). The subsection 3.1.4.3 ("The Jablonski Diagram") provides a whole range of examples of clumsy or false formulations. The keyword "UV curing" provides an example of unnecessary repetition and illogical ordering. It already appears in many places in Chapter 1 and in the titles of subsections 1.6.1, 1.6.1.10 and 1.6.11 and then it reappears in subsections 3.4.4 and 3.5. The explanation of what is understood by "cure", however, is first to be found in the *last* and obviously subsequently added section of Chapter 3 (3.6 "The Concept and Measure of Cure").

Chapters 4 ("Radiometry", 45 pp., 154 refs.), 5 ("Incandescent Sources", 8 pp., 2 refs.) and 6 ("Gas Discharges", 14 pp., 14 refs.) lead then to the main portion of the book: Chapter 7 ("The Low Pressure Mercury Lamp", 19 pp., 62 refs.), 8 ("The Medium Pressure Mercury Lamp", 66 pp., 53 refs.), 9 ("Metal Halide Lamps", 16 pp., 71 refs.), 10 ("Electrodeless Lamps", 16 pp., 16 refs.) and 11 ("Xenon Lamps", 33 pp., 91 refs.). Of these, chapter 8 is the most important because it includes results of the author's own investigations. Considerable knowhow is to be expected of the author here. But, once again one must cast doubts upon his competence, when on page 208 in connection with the Richardson-Dushmann equation $J = AT^2 \exp(-e\phi/kT)$ for thermal electron emission, it is stated "... where ... e is the electronic charge (1.60×10^{-19} e.s.u.), ϕ is the work function ... with units of electron volts, k is Boltzmann's constant (1.372×10^{23} JK^{-1} ..." It is almost a work of art to introduce an error into each of the three definitions! On page 239 of the same chapter the author reveals that he has no notion of optical spectroscopy. He maintains that the dispersion of a grating monochromator is independent of the wavelength and that the asym-

metry of the lines of an Hg spectrum recorded at low resolution is caused by pressure broadening of the lines (instead of being caused by the curvature of the image of the monochromator entry slit in the plane of the exit slit).

Chapters 12 ("Lasers", 19 pp., 120 refs.) and 13 ("Miscellaneous Sources", 9 pp., 23 refs.) are probably intended to justify the general title of the book. The inconsequence of the author in chapter 12 is quite remarkable, for he writes a relatively large amount on an infrared laser (CO_2 laser), but is satisfied in the case of the argon and krypton ion laser with the statement that both lasers can lase at various wavelengths in the UV and visible range. Chapter 13 is typical of the style of this book. Here sunlight, the deuterium lamp, synchrotron radiation and the high pressure mercury lamp all come together under the title "Miscellaneous".

Chapter 14, ("Ultraviolet Irradiators", 36 pp., 80 refs.) contains alongside 80 literature references a list of 58 chosen journal articles (with titles) concerning the design (or construction) and analysis of photochemical reactors. Finally chapter 15 (17 pp., 72 refs.) treats "Hazards of Ultraviolet Radiation".

It can be seen from these critical remarks and the contents of the book that this book—in contrast to the very generally formulated title—is only directed at a very limited circle of readers. This is clearly expressed by the author in the first sentence of his foreword: "This book has been written primarily for the benefit of those who have a responsibility for, or an interest in, the design, construction, purchase or operation of the "hardware" associated with applied photochemistry". The book is useless—whether as textbook or as reference source—for everyone else and particularly for those who work in the field of photophysics.

Finally it may be useful for the reader to know that there are two very good older books with similar titles. (I) "Ultraviolet Radiation" by *L. R. Koller* (Wiley, New York 1965, 312 pp.) and (II) "Ultraviolette Strahlen" edited by *J. Kiefer* (de Gruyter, Berlin 1977, 661 pp.). Both books were known to the author of the book that has been reviewed, but they have obviously only served him as a model for his choice of title. The application of UV radiation is described in (II) by means of examples; it is thus very suitable for use as a textbook.

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Methods of Enzymatic Analysis. Vol. 2. Samples, Reagents, Assessment of Results. Edited by *U. Bergmeyer, J. Bergmeyer,* and *M. Grassl.* Verlag Chemie, Weinheim 1984. xvi, 539 pp., bound, DM 215.00 (when ordering all ten volumes).—ISBN 3-527-26040-4 (complete work)

Publication of Bergmeyer's 3rd edition of "Methods of Enzymatic Analysis" proceeds with volume 2 which marks the transition to practice from the theory presented in volume 1.[*] Volume 2 "covers the three steps in obtaining results from laboratory: the pre-analytical phase, the post-analytical phase, and the analysis itself." This objective is achieved in a straightforward and concise manner.

The first chapter in volume 2 deals with specimens and samples. The first section describes preparation and processing methods for samples in clinical laboratory sciences, food chemistry, cosmetics and pharmacy. The next section discusses cell and tissue disintegration and includes methods for animal tissues, subcellular fractionation, microorganisms and plant tissues. The third section describes and compares methods for protein determination. Throughout this chapter, factors which influence and interfere with these various methods are described, as well as ways to avoid potential pitfalls.

Reagents for enzymatic analysis are the focus of the second chapter. This chapter includes a section discussing the handling of reagents (nomenclature, quality requirements, storage and stability), and diagnostic kits. The compendium of reagents for enzymatic analysis found in the previous edition has been expanded and is included in this section; assays and characteristics of 143 enzymes and 119 coenzymes, metabolites and reagents are now described. A new addition is a section including descriptions and characteristics of standard reference materials for biochemistry.

The third chapter is titled "Evaluation of Experimental Results." The first section in this chapter discusses transformation of experimental data into results, end-point determinations, non-linear reaction curves, use of standard curves, standard substances and their terminology and definitions. Equations useful for calculating metabolite concentrations and enzyme activities from photometry, radiometry and related techniques are included along with specific illustrative examples. A second section covers the topic of quality control. After a discussion of errors, precision and accuracy, the principles of quality control and its applications in clinical chemistry are described. A subsection on the use of statistics in quality control covers basic concepts, evaluation of results, and curve fitting.

This volume concludes with a useful appendix with lists of symbols, quantities, units and constants; chemical and biochemical abbreviations; NAD(P)H absorption coefficients; numbering and classification of enzymes; and a table of atomic weights. This volume should find daily use in the biochemical laboratory as a handbook of both methods and data.

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Einführung in die Pharmazeutische Chemie. 2nd completely revised edition. By *O.-E. Schultz* and *J. J. Schneckenburger.* Verlag Chemie, Weinheim 1984. xv, 510 pp., bound, DM 68.00.—ISBN 3-527-26098-6

At the moment, pharmaceutical chemistry is undergoing a change into medicinal chemistry. In this process the main emphasis is moving from the chemical via the biochemical into the medical field. Whether this is an advantage for the subject of pharmaceutical chemistry and the education of pharmacists really remains to be seen. This book places the medicament with its synthesis, properties and analysis in the forefront again. The compounds are summarized according to their pharmacological properties, but described from a chemical point of view. This system is occasionally abandoned, if this is practically forced by chemical analogy; thus the antitussive normethadone is treated alongside methadone which is an analgesic. This is acceptable because there is a cross-reference under the antitussives. The individual substances are specified under

[*] Cf. *Angew. Chem. Int. Ed. Engl. 23* (1984) 171.

their proprietary and international nonproprietary names, so that rapid access is available for the practitioner; then follow synthesis, analysis and details of action and application. References to metabolization are rare; interactions are not described. It should be remembered here that this book is neither intended to nor can act as a substitute for a pharmacology textbook, although physiological-anatomical comments, which make understanding of the action or application easy, preface individual chapters (e.g. diuretics, saluretics, antirheumatics, cardiac glycosides). The collaboration of a specialist for internal medicine *(Hg. Lahrtz)*, who receives the authors' thanks in the foreword, is evident in these chapter introductions. Clear synopses provide information rapidly, e.g. concerning the semisynthetic penicillins.

This introduction to pharmaceutical chemistry only deals with organic medicaments. It is true that inorganics have, in general, lost in importance, nevertheless today we understand many physiological processes that are changed by the intervention of drugs as reactions of inorganic ions. In my opinion inorganic medicaments ought not to have been ignored and the physiological chemistry of the more important inorganic ions ought to have been given more emphasis.

In the generally very clear presentation of formulas for the syntheses the authors assume a basic knowledge of organic chemistry; however, I have doubts in many cases as to whether the student will understand the reactions without any explanation. References to textbooks of organic chemistry could provide a better understanding (e.g. ketamine: comparison with pinacol and benzilic acid rearrangements, cephalosporins from penicillins: indication of sulfinic acid intermediates). Occasional references to the reaction type (e.g. as with ciclonium bromide) would not disturb the structure of the book. Original papers could be referred to in the case of complex reactions (e.g. primary amines and 1,2-naphthoquinone-4-sulfonic acid) and in other cases (e.g. the van-Urk reaction with the rearrangement of C-3 substituted indoles to C-2 derivatives) reviews could be employed. The good student would thus be led into reading the literature, a possibility also for the practicing professional to keep up to date. Such additions naturally require space and it is for the authors to consider.—On the basis of the investigations of *Neumeyer* (Boston) the apomorphine rearrangement should not be formulated any longer via a primary carbenium ion.—Enantiomers are finding increasing therapeutic employment; for this reason the formulas should be checked for stereochemical content (e.g. L-α-methyldopa described, D-form represented, (*S*)-propranolol represented, racemate employed commercially; ethambutol: (*R,R*)-form active, *meso* form represented).

If the picture of pharmaceutical chemistry that *Richard Kuhn* sketched in Berlin in 1965 is accepted, then the subject embraces so much that it is scarcely possible to cover it in a textbook. Synthesis and analysis will continue to be important viewpoints. This book is a comprehensive introduction to this part of pharmaceutical chemistry and is worthy of recommendation.

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New Books

The following books have been received by the editor. All the publications listed are available through W & P Buchversand für Wissenschaft und Praxis, Boschstrasse 12, D-6940 Weinheim (Federal Republic of Germany). Tel. (06201) 606-0, Telex 465516 vchwh d, Telefax (06201) 602328.

Lebensmittel—mit allen Sinnen prüfen! Qualität, Aromastoffe, Geschmack, Sensorik. By *A. Fricker*. Springer-Verlag, Berlin 1984. ix, 165 pp., stitched, DM 28.00.—ISBN 3-540-13636-3

Computer Education of Chemists. Edited by *P. Lykos*. John Wiley, Chichester 1984. xii, 223 pp., bound, £ 37.60.—ISBN 0-471-88872-9

Organic Reactions. Vol. 32. Edited by *W. G. Dauben*. John Wiley, Chichester 1984. vii, 533 pp., bound, £ 63.50.—ISBN 0-471-88101-5

Food. The Chemistry of its Components. By *T. P. Coultate*. The Royal Society of Chemistry, London 1984. 197 pp., paperback, £ 5.95.—ISBN 0-85186-483-x

Pergamon Series in Analytical Chemistry. Vol. 8: The Analysis of Plastics. By *T. R. Crompton*. Pergamon Press, New York 1984. ix, 445 pp., bound, £ 29.50.—ISBN 0-08-026251-1

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Solid Phase Synthesis (Nobel Lecture)**

By Robert Bruce Merrifield*

The proteins, as the Greek root of their name implies, are of first rank in living systems, and their smaller relatives, the peptides, have now also been discovered to have important roles in biology. Among their members are many of the hormones, releasing factors, growth factors, ion carriers, antibiotics, toxins, and neuropeptides. Herein, I wish to describe the chemical synthesis of peptides and proteins and to discuss the use of the synthetic approach to answer various biological questions.

The story begins with *Emil Fischer*[1] at the turn of this century when he synthesized the first peptide and coined the name. The general chemical requirements were to block the carboxyl group of one amino acid and the amino group of the second amino acid. Then, by activation of the free carboxyl group the peptide bond could be formed, and selective removal of the two protecting groups would lead to the free dipeptide. *Fischer* himself was never able to find a suitable reversible blocking group for the amine function, but his former student *Max Bergmann*, with *Zervas*, was successful.[2] Their design of the carbobenzoxy group ushered in a new era. When I began working on the synthesis of peptides many years later this same general scheme was universally in use and was very effective, having led, for example, to the first synthesis of a peptide hormone by *du Vigneaud* in 1953.[3] It soon became clear to me, however, that such syntheses were difficult and time consuming and that a new approach was needed if large numbers of peptides were required or if larger and more complex peptides were to be made.

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[**] Copyright © The Nobel Foundation 1985.—We thank the Nobel Foundation, Stockholm, for permission to print this article.

Synthesis on a Solid Matrix

One day I had an idea about how the goal of a more efficient synthesis might be achieved. The plan[4] was to assemble a peptide chain in a stepwise manner while it was attached at one end to a solid support. With the growing chain covalently anchored to an insoluble matrix at all stages of the synthesis the peptide would also be completely insoluble and, furthermore, would be in a suitable physical form to permit rapid filtration and washing. Therefore, after completion of each of the synthetic reactions the mixture could be filtered and thoroughly washed to remove excess reactants and by-products. The intermediate peptides in the synthesis would thus be purified by a very simple, rapid procedure rather than by the usual tedious crystallization methods. When a multistep process, such as the preparation of a long polypeptide or protein is contemplated the saving in time and effort and materials could be very large. The fact that all of the steps just described are heterogeneous reactions between a soluble reagent in the liquid phase and the growing peptide chain in the insoluble solid phase led to the introduction of the name "solid phase peptide synthesis."

The general scheme for solid phase synthesis is outlined in Figure 1. It begins with an insoluble particle, indicated by the large circles, which is functionalized with a group X. The first monomer unit, small circles, is blocked at one end and at the reactive side chain groups (black dots) and anchored to the support by a stable covalent bond. The α protecting group is then removed and the second monomer unit is added to the first by a suitable reaction. In a similar way the subsequent units are combined in a stepwise manner until the entire polymeric sequence has been assembled. Finally, the bond holding the chain to the solid support is selectively cleaved, together with the side chain pro-

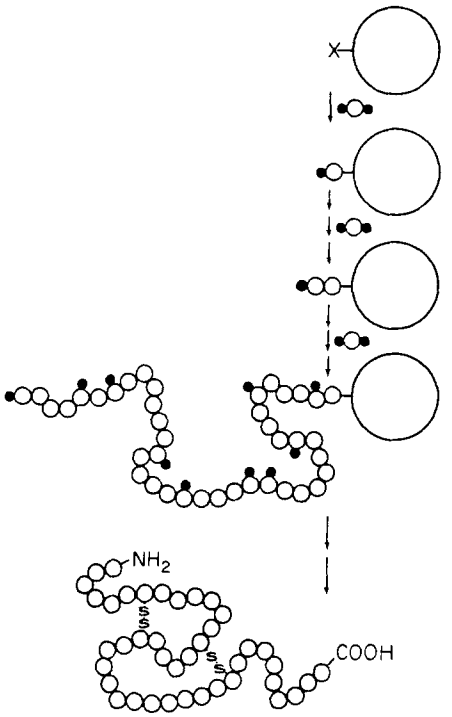


Fig. 1. The general scheme for solid phase synthesis (see text).

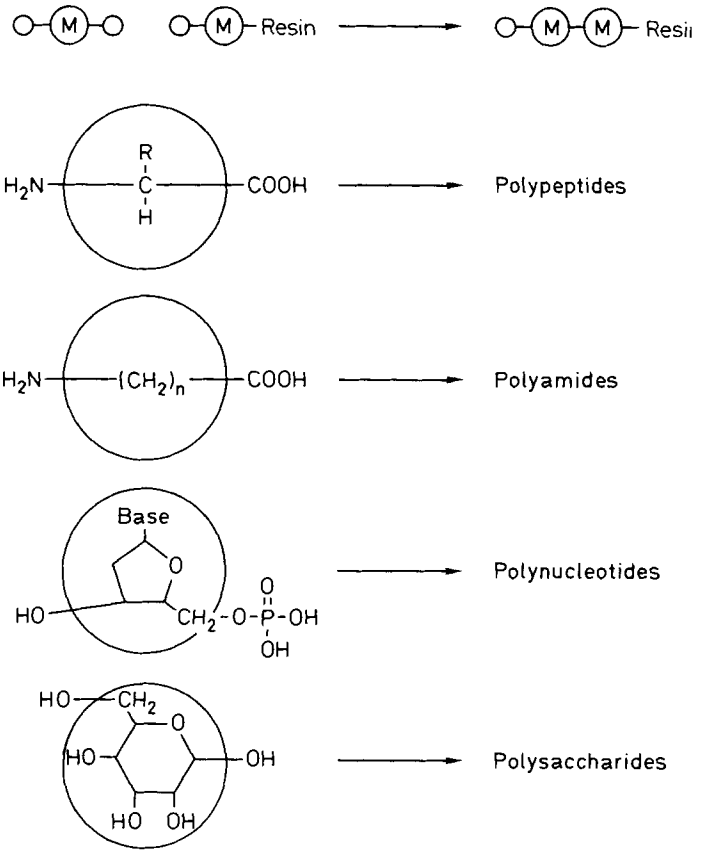


Fig. 2. Solid phase syntheses with various monomers.

tecting groups, and the product is liberated into solution. Such a system offers four main advantages:

- It simplifies and accelerates the multistep synthesis because it is possible to carry out all the reactions in a single reaction vessel and thereby avoid the manipulations and attendant losses involved in the repeated transfer of materials.
- It also avoids the large losses which normally are encountered during the isolation and purification of intermediates.
- It can result in high yields of final products through the use of excess reactants to force the individual reactions to completion.
- It increases solvation and decreases aggregation of the intermediate products.

The task now was to translate the general idea into a workable set of reactions.

Although the plan was originally conceived as a way to synthesize peptides, the general scheme does not specify the nature of the monomer units. It soon became apparent that the technique should be applicable to units other than amino acids, such as those shown in Figure 2. We extended it to the synthesis of depsipeptides[5] and other laboratories succeeded in synthesizing polyamides,[6] polynucleotides[7] and polysaccharides.[8] In principle, the monomer may be any bifunctional compound that can be selectively blocked at one end and activated at the other. In addition, the solid support idea can be applied to a variety of conventional reactions in organic chemistry to aid in directing the course of the reaction or in the separation of the products from reagents and by-products. It also led to the solid phase sequencing technique.

Solid Phase Peptide Synthesis

A detailed scheme for the synthesis of peptides is shown in Figure 3. Each of the steps has been modified in many ways, but the chemistry shown here has served well and has been applied to the synthesis of large numbers of peptides.[9] The carboxy-terminal amino acid is blocked at the amino end by a *tert*-butyloxycarbonyl (Boc) group and is covalently attached to the resin support as a benzyl ester via the chloromethyl group. Side-chain functional groups must also be blocked, usually with benzyl-based derivatives. The synthesis depends on the differential sensitivity of these two classes of protecting groups to acid, which is greater than 1000 : 1. The Boc group is completely removed with 50% trifluoroacetic acid in dichloromethane, with minimal loss of the anchoring bond or of the other protecting groups. The resulting ammonium salt is neutralized with a tertiary amine such as *N,N*-diisopropylethylamine and the free amino group of the resin-bound amino acid is then ready to couple with a second Boc-amino acid. The latter must be activated for the reaction to occur. The simplest and most often used procedure is activation with dicyclohexylcarbodiimide (DCC)[10] (Fig. 3), but active esters,[11] anhydrides,[12] and many other activated derivatives have been successfully applied. All of these reactions are carried out under non-aqueous conditions in organic solvents that swell the resin and accelerate the rates. Dichloromethane and dimethylformamide are the solvents of choice.

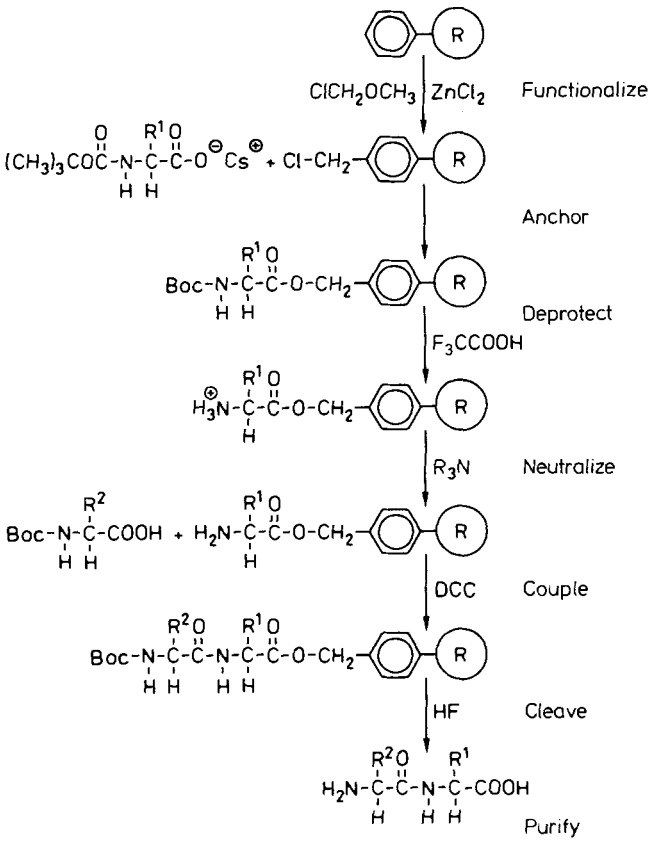


Fig. 3. Scheme for solid phase peptide synthesis (see text).

To extend the peptide chain the deprotection, neutralization and coupling steps are repeated for each of the succeeding amino acids until the desired sequence has been assembled. Finally, the completed peptide is deprotected and cleaved from the solid support. With the chemistry described here, this is accomplished by treatment with a strong anhydrous acid such as HF.[13] The free peptide is then purified by suitable procedures.

It is very important that the repetitive steps proceed rapidly, in high yields, and with minimal side reactions in order to prevent the accumulation of excessive amounts of by-products. Much of our effort has been directed toward developing and evaluating these requirements.

Solid Phase Nucleotide Synthesis

Similar schemes for the solid phase synthesis of oligonucleotides have now been developed which are rapid and give relatively high yields.[14,15] They employ protected nucleotides as monomer units and make use of either phosphotriester or phosphite triester chemistry. One such procedure is outlined in Figure 4. The resin is first functionalized with an aminomethyl group and the nucleotide derivative is coupled to it, through a spacer, by a stable amide bond. In this example the 5'-hydroxy group is esterified with the spacer and the 3'-hydroxy group is temporarily blocked with a dimethoxytrityl (DMT) group. The latter is removed with acid or $ZnBr_2$ and the chain is extended at the 3' end by coupling with the next protected nucleotide by activation with 1-(mesitylene-2-sulfonyl)-3-nitro-1,2,4-triazolide (MSNT). The completed oligonucleotide is finally cleaved from the solid support and deprotected by treatment with a base such as NH_4OH or tetramethylguanidine and then with hot acetic acid. The products are readily purified by ion-exchange chromatography or by electrophoresis where the desired product always has the greatest negative charge. I will not deal further with polynucleotides and their use in site-specific mutagenesis or with synthetic genes in this presentation but will concentrate instead on peptides and proteins.

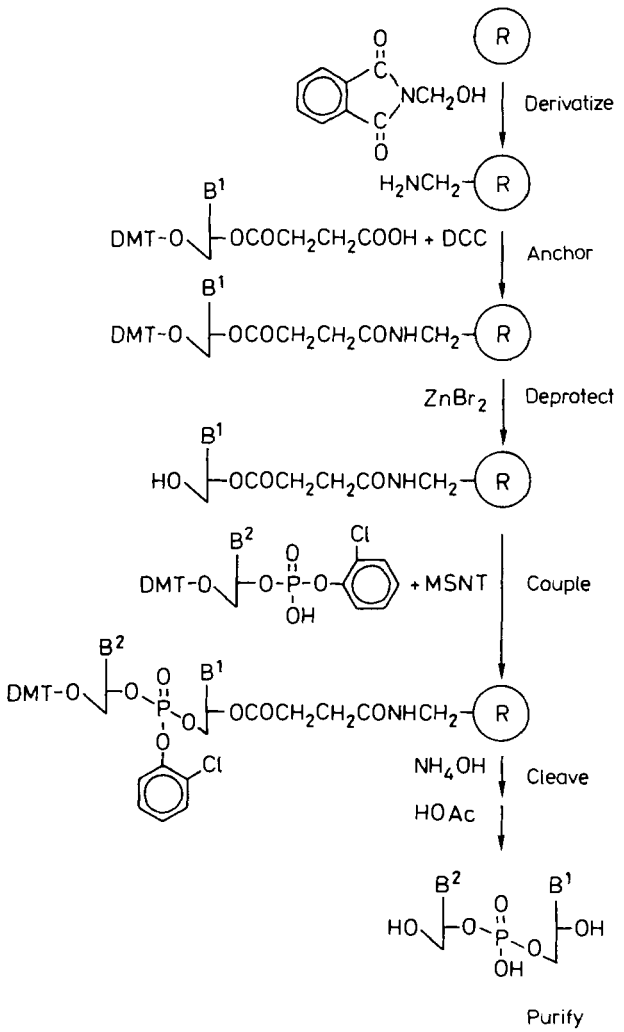
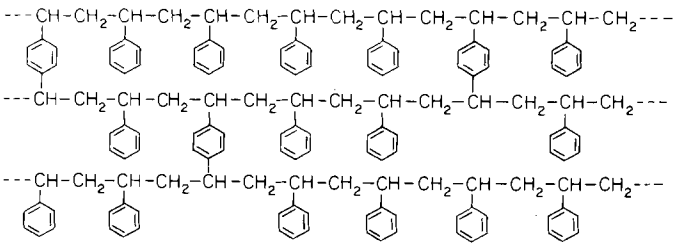


Fig. 4. Scheme for solid phase nucleotide synthesis (see text).

The Support

The first requirement for the development of solid phase synthesis was a suitable support. After examination of many potential supports it was found that the most satisfactory one was a gel prepared by suspension copolymerization of styrene and 1% of divinylbenzene as cross-linking agent.[4] The resulting spherical beads (Fig. 5) are about 50 μm in diameter when dry, but in organic solvents such as dichloromethane they swell to five or six times their original volume. Furthermore, as peptide chains grow the dry volume increases to accommodate the added mass and, most importantly, the swollen volumes continue to in-



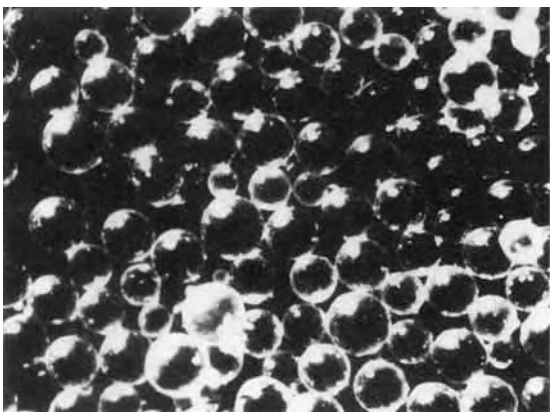


Fig. 5. Copolymer of styrene and divinylbenzene (1%). Top: structural formula. Bottom: photomicrograph of the resin beads.

crease. Values up to 25-fold have been measured and calculations indicate that the maximum expansion should be about 200-fold.[16] This means that the polystyrene matrix and the pendant peptide are highly solvated during the chemical reactions and are freely accessible to diffusing reagents. The reactions occur not only at the surface of the bead but, in major part, within the interior of the cross-linked polymeric matrix. This could be demonstrated by autoradiography of a cross section of a bead containing a synthetic tritium-labeled peptide.[17] At this resolution the silver grains were located uniformly throughout the bead, although the distribution is not known at the molecular level. Because of the solvation and swelling of the beads, the reactions are very fast, with half-times in the order of seconds for both the coupling and the deprotection steps. Current efforts to evaluate the effects of mass transfer and diffusion indicate that they are not rate determining. We believe the solid matrix not only does not have detrimental effects on the synthesis but actually has beneficial effects in certain instances.

One of the well recognized difficulties with the classical peptide synthesis in homogeneous solution is the insolubility of some intermediates. This problem can be overcome in many cases by the use of solid supports, where the peptide chain and the lightly cross-linked polymer chain become intimately mixed and exert a mutual solvating effect on one another. It becomes thermodynamically less favorable for the peptide to self aggregate and it remains available for reaction. For this to occur the solvated state of the bound peptide needs only to be favorable relative to the amorphous unsolvated state within the peptide-resin matrix.[16] Similar solubilizing properties of linear polymers for covalently attached components are known, but the effect will be greater for a lightly cross-linked polymer network. The phenomenon can be illustrated by the synthesis of oligoisoleucines.[18] The standard solution synthesis failed after the tetrapeptide stage because of aggregation and insolubility, whereas the chain could be extended up to eight residues on linear poly(ethylene glycol). A solid phase synthesis proceeded smoothly at least as far as the dodecamer, where the experiment was stopped. There is very significant polymer chain motion in these cross-linked polystyrene resins. Both ^{1}H- and ^{13}C-NMR measurements[19] have shown that the motional rates for the aromatic groups and the aliphatic backbone atoms in CH_2Cl_2 are high and equivalent to linear soluble polystyrene ($\tau_c = 10^{-8}$ s). The ^{13}C-NMR signals of the α carbon atoms of model resin-supported peptides were as sharp as the solvent peak in CH_2Cl_2 or dimethylformamide and similar to those of small molecules in solution ($\tau_c = 10^{-10}$ s). A variety of chemical experiments also have shown polymer flexibility. For example, short resin-bound peptides that were too far apart on average to reach one another if the resin were rigid could be shown to react to the extent of 99.5%, indicating considerable motion of the polystyrene segments within the matrix.[20]

Many other solid supports have also been examined and several have been satisfactory for peptide synthesis. These have included polymethylmethacrylate, polysaccharides, phenolic resins, silica, porous glass and polyacrylamides, but only the latter have seen widespread use.[21] Comparative studies with polystyrene and polyacrylamide have shown that they can be equally effective, even with difficult peptides.

Automation

The ability to purify after each reaction by simple filtration and washing and the fact that all reactions could be conducted within a single reaction vessel appeared to lend themselves ideally to a mechanized and automated process. Initially, a simple manually operated apparatus was constructed (Fig. 6). This system was first used to work out the methodology and to synthesize bradykinin,[22] angiotensin,[23] oxytocin[24] and many other small peptides. In order to accelerate the process we undertook the design

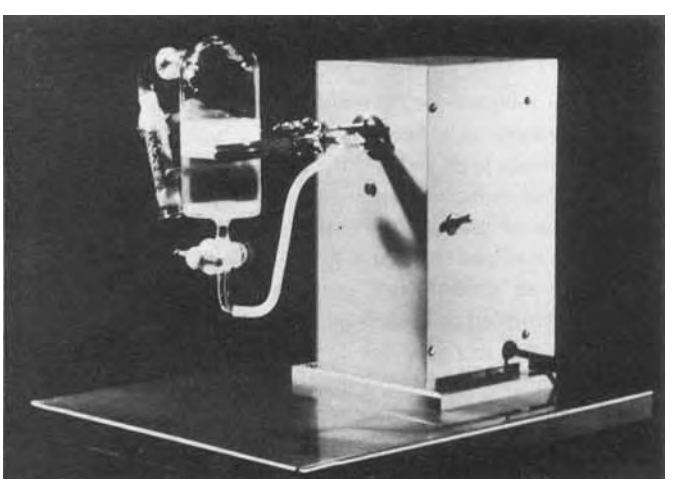


Fig. 6. Manually operated apparatus for peptide synthesis.

and construction[25] of the automated instrument shown in Figure 7. The essential features are the reaction vessel, containing the resin with its growing peptide chain, and the necessary plumbing to enable the appropriate solvents and reagents to be pumped in, mixed, and removed in the proper sequence. These mechanical events are under the control of a simple stepping drum programmer and a set of timers. In the past few years many commercial instruments have been constructed in several countries. They differ considerably in detail, particularly in the sophistication of the electronic program mechanisms but are designed to carry out the same chemistry.

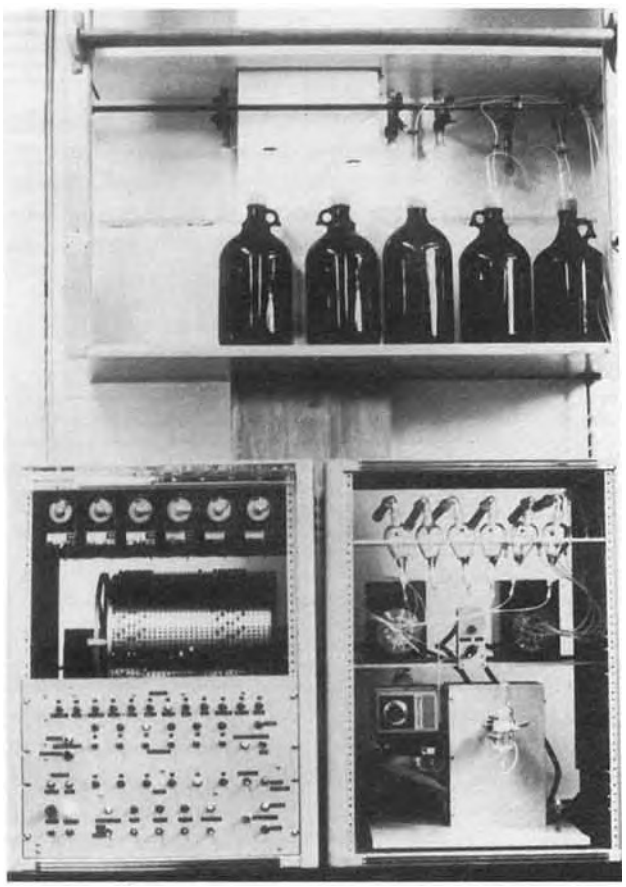


Fig. 7. Automated peptide synthesizer.

The Synthesis of Ribonuclease A

The idea of chemically synthesizing an enzyme must have occurred to many people over the years. There was a time when such a thought would have been unacceptable even on philosophical grounds, but from the period when enzymes were shown to be proteins, and proteins were shown to be discrete organic molecules, it was a goal that chemists could begin to think about. If an enzyme could be made in the laboratory, then it should become possible to learn new things about how these large and very complex molecules function. Specific changes could be made in their structures that could not be made readily by altering the native protein and data should be forthcoming that would supplement the information already obtained from the natural enzymes themselves. In this regard, a quotation from *Emil Fischer* in 1906[26] is pertinent:

> "Whereas cautious professional colleagues fear that a rational study of this class of compounds [proteins], because of their complicated structure and their highly inconvenient physical characteristics, would today still uncover insurmountable difficulties, other optimistically endowed observers, among which I will count myself, are inclined to the view that an attempt should at least be made to besiege this virgin fortress with all the expedients of the present; because only through this hazardous affair can the limitations of the ability of our methods be ascertained."

With the development of solid phase peptide synthesis and its automation the time seemed right to attempt the total synthesis of an enzyme. Dr. *Bernd Gutte* and I selected bovine pancreatic ribonuclease A because it was a small stable protein of known amino acid sequence,[27] and the three-dimensional structure was known from X-ray diffraction studies.[28] Much of the detailed mechanism by which this enzyme hydrolyzes and depolymerizes ribonucleic acid was also known. The purpose of a chemical synthesis of this 124-residue molecule was, first, simply to demonstrate that a protein with the high catalytic activity and specificity of a naturally occurring enzyme could be synthesized in the laboratory. For the long term the more important purpose was to provide a new approach to the study of enzymes. We believed it should be possible to modify the structure and to alter the activity and the substrate specificity of the enzyme.

The synthesis[29] was carried out on a copolymer of styrene and divinylbenzene (1%) using the general methods described above. The *C*-terminal Boc-Val was anchored to the solid matrix by a benzyl ester bond, the usual benzyl-based side-chain protecting groups were used and the Boc group provided the reversible N^{α} protection. The deprotection steps were carried out with trifluoroacetic acid and the coupling reactions with dicyclohexylcarbodiimide activation. Figure 8 shows the final protected derivative of ribonuclease. It contained a total of 67 side-chain protecting groups and had a molecular weight of 19791. The synthesis is summarized in Table 1. The overall yield after several purification steps was about 3% based on the original amount of valine attached to the resin. There was a large (83%) loss of chains during the assembly of the peptide chain due to partial instability of the anchoring bond, and the accumulated losses during HF cleavage from the resin and the purification steps amounted to another 80%. The crude cleaved product was air oxidized to form the four disulfide bonds and the monomer fraction was isolated by gel filtration. The monomers with incorrect disulfide pairing or incorrect folding were digested by trypsin and the small fragments were separated from the stable protein with the correct structure. An ammonium sulfate fractionation gave the final purified enzyme possessing approximately 80% specific activity compared with native ribonuclease A. We could not claim that our product was completely pure or that the synthesis constituted a structure proof for RNase, only that the molecule showed a close chemical and physical resemblance to the native protein and that it was a true enzyme. The chemical and physical comparisons were based on amino acid analysis, enzyme

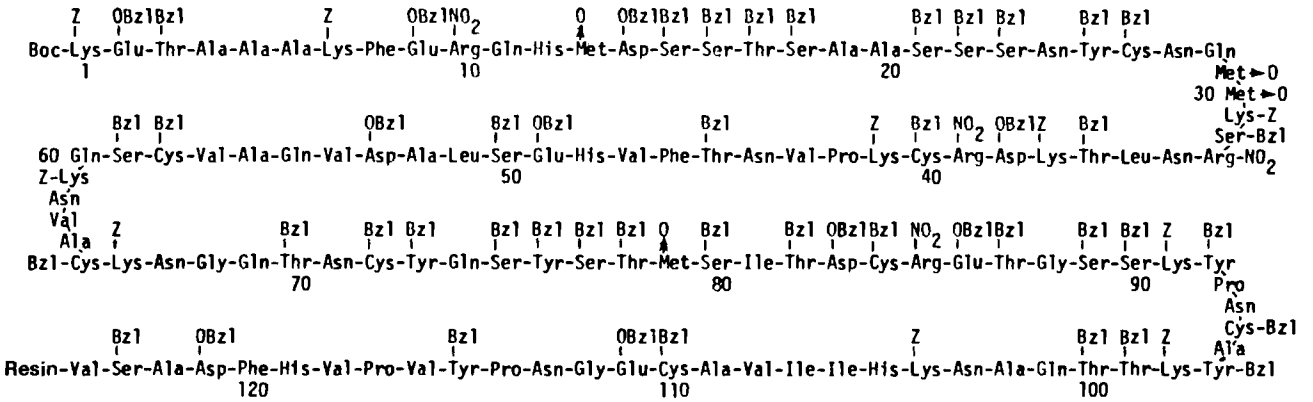


Fig. 8. Resin-bound, protected ribonuclease.

Table 1. Summary of ribonuclease(RNase) A synthesis.

Stage of synthesis	Overall yield [mg]	[%]
Boc-Val-Resin	2000	100
↓ deprotect, neutralize, couple } repeat 123 times		
Protected RNase-resin	3430	17
↓ cleave and protect with HF		
Crude RNase $(SH)_8$	697	12
↓ Sephadex G-75		
RNase A (monomer fraction)	373	6.4
↓ trypsin digestion, Sephadex G-50		
RNase A (trypsin resistant fraction)	256	4.4
↓ $(NH_4)_2SO_4$ fractionation		
RNase A	169	2.9

digestions, peptide maps, paper electrophoresis, gel filtration, ion-exchange chromatography, and antibody neutralization. At that time we did not have HPLC or an affinity chromatography system.

Table 2. Ribonuclease A activity.

Purification stage	Specific activity [%]	Total activity mg RNase / 2g resin
HF cleavage	2	14
Sephadex G-75	9	33
IRC-50	13	53
Trypsin	61	156
$(NH_4)_2SO_4$	78	132

Table 2 summarizes the activity data at various stages of purification of the synthetic enzyme. Both the specific activity and the total number of units of RNase increased as the purification proceeded, indicating either that inhibitory impurities were being removed or that the molecule was gradually refolding into a conformation that more closely resembled the native structure. The substrate specificity of the synthetic enzyme was consistent with that to be expected for RNase A: it was able to cleave both large (RNA) and small (cyclic cytidine 2′,3′-monophosphate) substrates and therefore to catalyze both the transphosphorylation and the hydrolysis steps; it was specific for D-ribose instead of D-deoxyribose and for a pyrimidine instead of a purine at the 3′ position of the phosphodiester substrate (Table 3). The K_M values toward RNA were also the same for the natural and synthetic enzymes.

Table 3. Substrate specificity of synthetic ribonuclease A.

Substrate		Activity [%]
Ribonucleic acid	(RNA)	78
Deoxyribonucleic acid	(DNA)	0
Cyclic cytidine-2′,3′-monophosphate	(C>p)	65
Cyclic guanosine-2′,3′-monophosphate	(G>p)	0
5′-(3′-Guanylyl)cytidylic acid	(GpCp)	0
5′-(3′-Adenylyl)adenylic acid	(ApAp)	0

The purified RNase A was compared on a CM-cellulose column with natural RNase A and with reduced and reoxidized natural RNase A. They were identical by this criterion, which was the one first used by *White*[30] to show that RNase A after reduction and reoxidation of the disulfide bonds was indistinguishable from the native enzyme. It was *White*'s experiments[30] that led to the hypothesis that the primary structure of the protein determined its tertiary structure.[31] Our synthesis provided a new kind of evidence for this hypothesis. The fact that the only information put into the synthesis was the linear sequence means that the primary structure must be sufficient to direct the final folding of the molecule into its active tertiary structure. The synthesis of an active enzyme containing no substituents except amino acids also provided a new proof for the now well established belief that enzymatic activity can be attributed to a simple protein containing no other components.

Structure-Function Studies on Ribonuclease

The synthesis of ribonuclease provided answers to several fundamental questions and laid the foundation for new studies on the relation of structure to function in the enzyme. The classic *S*-peptide/*S*-protein system discovered by *Richards*[32] provided an ideal way to study such re-

lations because a small peptide (residues 1–20) and a large protein component (residues 21–124) could be combined noncovalently with regeneration of nearly full enzymatic activity. The extensive work from the *Hofmann*[33] and *Scoffone*[34] laboratories on the synthesis of the *S*-peptide and its combination with the natural *S*-protein had already provided a great amount of information about the role of individual residues in the *N*-terminal region of the enzyme. We undertook to study this region of RNase by total synthesis (Fig. 9). During the initial synthesis we removed

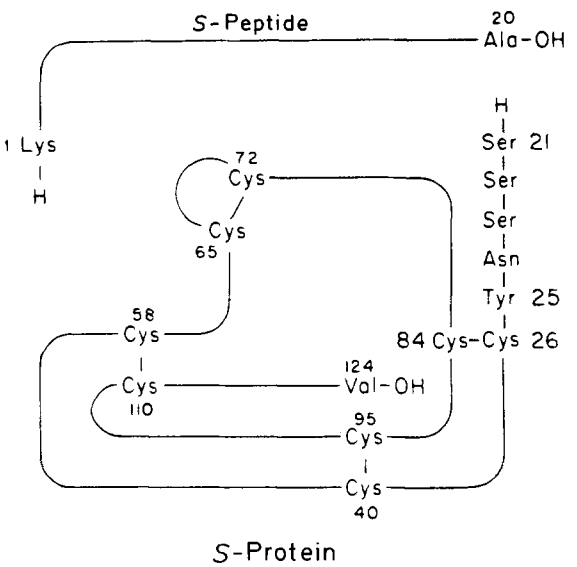


Fig. 9. The *S*-peptide *S*-protein system.

samples after coupling Cys 26 and again after Ser 21 and in that way prepared synthetic *S*-protein (21–124) and *S*-protein (26–124). The partially purified proteins were reduced at their four disulfide bonds, each mixed with synthetic *S*-peptide, reoxidized, and assayed for enzymatic activity. Each of the crude mixtures was found to have as much activity as the product derived from native *S*-protein by the same treatment. From these data it was concluded, first, that *S*-protein had been synthesized and, second, that the five residues 21–25 were definitely not necessary for the binding and reactivation to occur. Earlier X-ray data[35] had predicted that the serine residues at positions 21, 22 and 23 would probably not be necessary, but Asn 24 and Tyr 25 appeared to be involved in a total of five hydrogen bonds in RNase S and it was expected that they might be necessary for the formation of an active complex. The synthetic studies showed that they were not.

Several years earlier I had been interested in the question of whether or not a peptide from the carboxyl end of RNase might function in a manner similar to that of the *S*-peptide at the amino end. We therefore synthesized and purified the tetradecapeptide RNase 111–124. RNase was inactivated by carboxymethylation of the imidazole ring of His 119. Attempts to reactivate the enzyme by addition of the synthetic peptide were uniformly unsuccessful. Somewhat later in a separate study *Lin* et al.[36] succeeded in preparing a series of shortened RNases. They made RNase 1–120, RNase 1–119 and RNase 1–118 by enzymatic digestion. When the synthetic peptide 111–124 was assayed in the presence of these inactive proteins, high enzymatic activity was generated[37] and it became clear that a system existed at the *C*-terminus of RNase that was similar to the one at the *N*-terminus.

We then made the interesting discovery that the *C*-terminal peptide 111–124 containing His 119, the *N*-terminal peptide 1–20 containing His 12, and the central protein component 21–118 containing Lys 41 could be mixed together non-covalently and ribonuclease activity would be generated. Therefore, three components, each containing one of the known residues required for enzymatic activity could bind together and form the specific well ordered structure necessary for substrate binding and catalytic activity.

A series of synthetic studies was then undertaken to define the roles of some of the individual residues in the *C*-terminal region. These can be summarized and discussed by referring to Figure 10. When peptides shorter than 111–124 were prepared and combined with RNase 1–118, both the binding constant and the activity were progressively decreased and peptide 117–124 was inactive indicating that each residue contributed to the binding energy.[38] However, even in the complex 1–118 + 116–124 there were three overlapping residues. It was then found that the complex 1–115 + 116–124, in which there were no overlapping residues, had a binding constant 100 times larger.[39] In these experiments it could also be shown that Tyr 115 was not necessary for enzymatic activity.

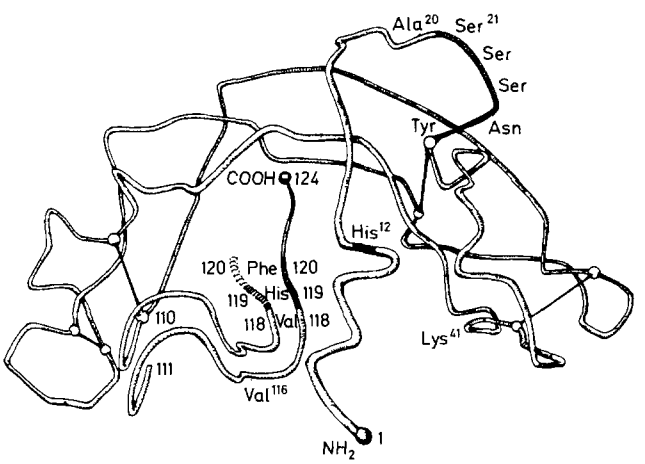


Fig. 10. A 3-dimensional representation of ribonuclease fragments 1–20, 21–118 and 111–124.

Phenylalanine-120 was shown by transition temperature studies to be important in stabilizing the ribonuclease structure and by X-ray and NMR studies to interact with the pyrimidine substrate. Our synthetic-analogue work on the 1–118 + 111–124 system showed that replacement of Phe 120 by Leu 120 or Ile 120 reduced the binding by 5- and 17-fold and reduced the maximum enzymatic activity to 10% and 5% respectively, indicating that the aromatic side chain of phenylalanine was of considerable importance in binding the peptide to the protein.[40] It could only be partially replaced by a hydrophobic aliphatic chain, indicating an inexact alignment of the catalytic site. The

small residue Ala 120 and the bulky aromatic residue Trp 120 were inactive. Replacement of Phe 120 by an aromatic residue of similar size, Tyr 120, in the 111–124 peptide gave a complex with 1–118 that was fully active toward cyclic cytidine 2′,3′-monophosphate substrate and 190% as active toward cyclic uridine 2′,3′-monophosphate.[41] A semisynthetic enzyme with enhanced activity was a novel finding. K_M and K_i data led to the conclusion that Phe 120 does not have a unique role in the binding of substrate but is important for stabilizing the peptide-protein complex and the native enzyme itself. Nevertheless, the presence of substrate increased the binding constant between RNase 1–118 and RNase 111–124 by a factor of 50.

Similar experiments with the aspartic acid residue at position 121 have shown that it can be partially replaced (ca. 20%) by glutamic acid, but the Asn 121 and Ala 121 analogues did not show measurable binding. Removal of Val 124 from RNase A does not affect the enzymatic activity and removal of Val 124 from *S*-protein does not reduce the activity of the complex with *S*-peptide. In contrast, omission of Val 124 from the *C*-terminal tetradecapeptide produced an essentially inactive complex with RNase 1–118, indicating an important hydrophobic interaction necessary for peptide-protein binding. The smaller aliphatic residue Ala 124 could only restore half of the binding energy.[41]

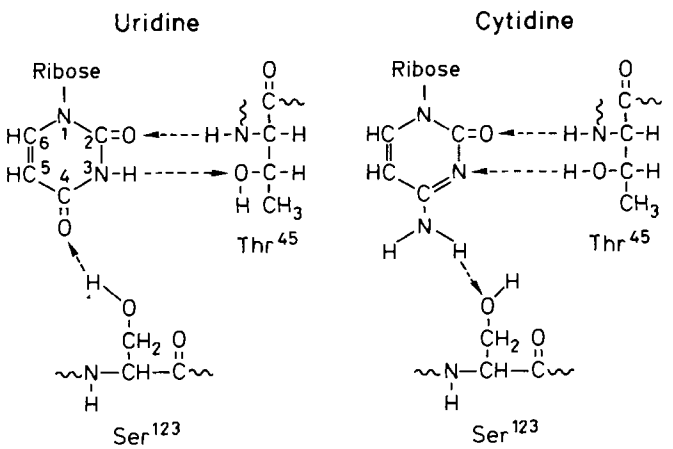


Fig. 11. Postulated hydrogen bonding of uracil and cytosine substrates to ribonuclease.

X-ray data[42] indicate that the uracil and cytosine residues of RNA and the cyclic nucleotides probably bind to ribonuclease through the series of hydrogen bonds shown in Figure 11. For uracil, the hydroxyl group of Thr 45 is a hydrogen acceptor and for cytosine it is a hydrogen donor. Conversely, the hydroxyl group of Ser 123 is a donor for uracil and an acceptor for cytosine. We reasoned that if these two hydroxyl groups were blocked as methyl ethers they could only be hydrogen acceptors and if replaced by Ala they could be neither donor nor acceptor. A suitable combination of these residues in replacement analogues might, therefore, lead to a synthetic ribonuclease with altered substrate specificity. Such analogues have been made for Ser 123.[43]

The tetradecapeptide containing Ala 123 gave a complex with RNase 1–118 that showed appreciable selectivity for substrates containing cytosine relative to those containing uracil (either the cyclic 2′,3′-nucleotides or polynucleotides) (Table 4). Replacement with *O*-methylserine did not result in differential substrate specificity. It was concluded that a hydrogen bond between the hydroxyl group of Ser 123 and the C^4 amino group of cytosine is not important for substrate binding and catalytic activity, but that the hydrogen bond between the hydroxyl group of Ser 123 and the C^4 carbonyl of uracil contributes significantly to the binding and activity; when Ser is replaced by Ala the H-bond is absent and the activity is reduced. The corresponding studies with replacement of Thr 45 by Ala 45 and *O*-Me-Ser 45 involve total synthesis of the enzyme; these much more difficult experiments have not yet been completed. We believe that the substrate binding at Thr 45 is much tighter than at Ser 123 and that changes at this residue will lead to much greater substrate selectivity.

Table 4. Substrate selectivity of [Ala[123]]-RNase complexes.

Enzyme	Selectivity (k_s/K_m) $\frac{C>p}{U>p}$
RNase A	4.6
[Ser[123]]-RNase 111–124 + RNase 1–118	5.0
[Ala[123]]-RNase 111–124 + RNase 1–118	19

Recent Improvements in Solid Phase Peptide Synthesis

Although the earlier solid phase chemistry was very useful for these studies on ribonuclease, it was clear that there was a need for improvement in several areas. One was the mode of attachment of the peptide to the resin. If the strategy of differential stability toward acid for the N^α and C^α groups was to be continued, a more acid-stable anchoring bond was needed. We predicted that the insertion of an acetamidomethyl group between the benzyl ester and the polystyrene matrix would increase the stability of the benzyl ester toward trifluoroacetic acid by a factor of approximately 25 to 400 times. When such a linkage was finally constructed it was found to be 100 times more stable.[44] A new synthesis of aminomethyl-resin was first developed in which *N*-hydroxymethylphthalimide and polystyrene resin were reacted under acid catalysis with F_3CSO_3H, HF, or $SnCl_4$.[45] This product was then coupled with a derivative of the *C*-terminal amino acid. Thus, N^α-Boc-aminoacyloxymethylphenylacetic acid was prepared and activated with dicyclohexylcarbodiimide for the reaction. The product was a copolymer of polystyrene and divinylbenzene (1%) bearing acyloxymethylphenylacetamidomethyl groups (acyloxymethyl-Pam-resin) (Fig. 12). This new preparation has the advantages that it is more acid stable, and it is made from purified, well characterized intermediates, which give a cleaner product with fewer side reactions. It is free of chloromethyl groups that can give rise to quaternization and ion-exchange reactions and is free of hy-

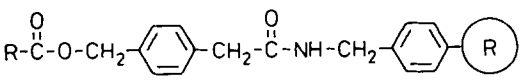


Fig. 12. Acyloxymethyl-Pam resin.

droxyl groups that can lead to peptide chain terminations via trifluoroacetylation.[46]

An alternative protecting group strategy is to make use of an orthogonal system[47] in which the N^{α}, C^{α}, and side chain groups represent three different classes of compounds that are cleavable by three different kinds of reactions. In this way any one of the functional groups can be

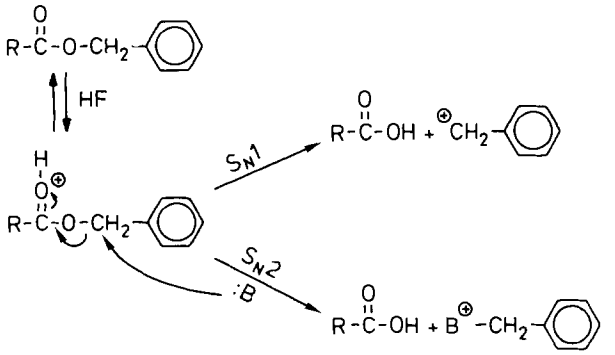


Fig. 14. The S_N1 and S_N2 acidolysis mechanisms.

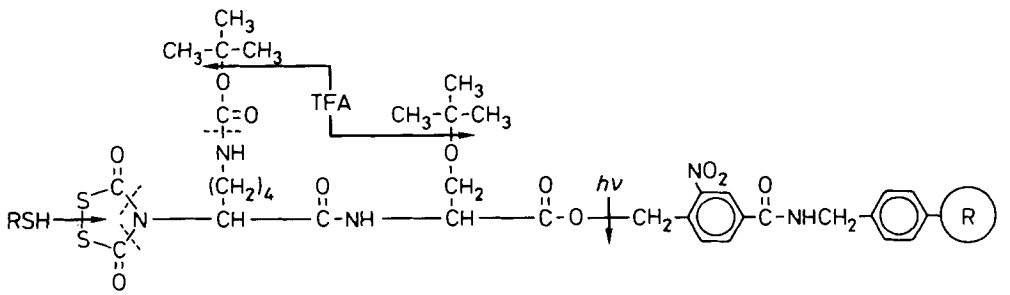


Fig. 13. A scheme for "orthogonal" protecting groups.

selectively removed in the presence of the other two. Figure 13 illustrates such a system in which the anchoring *O*-nitrobenzyl ester is photolabile but stable to acid or nucleophiles, the side chain groups are based on *tert*-butyl derivatives that are very acid labile but stable to light or nucleophiles, and the N^{α} protecting group is the dithiasuccinoyl group which is removed by nucleophilic thiols but is stable to acid and photolysis. This scheme has recently been put to the test and found to give excellent results.[48]

Anhydrous hydrogen fluoride, the usual cleavage reagent for solid phase peptide synthesis, is a very strong acid ($pK_a = -10.8$) and is known to promote a number of side reactions. In particular, it leads to the formation of carbonium ions which then can alkylate tyrosine, tryptophan, methionine and cysteine residues of the peptide. In addition, HF can protonate and dehydrate the side-chain carboxyl group of glutamic acid residues with formation of the very reactive acylium ion, which has been shown to acylate the aromatic rings of anisole and other scavengers present in the mixture. Activated glutamyl residues can also form pyrrolidone (pyroglutamic)-containing products. Aspartyl residues can close in HF to give the aspartimide derivative and subsequently open to produce β-aspartyl residues. All of these undesired reactions result from the S_N1 mechanism of the cleavage reaction under the usual conditions (90% HF + 10% anisole, 0°C, 1 h). We reasoned that if conditions could be found that would change the reactions to an S_N2 mechanism in which the acidolysis is aided by a nucleophile and carbocation is never formed (Fig. 14) it should be possible to minimize or avoid these problems. Dr. *James Tam* and *Bill Heath*, a graduate student, have succeeded in developing such conditions and in demonstrating marked improvements in solid phase peptide synthesis.[49]

The problem was to find a suitable weak base which would reduce the acidity function of the HF but which would remain largely unprotonated and nucleophilic under the resulting acidic conditions. It should be a weaker base than the groups to be cleaved so that they would be largely protonated under the same conditions. Dimethyl sulfide (DMS) was found to be an ideal base for this purpose. It has a pK_b of -6.8 compared with values of -2 to -5 for the benzyl ethers, esters and carbamates to be cleaved. It is a good solvent for HF and it is volatile and easily removed from the reaction mixture. A 1:1 molar mixture of HF and DMS (1:3 by volume) was determined by Hammett indicators to have a pK_a value between -4.6 and -5.2. The mechanisms of removal of various benzyl-based protecting groups by HF/DMS mixtures were tested by kinetic and product analysis experiments. Based on earlier work with H_2SO_4 hydrolysis of alkyl acetates,[50] a sharp upward break in the rate constant was expected when the acid concentration was increased. At the break point the mechanism changed from S_N2 to S_N1. A similar change was found in the cleavage of *O*-benzylserine by HF/DMS mixtures; above HF concentrations of 50% by volume the rate increased rapidly, indicating the change in mechanism. Product analysis for the deprotection of tyrosine benzyl ether as a function of HF concentration is shown in Figure 15. Above 15% HF in DMS the yield (after 1 h, 0°C) of tyrosine was quantitative and the other product was the benzyl(dimethyl)sulfonium salt. In the range of 40–50% HF the amount of sulfonium salt began to decrease and the level of the undesirable by-product, 3-benzyltyrosine, increased. Again, there was a change from the S_N2 to the S_N1 mechanism at an HF concentration around 40–50%. The reactions were accelerated in the presence of 5–10% of cresol. We selected 25% HF/65%

DMS/10% cresol as the best reagent and refer to it as "low HF."

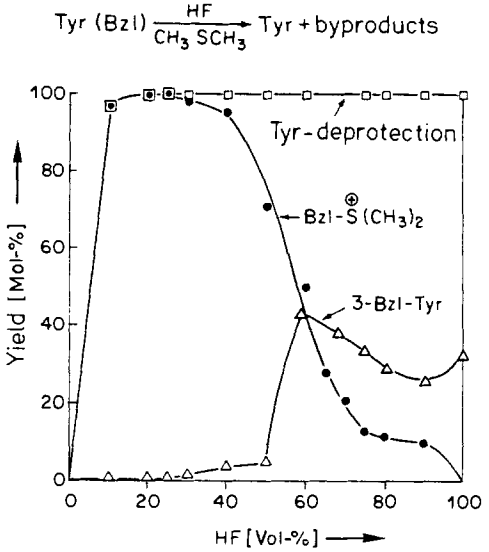


Fig. 15. Product analysis for the deprotection of tyrosine benzyl ether in mixtures of HF and dimethyl sulfide.

This reagent was also effective in preventing acylium ion formation in glutamyl and aspartyl peptides and avoided the acylation and imide side reactions. It was also found to be very effective in converting methionine sulfoxide into methionine, with formation of dimethyl sulfoxide as coproduct. Furthermore, in the presence of 5% of a thiol such as thiocresol a nearly quantitative removal of the formyl protecting group from the indole nitrogen atom of tryptophan was possible. The coproduct was $HC(SR)_3$. The last two reactions do not occur at high (90%) HF due to protonation of the reagents.

The derivatives Arg(Tos), Arg(NO_2), Cys(4-MeBzl), or Asp(OcHex) will not be deprotected under the low HF conditions, and peptides containing these and certain other residues must be re-treated in high HF (90%) after removal of the DMS. However, since most of the potential carbocations in the peptide will already have been trapped as the less reactive dimethylsulfonium salt, very few by-products will be formed even upon reaction with 90% HF.

The Need to Pay Attention to Details

I cannot emphasize enough how important it is to be attentive to even the smallest of details if one expects to synthesize a peptide of high quality. The principal by-products of solid phase peptide synthesis can be classified as termination, deletion, or modification peptides. Much effort has gone into identifying these problems, developing ways to quantitate them, and finding ways to eliminate them. First of all, it is important to begin with clean well characterized resins, clean amino acid derivatives, and clean solvents. Most of the known side reactions can now be eliminated or greatly minimized if the proper coupling methods and conditions are selected.[51] It is important to monitor coupling reactions to determine that they have proceeded to completion so that deletion peptides missing one or more residues will be avoided. The quantitative ninhydrin reaction[52] is useful for this purpose and can detect the presence of 0.1% unreacted chains (i.e., 99.9% coupling). After a peptide chain has been assembled it can be analyzed by solid phase sequencing methods[53] to quantitate the levels of preview and therefore of deletion sequences.[54] Except for special cases, racemization is not usually a problem in stepwise solid phase synthesis, but sensitive methods for its detection are available.[55] If the various precautions alluded to here are taken, satisfactory results can be expected in most instances.

Some Recent Syntheses of Peptides

Numerous peptides have been synthesized in recent years by the techniques that have been discussed and I cannot begin to cover them here. From our own laboratory we have reported recent synthetic studies on apamin,[56] thymosin α_1,[57] glucagon,[58] and cecropin A.[59,60] For this discussion I have selected examples of syntheses that serve to illustrate certain areas of interest.

An excellent example of a synthetic peptide study leading to useful drugs is that of *Manning* and *Sawyer* on the development of vasopressin analogues with high antidiuretic activity and essentially no remaining pressor activity for treatment of Diabetes insipidus.[61] The best was 1-deamino-(4-valine, 8-D-arginine) vasopressin. They have also discovered, through synthesis, arginine vasopressin analogues that are strong inhibitors of both antidiuretic and pressor activity for use in patients with hyponatremia due to excessive retention of water.[62] The best was [1-(β-mercapto-β,β-cyclopentamethylenepropionic acid), 2-D-phenylalanine, 4-valine]arginine vasopressin.

In a few instances solid phase syntheses have been scaled up for commercial purposes. A good example is salmon calcitonin.[63] It has been prepared in 50–100 g batches of highly purified peptide. This 32-residue hormone is highly effective for the treatment of Paget's disease and other conditions of hypercalcaemia.

The area of greatest current interest and activity is undoubtedly the synthesis of peptides for the elucidation of the immunogenic determinants of proteins and for the development of synthetic vaccines against viral and other infectious diseases. The work from *Lerner*'s laboratory[64] has given an important impetus to this field. Synthetic antigens are also useful for the development of diagnostics and for the production of antibodies as aids in detecting and isolating unidentified gene products.

As an illustration of my emphasis on the importance of new chemistry and the need to pay attention to the details when utilizing solid phase peptide synthesis I would mention some new work on the epidermal growth factor (EGF) by *Bill Heath*.[65] EGF stimulates cellular proliferation, inhibits gastric acid secretion, and plays a role in embryonic development. The structure of this 53-residue peptide[66] is shown in Figure 16. It is a hydrophobic, highly cross-linked, compact molecule that others have found very difficult to synthesize in the past. By using the newly developed Pam-resin support, several new protecting groups,

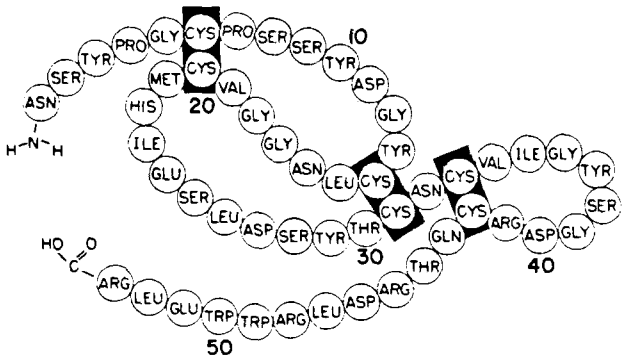


Fig. 16. Structure of mouse epidermal growth factor.

pure reagents, the quantitative monitoring procedures, the new HF cleavage methods, and by taking all the other known precautions against side reactions, he succeeded in obtaining an essentially quantitative assembly of the peptide chain and a 97% cleavage yield, leading to a crude unpurified product that contained 65% of the desired EGF. It could be readily isolated in a highly purified form which eluted from a C_{18} HPLC column at exactly the same time as natural EGF (Fig. 17). In the sensitive and discriminating Leydig cell growth assay the synthetic and natural EGF had identical activity.

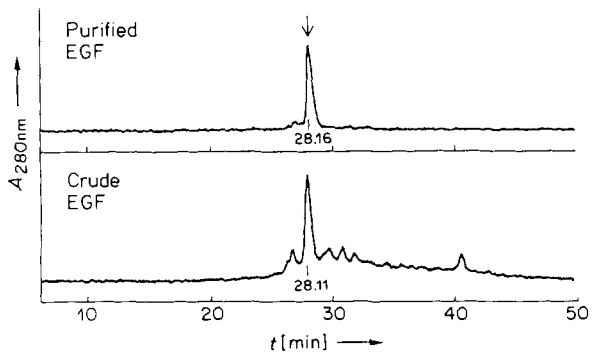


Fig. 17. HPLC analysis of synthetic EGF.

From the accumulated data presented, we conclude that the solid phase synthesis of peptides up to a length of 50 or somewhat more residues can be readily achieved in good yield and purity; and this is a far better situation than I could have expected when this technique was first proposed.

As example of a synthesis of a protein I have selected our recent studies on interferon. The sequence of human leucocyte interferon α_1 was first deduced from the DNA sequence of the cloned gene.[67] It contains 166 amino acids with five cysteine residues (Fig. 18). The amino acid sequence of the isolated protein of human leucocyte interferon α_2 was also sequenced[68] and found to have only 155 residues. There is a high degree of homology between the two, but the latter has one deletion at Asp44 and is missing the last ten residues predicted from the DNA sequence (Fig. 18). We have synthesized these two proteins and also their Ser1 analogues and purified them by reduction, gel filtration, reoxidation, gel filtration, and affinity purification on a column of supported antibodies to polyclonal human leucocyte interferon.[69] The synthetic proteins and the natural and recombinant interferon all had 10^8 to 10^9 units/mg in antiviral assays against a broad spectrum of cell lines. The development and duration of the antiviral state were also similar. Synthetic [Ser1]IFN-α_2 and natural Hu-Le-IFN-α showed similar growth inhibition of K 562 cells. [Cys1]IFN-α_2 and natural Hu-Le-IFN-α caused a similar increase of natural killer cell activity whereas synthetic [Ser1]IFN-α_2 caused a decrease. All four synthetic interferons bind to and are eluted from polyclonal anti-Hu-Le-IFN-α antibodies under similar conditions.

α_1 / α_2	1	Cys-Asp-Leu-Pro Glu/Gln Thr-His-Ser-Leu Asp-Asn/Gly-Ser Arg-Arg-Thr-Leu-
	16	Met-Leu-Leu-Ala-Gln-Met Ser-Arg/Arg-Lys Ile-Ser Pro-Ser/Leu-Phe Ser-Cys-Leu-
	31	Met/Lys Asp-Arg-His-Asp-Phe-Gly-Phe-Pro-Gln-Glu-Glu-Phe Asp/- Gly-
	46	Asn-Gln-Phe-Gln-Lys-Ala Pro-Ala/Glu-Thr Ile Ser/Pro Val-Leu-His-Glu Leu/Met
	61	Ile-Gln-Gln-Ile-Phe-Asn-Leu-Phe Thr/Ser Thr-Lys-Asp-Ser-Ser-Ala-
	76	Ala-Trp-Asp-Glu Asp/Thr Leu-Leu-Asp-Lys-Phe Cys/Tyr Thr-Glu-Leu-Tyr-
	91	Gln-Gln-Leu-Asn-Asp-Leu-Glu-Ala-Cys-Val Met/Ile Gln Glu-Glu-Arg/Gly-Val-Gly
	106	Val Gly/Thr Glu-Thr-Pro-Leu-Met Asn-Ala/Lys-Glu Asp-Ser-Ile-Leu-Ala-Val-
	121	Lys/Arg Lys-Tyr-Phe Arg/Gln Arg-Ile-Thr-Leu-Tyr-Leu Thr/Lys Glu-Lys-Lys-
	136	Tyr-Ser-Pro-Cys-Ala-Trp-Glu-Val-Val-Arg-Ala-Glu-Ile-Met-Arg-
	151	Ser Leu/Phe Ser-Leu-Ser-Thr Asn-Leu-Gln-Glu-Arg-Leu-Arg-Arg-Lys-Glu (166)

Fig. 18. Sequences of leucocyte interferons α_1 and α_2.

These results are encouraging, but much more needs to be done to assure that even small proteins can be synthesized readily in high yield and purity. I think we can be optimistic about the future.

I owe a very special debt of gratitude to my teachers, Dr. M. S. Dunn of U.C.L.A. and Dr. D. W. Woolley of The Rockefeller University. Several of the past and present members of my laboratory have been referred to here, but to the many others who have not been specifically mentioned I am equally grateful because they all have contributed to the progress of our work. Finally, I wish to acknowledge the continuing support of The Rockefeller University and of the National Institutes of Health of the United States.

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The Generative Grammar of the Immune System (Nobel Lecture)**

By Niels K. Jerne*

Grammar is a science that is more than 2000 years old, whereas immunology has become a respectable part of biology only during the past hundred years. Though both sciences still face exasperating problems, this lecture attempts to establish an analogy between linguistics and immunology, between the descriptions of language and of the immune system. Let me first recall some of the essential elements of the immune system, with which I shall be concerned. In 1890, *von Behring* and *Kitasato*[12] were the first to discover antibody molecules in the blood serum of immunized animals, and to demonstrate that these antibodies could neutralize diphtheria toxin and tetanus toxin. They also demonstrated the *specificity* of antibodies: tetanus antitoxin cannot neutralize diphtheria toxin, and vice versa. During the first 30 years, or more, after these discoveries, most immunologists believed that all cells of our body are capable of producing antibodies, and it took until the 1950's before it became clear, and until 1960 before it was demonstrated,[13] that only white blood cells, named lymphocytes, can produce antibodies. The total number of lymphocytes represent a little more than 1% of the body

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weight of an animal. Thus, it would not be wrong to say that our immune system is an organ consisting of about 10^{12} lymphocytes, or in a mouse that is 3000 times smaller than we, 3×10^8 lymphocytes.

(human) immune system = 10^{12} lymphocytes
(mouse) immune system = 3×10^8 lymphocytes

This brief description of the immune system disregards the fact that lymphocytes interact with most other cells in the body, which in my definition do not belong to the immune system *sensu strictu*.

Let me draw attention to the fact that this number of lymphocytes in the immune system is at least one order of magnitude larger than the number of neurons in the nervous system. Also, we should note that lymphocytes travel among most other cells of our body, that they circulate in blood and lymph, and occur in large concentrations in spleen, lymph nodes, appendix, thymus and bone marrow. Strangely enough, however, they seem to be excluded from the brain. The 1960's was a very fruitful decade of immunological discoveries, of which I shall name a few: In the beginning of the decade, the primary structure of antibody molecules was clarified;[14, 15] then followed the demonstration that the dictum of *Burnet*[2, 16] was correct, namely that all antibody molecules synthesized by one given lymphocyte are identical, and finally, towards the end of that decade, lymphocytes were shown to fall into two classes, called T cells and B cells, existing in the body in almost equal numbers.[17, 18, 5] Only B lymphocytes, or B cells, however, can produce and secrete antibody molecules.

Schematically, I could picture this as in Figure 1.

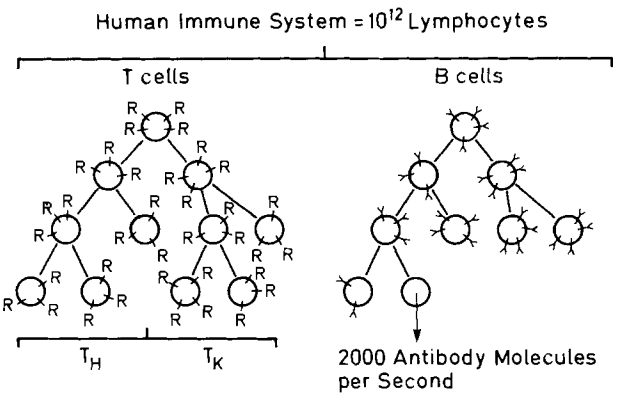


Fig. 1.

What I should like you to retain from this picture is both what we know as well as what we do not know at present. Thus, B lymphocytes are known to carry so-called receptor molecules on their surface (about 10^5 identical receptors per B cell), and when such a "resting" B cell is properly stimulated to divide and to mature, it will end up excreting about 2000 antibody molecules per second, all of which are identical, and similar or identical to the receptors that the resting B cell originally displayed. This clonal nature of antibody formation was clearly demonstrated in the early 1970's.[19, 20] The normal antibody response of an animal to a foreign antigen involves a large number of different clones, however, and is characterized by the production, usually, of several hundreds of different antibody molecules.[21] T lymphocytes are also known to carry receptor molecules on their surface, but firstly these molecules are not well known yet because they have been discovered only during the past two years and secondly, the T cells do not excrete such molecules: these T cell receptors are antigen-recognizing molecules, but they do not contribute to the population of freely circulating antibody molecules which are purely B cell products. Furthermore, there are at least two different types of T cells, one of which is called T helper cells (T_H)[22] because they help B cells to become stimulated (or, in their absence, they prevent B cells from receiving a proper stimulus); the other type is called T killer cells (T_K)[23] because they are capable of killing other cells which they consider undesirable (such as virus-infected cells); moreover, as suppressor cells, they may prevent B cells from being stimulated.[6]

Thus, in this picture, B cells have the single-minded desire to express their antibody language, but are subordinate to the T cells, which can either enhance or suppress this capacity.

Before looking at grammar, I must briefly describe the structure of an antibody molecule. No matter what you try to investigate in biology turns out to become increasingly complex—thus also the structure of antibody molecules. The basic element of all antibody molecules has been shown to be a Y-shaped protein structure[26] of about 150000 daltons molecular weight. This is a three-dimensional structure, like all molecules and cells that biology has to deal with. Three-dimensionality tends to perplex our mind, which is most at ease with one-dimensional, linear sequences, but I shall try to make a rough two-dimensional sketch of an antibody in Figure 2.

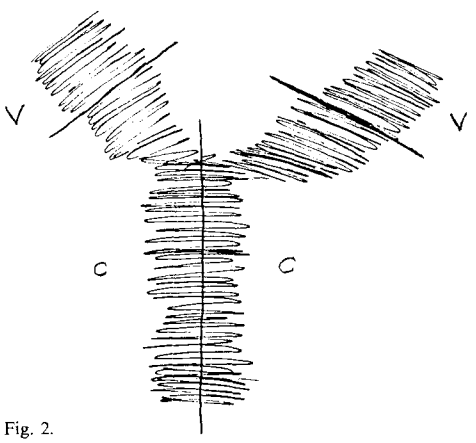


Fig. 2.

We can make some important cuts through this molecule. The vertical cut shows symmetry. It divides the antibody molecule in two identical halves. The two other cuts separate a so-called "constant" part (c) from a "variable" part (v). By constant part, we mean that molecules of different antibody specificity have this part in common (such as, for example, diphtheria antitoxin and tetanus antitoxin). By variable part, we mean that this is the region of the antibody molecule that determines its "specificity." The two variable parts are identical: that is to say that the molecule, with regard to specificity, is divalent. The difficulty

we face is not to transform this sketchy two-dimensional picture into a one-dimensional primary structure, but into a three-dimensional tertiary structure. The primary structure[14, 15] has been clarified: the half molecule is made up of a light polypeptide chain of about 214 amino acid residues, and a heavy polypeptide chain of a little more than 400 amino acid residues, as shown in Figure 3.

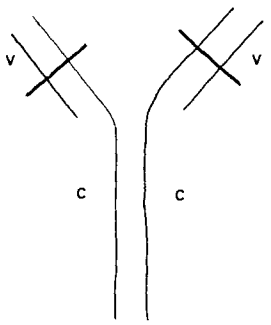


Fig. 3.

It turned out that antibody molecules of different specificity have identical amino acid sequences in their carboxyl-terminal regions, but that they vary with respect to the amino acid sequences in the amino-terminal regions of both heavy and light chains.[24] It became obvious immediately that the great diversity of antibody molecules, the great number of different molecules which antibodies can recognize, or in other words, the great repertoire of antibody specificities, must result from an enormous number of varieties in the variable regions with respect to amino acid sequences. This insight does not solve our problems, however. It is like saying that the great variety of words or sentences in a language results from the enormous number of varieties with respect to the sequences of letters or of phonemes.

The interpretation in immunology remained practically as it had traditionally been, namely that the variable region of an antibody molecule forms a three-dimensional "combining site," and that "specificity" simply means that this combining site is complementary in shape to the shape of part of the three-dimensional profile of an antigen molecule. Antigen is the word that was given, and is still in use, for molecules that can induce the immune system to produce specific antibodies which can recognize these antigens. The antibody combining site was conceived of as a cleft which recognizes a protruberance on the outer shape of an antigenic molecule, and all antibodies were named after the antigens that they recognized, such as diphtheria antitoxin, anti-sheep red blood cell antibodies, anti-TNP, etc.[25] I shall now try to give you an impression of the size of this system of antigens and specific antibody molecules. Let us first consider macromolecules of molecular weights exceeding 10000 daltons; they may be polysaccharides, proteins, lipoproteins, nucleic acids, viruses, bacteria—in fact any such molecule or particle existing in the world is an antigen to which the immune system can make specific antibodies. Moreover, molecules such as nitrophenol, or arsonate, or any inorganic molecules you care to mention are antigenic when attached to a so-called carrier molecule, for example to a protein: the immune system will then produce antibodies that specifically recognize these molecules, even if they have been synthesized in a chemical laboratory without ever before having existed in the world.[1] How is this possible? For example, the immune system of a mouse possesses no more than about 10^8 B lymphocytes, which would be the maximal available repertoire of variable regions on its antibody molecules. We realize that "recognition" need not be perfect, and that the same "combining site" might recognize, with more or less precision, a number of similar antigens.

I shall now turn to some remarkable discoveries, made during the past 25 years, showing that the variable regions of antibody molecules are themselves antigenic and invoke the production of anti-antibodies. *Kunkel*[27] showed that monoclonal myeloma antibodies, when injected into another animal, induce specific antibodies which recognize the particular myeloma antibodies used, but which do not recognize any other myeloma antibodies isolated from other myeloma patients. This work was extended by others, but mainly by *Jacques Oudin* and his colleagues in Paris, who showed that ordinary antibody molecules that arise in an immunized animal are antigenic and invoke the formation of specific anti-antibodies.[28–31] In other words, the variable region of an antibody molecule constitutes not only its "combining site," but also presents an antigenic profile (named its idiotype) against which anti-idiotypic antibodies can be induced in other animals. Moreover, it turned out that this antigenic, idiotopic profile of the variable region of a given antibody molecule is not a single site, but consists of several distinct sites against which a variety of different anti-idiotypic antibody molecules can be made. These individual sites are now named idiotopes, implying that the idiotype of one antibody molecule can be described as a set of different immunogenic idiotopes. And finally, it has been shown that the immune system of a single animal, after producing specific antibodies to an antigen, continues to produce antibodies to the idiotopes of the antibodies which it has itself made. The latter anti-idiotopic antibodies likewise display new idiotypic profiles, and the immune system turns out to represent a network of idiotypic interactions.[7–11]

I shall now show, in Figure 4, a preliminary picture of how we might vaguely try to imagine the shape of the variable region of an antibody molecule.

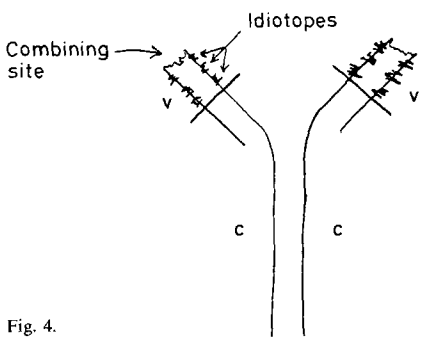


Fig. 4.

This picture is a historical compromise: we uphold our antigen-centered tradition[25] by retaining the notion of a "combining site" which enables the antibody molecule to recognize the antigenic molecule that induced its produc-

tion, and we simply add a number of idiotopes on the same variable region, which are capable of inducing the production of other antibody molecules that have "combining sites" recognizing these idiotopes.

We are now getting into trouble, however, when trying to interpret our experimental results. As I said earlier, a resting B lymphocyte displays on its surface about 100000 identical receptor molecules which are representations of the type of antibody molecules this B cell will produce if stimulated by an antigen.

Let us return to this picture for a moment, as in Figure 5, and let us make an enlargement, in Figure 6, of a small part of the surface of this B cell, focusing on one receptor molecule only, making the usual cuts between constant and variable regions.

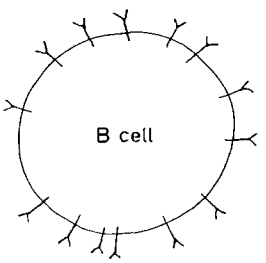


Fig. 5.

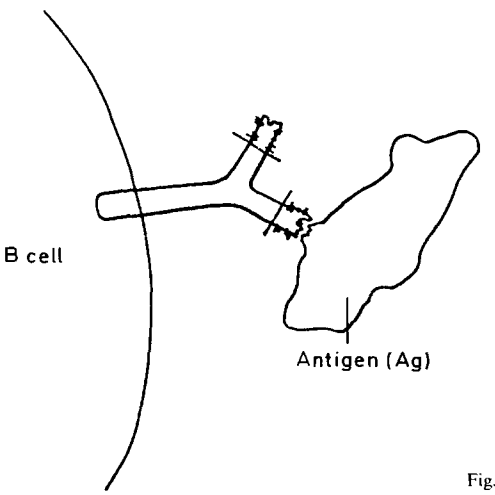


Fig. 6.

As you see, I have retained the traditional distinctions between the antigen-recognizing combining site, and a number of antigenic idiotopes (cf. Fig. 4). I have also added an imaginary profile of an antigenic molecule, part of which is recognized by the combining site of the B cell receptor. This is the basic picture of the selective theories of antibody formation, as most clearly formulated by *Burnet*.[16,2] The antigen "selects" the lymphocytes by which it is recognized, and stimulates these cells to proliferate, to mature, and to secrete antibodies with fitting combining sites. Clearly, T cell control is also involved, as well as growth factors, maturation factor, etc., but this picture remains the basic idea of antibody induction. Figure 7 shows one of these antibody molecules, which recognizes part of the surface profile ("epitope") of the antigen.

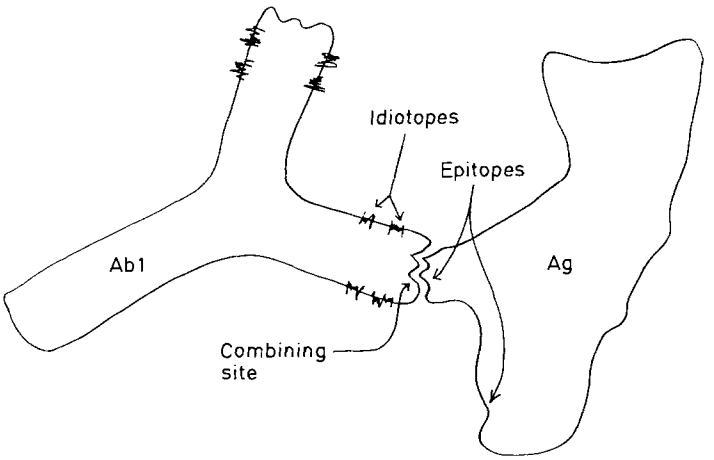


Fig. 7.

Now imagine, however, that this antibody molecule (Ab1), displaying both its combining site as well as its antigenic idiotopes, is itself used as antigen. It is then possible to envisage two situations. Figure 8 shows, schematically, a freely circulating Ab1 molecule which recognizes, and sticks to, a receptor of a B cell. The figure envisages the stimulation of two different B cells by Ab1 molecules now acting as antigens. In the α case, the combining site of the receptor on a B cell recognizes an idiotope of Ab1 and the cell may be stimulated to produce the corresponding anti-idiotopic antibodies (Ab2). In the β case, however, it is the combining site of the Ab1 molecule which recognizes an idiotope of the receptor on a B cell which may thus be stimulated to produce antibodies which possess idiotopes that have a shape that is similar to the epitope displayed by the original antigen. Experiments have shown both these situations actually to occur. For example, if the original antigen is insulin, and Ab1 is an anti-insulin antibody, then some of the anti-idiotypic antibodies (Ab2) of the β types show a similarity to insulin and can even be shown to function like insulin, as shown by *Sege* and *Peterson*.[32] Similar results in other systems have been obtained by *Cazenave* and *Roland*, by *Strosberg*, by *Urbain*, and their colleagues, and by others.[10,33-35]

The point I wish to make, however, is to consider whether the two situations α and β are fundamentally different, or not. Is there a difference between saying that Ab1 recognizes Ab2 or that Ab2 recognizes Ab1? Can we, at this three-dimensional molecular level, distinguish between "recognizing" and "being recognized"? If not, it becomes meaningless to distinguish between idiotopes and combining sites, and we could merely say that the variable region of an antibody molecule displays several equivalent combining sites, a set of idiotopes, and that every antibody molecule is multi-specific. I do not have to belabor this point which has been made repeatedly.[25,36-38] Instead, I should now like to introduce some numerology into this discussion. How large is the number of different antibodies that the immune system of one single animal (be it a human or a mouse) can make? This number, during the past few decades, has been estimated, on more or less slender evidence, to exceed ten million, and this enormous diversity has been designated as the "repertoire" of the B lym-

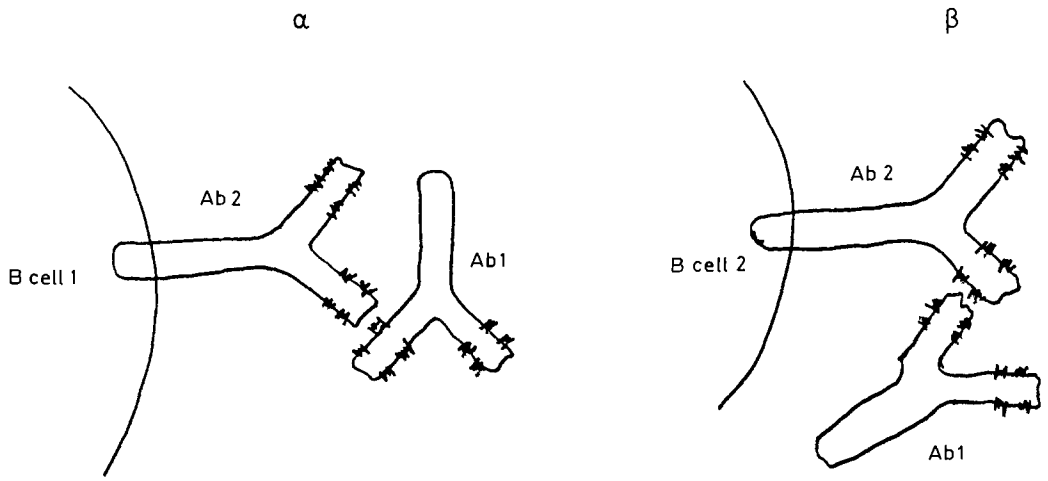


Fig. 8.

phocytes. Such a "repertoire" has been characterized by *Coutinho* as "complete."[39] "Completeness" means that the immune system can respond, by the formation of specific antibodies, to any molecule existing in the world, including, as I said earlier, to molecules that the system has never before encountered. Immunologists sometimes use words they have borrowed from linguistics, such as "immune response." Looking at languages, we find that all of them make do with a vocabulary of roughly a hundred thousand words, or less. These vocabulary sizes are a hundredfold smaller than the estimates of the size of the antibody repertoire available to our immune system. But if we consider that the variable region that characterizes an antibody molecule is made up of two polypeptides, each about 100 amino acid residues long, and that its three-dimensional structure displays a set of several combining sites, we may find a more reasonable analogy between language and the immune system, namely by regarding the variable region of a given antibody molecule not as a *word* but as a *sentence* or a phrase. The immense repertoire of the immune system then becomes not a vocabulary of words, but a lexicon of sentences which is capable of responding to any sentence expressed by the multitude of antigens which the immune system may encounter.

At this point, I shall give a few quotations from *Noam Chomsky*[3] concerning linguistics: "The central fact to which any significant linguistic theory must address itself is this: a mature speaker can produce a new sentence of his language on the appropriate occasion, and other speakers can understand it immediately, though it is equally new to them ... Grammar is a device that specifies the infinite set of well-formed sentences and assigns to each of these one or more structural descriptions. Perhaps we should call such a device a *generative grammar* ... which sould, ideally, contain a central syntactic component ..., a phonological component and a semantic component." That is the end of my quotation. For the size of the set of possible sentences in a language, *Chomsky* uses the word "open-endedness," and I now think that "open-ended" is the best description also of the "completeness" of the antibody repertoire. As for the components of a generative grammar that *Chomsky* mentions, we could with some imagination equate these with various features of protein structures. Every amino acid sequence is a polypeptide chain, but not every sequence will produce a well-folded stable protein molecule with acceptable shape, hydrophobicity, electrostatics, etc. Some grammatical rules would seem to be required. It is harder, however, to find an analogy to semantics: does the immune system distinguish between meaningful and meaningless antigens? It would seem, at first sight, that the immune response to a sentence presented by an invading protein molecule is merely to select, from amongst its enourmous preformed antibody repertoire, a suitable mirror image of part of this antigenic sentence. As you will know, *Leonardo da Vinci* wrote his private journal in the mirror image of ordinary handwriting. It is difficult, without considerable practice, to write and read mirror handscript. Let me show you an example in Figure 9.

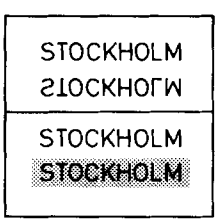


Fig. 9.

In Figures 10 and 11, as in Figure 9 (bottom), I shall use the device of showing ordinary letters in black, and of using gray zones to indicate the mirror images of these letters.

I should perhaps again emphasize that the sentences representing antibodies possess partial mirror images of an antigenic sentence. These antibodies are not echoes of the invading antigen, but were already available to the animal in its repertoire of B cells before the antigen arrived. This is the important insight that followed the introduction into immunology of the selective theories in the 1950's. Also, I

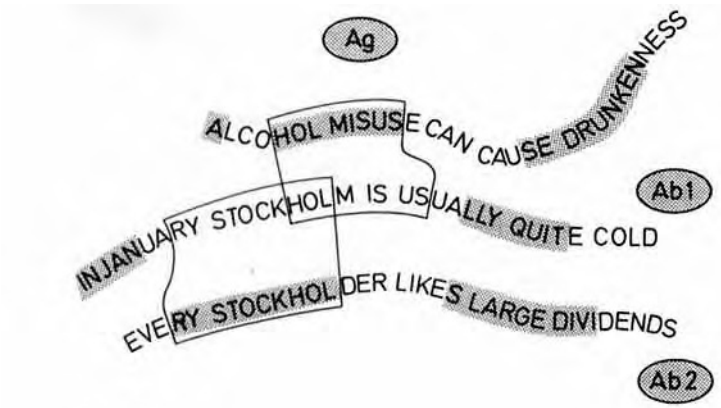


Fig. 10.

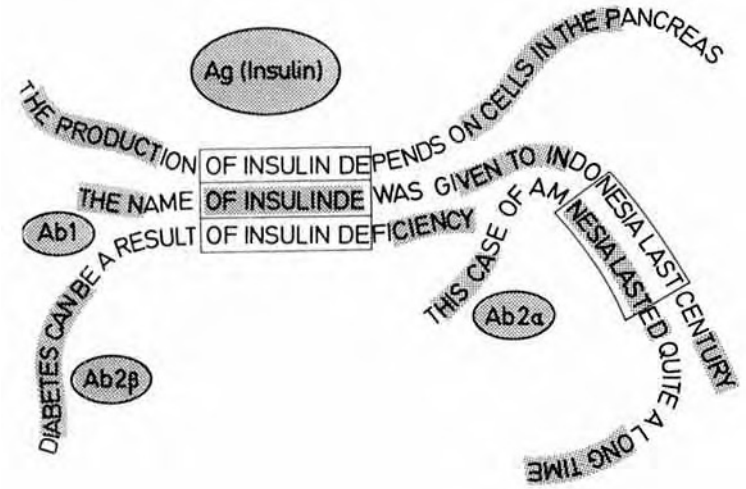


Fig. 11.

must emphasize another important quantitative aspect of the situation facing the immune system. It has been estimated that one human individual produces about 10000 different proteins, such as enzymes, hormones, cell surface proteins, etc. At the same time, we estimate that the immune system maintains a repertoire exceeding ten million different proteins, namely antibody molecules. This is a thousandfold more than all other body proteins taken together. Man and mice, normally, have about ten milligrams of antibodies in a milliliter of their blood. Thus, a normal human possesses from about 50 to 100 grams of freely circulating antibodies, called immunoglobulins. If we divide this figure by 10^7 different specificities, we are still left with an average of 5 to 10 micrograms of every specificity in the available repertoire, representing an average of about 3×10^{13} monoclonal antibodies of every specificity. For mice that are 3000 times smaller, we would have to divide these figures by 3000, which would still leave a mouse with an average of 2 to 3 nanograms of antibodies of each of 10^7 specificities. That even such nanogram quantities of monoclonal anti-idiotypic antibodies, when introduced into mice, produce remarkable effects has been shown by *Rajewsky* and his colleagues.[40–42]

I should therefore like to conclude that in its dynamic state our immune system is mainly self-centered, generating anti-idiotypic antibodies to its own antibodies, which constitute the overwhelming majority of antigens present in the body. The system also somehow maintains a precarious equilibrium with the other normal self-constituents of our body, while reacting vigorously to invasions into our body of foreign particles, proteins, viruses, or bacteria, which incidentally disturb the dynamic harmony of the system.

The inheritable "deep" structure of the immune system is now known: certain chromosomes of all vertebrate animals contain DNA segments which encode the variable regions of antibody polypeptides. Furthermore, experiments in recent years have demonstrated the generative capacities of this innate system. In proliferating B lymphocytes, these DNA segments are the targets for somatic mutations, which result in the formation of antibody variable regions which differ, in amino acid sequences, from those encoded by the stem cell from which these B cells have arisen.[43–47] The experiments showed that it was still possible, however, to identify the original stem cell genes that must have undergone these mutations. Expressed in linguistic terms, such investigations belong to the etymology of the immune system.

As immunologists, we should like to know the semantics of the inheritable gene structures. What is the meaning of the basic lexicon, or what are the specificities of the antibodies, B cell receptors, and T cell receptors as encoded in the genes of our germ cells? It is known that B cells recognize the language of the T cell receptors. I have said so little about the latter because T cell "receptorology" is still in too early a stage of development. An immune system of enormous complexity is present in all vertebrate animals. When we place a population of lymphocytes from such an animal in appropriate tissue culture fluid, and when we add an antigen, the lymphocytes will produce specific antibody molecules, in the absence of any nerve cells.[48] I find it astonishing that the immune system embodies a degree of complexity which suggests some more or less superficial though striking analogies with human language, and that this cognitive system has evolved and functions without assistance of the brain.

It seems a miracle that young children easily learn the language of any environment into which they are born. The generative approach to grammar, pioneered by *Chomsky*[4], argues that this is only explicable if certain deep, universal features of this competence are innate characteristics of the human brain. Biologically speaking, this hypothesis of an inheritable capability to learn any language means that it must somehow be encoded in the DNA of our chromosomes. Should this hypothesis one day be verified, then linguistics would become a branch of biology.

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From the Structure of Antibodies to the Diversification of the Immune Response (Nobel Lecture)**

By Cesar Milstein

> *Cuando se acerca el fin,* escribió Cartaphilus, *ya no quedan imágenes del recuerdo; sólo quedan palabras.* Palabras, palabras desplazadas y mutiladas, palabras de otros, fue la pobre limosna que le dejaron las horas y los siglos.
>
> *J. L. Borges*

When an animal is infected, either naturally or by experimental injection, with a bacterium, virus, or other foreign body, the animal recognizes this as an invader and acts in such a way as to remove or destroy it. There are millions of different chemical structures that the animal has never seen and yet which it is able to recognize in a specific manner. How is this achieved? Scientists have been fascinated by this question for most of this century, and we continue to be fascinated by the intricacies and complexities that still need to be clarified. Even so, looking back over the years since I myself became involved in this problem, progress in the understanding of the process has been phenomenal. Suffice it to remind our younger colleagues that 20 years ago we were still trying to demonstrate that each antibody differed in its primary amino acid sequence.

What attracted me to immunology was that the whole thing seemed to revolve around a very simple experiment: take two different antibody molecules and compare their primary sequences. The secret of antibody diversity would emerge from that. Fortunately at the time I was sufficiently ignorant of the subject not to realize how naive I was being.

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Back in 1962, when I had by accident become the supervisor of *Roberto Celis* in Argentina, it occurred to me that antibody diversity might arise from the joining by disulfide bridges of a variety of small polypeptides in combinatorial patterns. I don't know whether anybody else had the same idea at that time, but of all the prevailing theories about antibody diversity that I am aware of, this is one that was widest of the mark. I hold it to my credit that I never put it into print. But it was of great value to me as it provided an intellectual justification to work on disulfide bonds of antibodies. By the time I joined the Laboratory of Molecular Biology in 1963, the model of two heavy and two light chains joined by disulfide bonds (Fig. 1) had been established,[1] and I was eager to accept Dr. *Sanger*'s proposal that I should engage in studies of antibody combining sites.

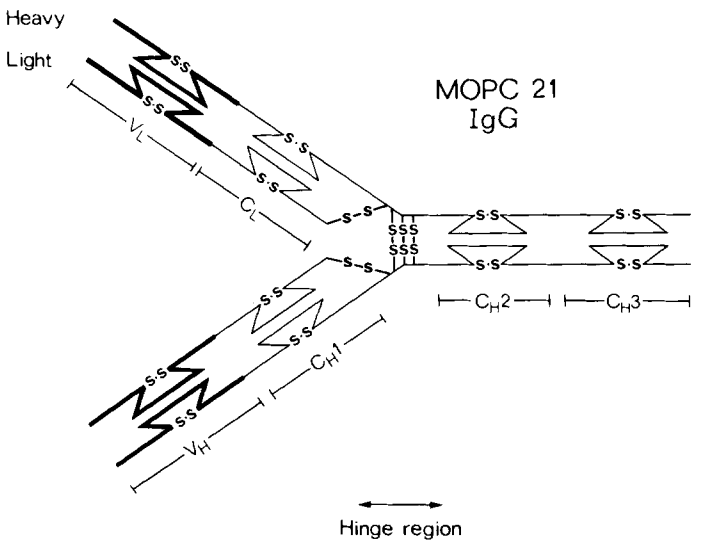


Fig. 1. Antibodies are made of two or more pairs of heavy and light chains joined by disulfide bonds. Each chain has two regions. The variable region differs in structure from one antibody to another and contains the combining site. The antibody combining site is located at the tips of a Y-shaped three-dimensional structure. The constant region is invariant within a given class or subclass, and is responsible for effector functions (complement binding, attachment to and transport across membranes, etc.). The number and position of the interchain disulfide bonds is characteristic for the different classes and subclasses. In this figure, the structure depicted is the mouse myeloma protein MOPC 21 which was the subject of much research in our laboratory.

The Nature of Antibody Diversity

At first I looked for differences in fingerprints of digests of iodinated antibodies directed against different antigens. The pattern that emerged from those studies implied that purified antibodies were too complex and differed only in a subtle quantitative way from the totally unfractionated immunoglobulin. I never published those results, which only led me to the conviction that the protein chemistry of antibodies at that level was too difficult to tackle, and that a different approach was needed.

The study of the amino acid sequence around the disulfide bonds of the immunoglobulins was my own short-cut to the understanding of antibody diversity. I soon recognized the existence of what appeared to be a variable disulfide bridge and a common disulfide bridge,[2,3] but the full meaning of that observation only became obvious when *Hilschmann* and *Craig* described the variable and constant halves of antibody light chains.[4] The variable half contained one disulfide bond, and the constant half the other. This was followed, in later studies with *Pink, Frangione, Svasti,* and others, by the observation of the repeating pattern of similar S-S loops as a distinctive common architectural feature of the different classes and subclasses of immunoglobulin chains. What distinguished them from each other was the diversity of interchain S-S bonds.[5]

The period between 1965 and 1970 was full of excitement, both at the experimental and theoretical level. How were these variable and constant regions going to be explained? It was now not only a problem of millions of antibody structures, but that in addition those millions of structures were part of a polypeptide which otherwise had an invariant primary sequence encoded by only one or very few genes. How to solve the puzzle? *Dreyer* and *Bennett*[6] suggested that there were thousands of genes in the germ line and that the paradox was easy to solve if we postulated a completely unprecedented scheme. This became known as the "two genes-one polypeptide" hypothesis. At the time we did not like that, and proposed a mechanism of hyper-mutation operating on selected segments of a gene.[7] There were other ideas at the time to generate antibody diversity. One of them, widely discussed in a Cold Spring Harbor Symposium in 1967, was based on a mechanism of somatic cross-over between gene-pairs.[8] It was very exciting for me when soon after the symposium I could show that in the human kappa chains at least three genes must be involved.[9] The predicted thousands of V-regions could be grouped into a small number of families or subgroups. The fact that these families were encoded by non-allelic V-genes[10]—coupled to the genetics of the C-region, which indicated a single Mendelian C-gene—provided the experimental evidence that convinced me and many others that the "two genes-one polypeptide" hypothesis was inescapable.

After that, there was a period of consolidation and extension of the results. The concept of V-gene families or subgroups became firmly established, as was the existence of hypervariable residues within the variable segment.[9,11] Crystallographic data showed that such hypervariable residues were near to each other, justifying the idea that they were part of the antibody combining site. This was directly shown with crystals of myeloma protein-antigen complexes.[12] The work with myelomas was not only totally vindicated, but also generally accepted. The idea of separate pools of V- and C-genes that were under continuous expansion and contraction was the last element added to the picture. By 1970 we became convinced that "the section of the genome involved in the coding of immunoglobulin chains undergoes an expansion-contraction evolution: that the number of individual genes coding for basic sequences is not large, and that it varies in different species and even within species at different stages of its own history. The task of providing for the endless variety of individual chains is left to somatic processes."[13]

Light Chain mRNA and the Signal for Secretion

I now began to feel a bit restless. It seemed that protein chemistry alone was not going to get us much further. Furthermore, there was a lot of excitement in the laboratory with the new methods for sequencing RNA being developed by *Sanger* and his group. Perhaps even more important, one of my closest friends at the laboratory, *George Brownlee*, was beginning to feel that the time was ripe to attack molecules more complicated than 5S or 6S RNA. So we joined forces in an attempt to isolate immunoglobulin mRNA. This was a difficult problem and when *George*'s new research student, *Tim Harrison*, joined us we decided to move from solid tumors[14] to cell lines in culture which were kindly provided by colleagues from the Salk Institute.[15] The first important breakthrough in the field was a paper reporting in vitro synthesis of immunoglobulin light chains.[16] We immediately set to work to follow up that approach, and to our delight ran into the unexpected observation of the existance of a biosynthetic precursor of light chains. Further experiments led us to propose that the extra *N*-terminal sequence was a signal for vectorial transport across membranes during protein synthesis. That was the first evidence which indicated that the signal for secretion was an *N*-terminal segment, rapidly cleaved off during protein synthesis.[17,18]

However, our major concern remained the sequence of the messenger RNA for the light chains. In those days there was no DNA sequencing, only mRNA sequencing via elaborate fingerprints of radioactive mRNA. Every radioactive messenger preparation on which we could do sequence analysis involved the labeling of cells with inorganic ^{32}P-phosphate at levels of 100 mCi. So there we were, dressed up in our new-style laboratory coats (namely heavy lead aprons), behind a thick plastic screen, labeling cells and then frantically working up our messenger purification procedures and performing fingerprinting experiments, before the inexorable radioactive decay. Although we didn't go very far in our sequencing, we could isolate oligonucleotides that corresponded to the protein sequences.[19] Among these were oligonucleotides spanning the V- and C-regions, demonstrating that the protein chain was made from a single messenger RNA and that therefore integration of the V- and C-genes did not take place during or after protein synthesis. At this stage the radioactive approach was stopped and we tested alternative methods for the sequencing of mRNA, using synthetic primers and cDNA synthesis. This approach went on in the background while our main efforts were moving in a different direction. Eventually however, it paid off.[21] I will come back to that later, because it forms part of my story.

Spontaneous Somatic Mutants of a Myeloma Protein

The introduction of tissue culture methods to our laboratory had a major impact on the direction of our research. With my new research student, *D. S. Secher*, and soon after with *R. G. H. Cotton*, we decided to embark on an analysis of the rate and nature of somatic mutation of myeloma cells in culture. We were hoping that we might reveal a high rate of mutation of the hypervariable segments. (The protocol is described in Figure 2.) A continuous culture was grown for a minimum of three months to allow mutants to accumulate, and individual cells were taken and grown as colonies. These were incubated with labeled amino acids and the radioactive immunoglobulin analyzed to detect mutants with altered electrophoretic properties. Our first structural mutant appeared after a few thousand clones,[22] and the final analysis of 7000 individual clones gave us a pool of mutants which are described in Table I. We were relieved that this elaborate experiment provided the first evidence at the protein and nucleic acid

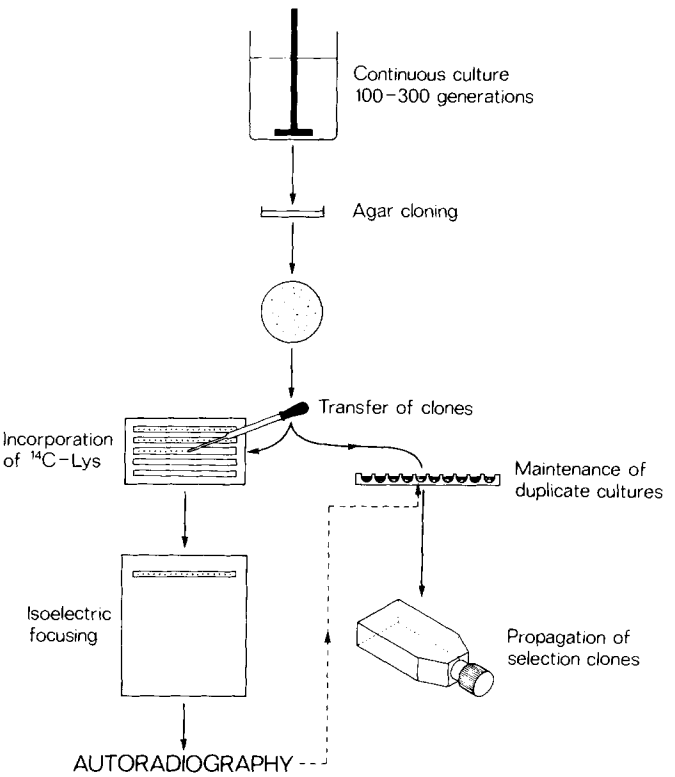


Fig. 2. Protocol used for the screening of the isoelectric focusing pattern of the immunoglobulin secreted by 7000 clones of P3 myeloma cells. Mutants were detected and their primary defect analyzed by amino acid and mRNA sequence analysis. The results are described in Table 1 (taken from ref. [23]).

Table 1. Spontaneous structural mutants of MOPC 21 heavy chains.

Mutant	Protein defect	Genetic defect
IF1	Last 82 residues of CH3 missing; carbohydrate difference	Ser(387)→Ter [a] small deletion?
IF2	Whole CH1 deleted	5.5 K bases deleted including CH1 exon. Aberrant switch?
IF3	Altered sequence of residues 367-380. Deletion of rest of CH3	Frameshift (−2). Premature "ochre" termination
IF4	Asparagine 452 to aspartic acid	A to G transition ("missense")
NSI1/1	Deletion of last 67 residues	Trp (406)→Ter G to A transition ("nonsense")

[a] Ter = termination.

levels of the existence of somatic mutations of mammalian cells.[23] Furthermore, the rate at which these mutations occurred suggested an important role in the generation of diversity.[24] But the mutations were not in the variable region, and we were forced to conclude that in the cells we were studying, there was no evidence for a hypermutable segment. So that in a sense we were back to square one.

Hybrid Myelomas

While this work was going on, *Cotton* was preparing another type of experiment which turned out to be more important than we anticipated.[25] This involved the fusion of two myeloma cells in culture (Fig. 3). That fusion demonstrated that the phenomenon of allelic exclusion was not dominant. On the contrary, fusion of two myeloma cells gave rise to a hybrid co-dominantly expressing the antibody chains of both parents. In addition, we proved that the expression of V- and C-regions was *cis*, probably because the V- and C-segments were already integrated at the DNA level by a translocation event in the precursors of plasma cells. This was in contrast to the assembly of heavy and light chains, which combined with each other to give rise to hybrid molecules.

Armed with these results, I went to Basel to give a seminar, and the important consequence was that *Georges Köhler* came to Cambridge. He joined in our main research project of looking at somatic mutants in immunoglobulin-producing cells, and in the other minor project concerning the phenotypic expression of somatic cell hybrids prepared between myelomas and myeloma mutants. It became increasingly clear that we could not go on looking for mutants by the procedure we had employed before, and the only way ahead was to use a culture of a myeloma cell line capable of expressing an antibody. Mutants from that cell could then be made based on the antibody activity. Although at that time there had been reports in the literature of myeloma cells capable of fulfilling that role, none proved suitable in our hands. The myeloma cell line P3 (MOPC 21) would have been ideal from a chemical point of view, because at the time the sequencing of the protein was a major undertaking and we knew how to deal with MOPC 21. But we were unable to find a suitable antigenic binding activity to this myeloma protein. We failed, but others who were pursuing similar types of experiments succeeded. *Scharff* and his co-workers were the first to demonstrate that one can isolate somatic mutants of a variable region in that way.[26]

And yet in a funny way our lack of success led to our breakthrough; because, since we could not get a cell line off the shelf doing what we wanted, we were forced to construct it. And the little experiment being done in the background concerning hybridization between myeloma cells developed into a method for the production of hybridomas. Thus, as illustrated in Figure 4, instead of hybridizing

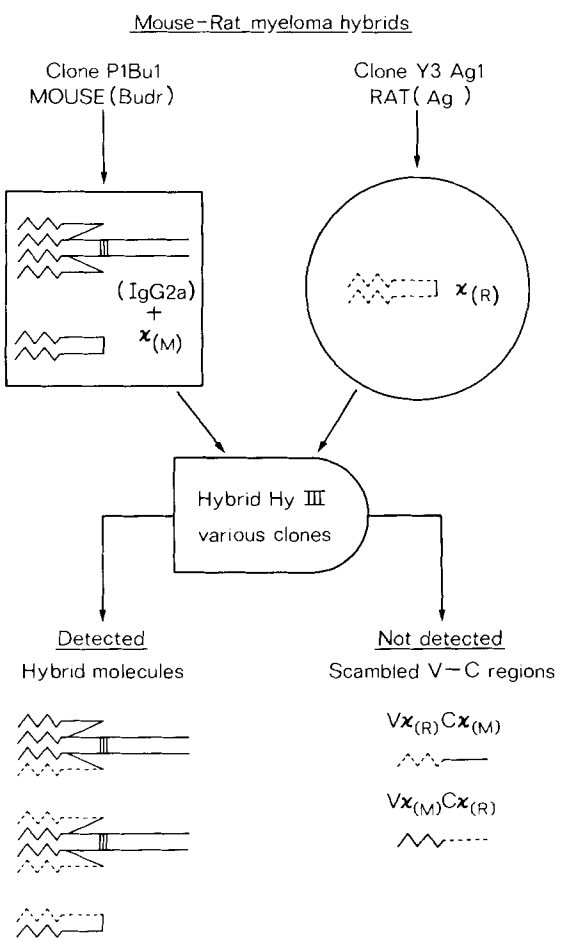


Fig. 3. Co-dominant *cis* expression of antibody genes in hybrids of myeloma cells. The diagram describes data taken from ref. [25].

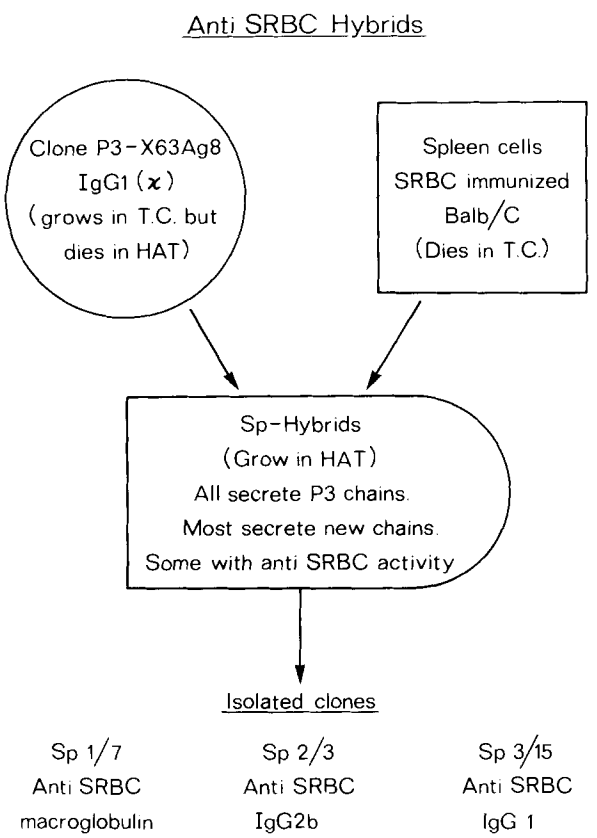


Fig. 4. The first successful hybridoma was prepared from cells from a mouse immunized with sheep red blood cells (SRBC) [56]. These were fused to a myeloma cell line producing the IgG protein MOPC 21 (see Fig. 1) growing in tissue culture and made resistant to azaguanine. Hybrids were selected by growth in HAT medium [57].

two myelomas, we hybridized a myeloma and an antibody producing cell. The resultant hybrid was an immortal cell capable of expressing the antibody activity of the parental antibody-producing cell, the immortality being acquired from the myeloma.

So finally, we were able to obtain a continuously growing cell line expressing a specific antibody and use it to search for mutants of the hypervariable region. This was undertaken by my research student, *Deborah Wilde*. While she got more and more discouraged by her lack of success in what she called "looking for a needle in a haystack," it dawned on me that it was up to us to demonstrate that the exploitation of our newly acquired ability to produce monoclonal antibodies "a la carte" was of more importance than our original purpose. After our early success we ran into technical difficulties and could not get our fusion experiments to work for quite some time. Then *Giovanni Galfré*, who had recently joined us, got us out of the deadlock when he discovered that one of our stock solutions had become contaminated with a toxic substance. After this an improved reliable protocol was developed (Fig. 5) and

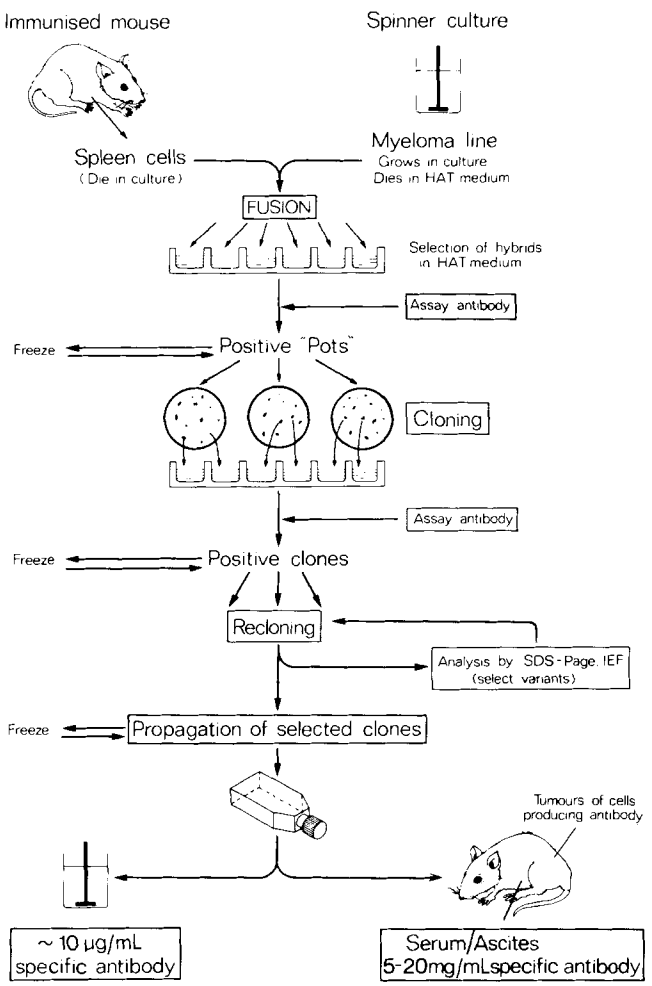


Fig. 5. Most generally used protocol for the derivation of hybridomas (taken from ref. [58]).

quick progress made towards the first practical applications of the technology. For several years I shelved the antibody diversity problem to demonstrate the practical importance of monoclonal antibodies in other areas of basic research and in clinical diagnosis (Table 2). We were able to show that the hybrid myelomas were capable of being used for the production of standard reagents such as anti-histocompatibility antigens[27] and anti Ig-allotypes.[28] The procedure was ideally suited to the study of cell surface and tumor antigens and to providing reagents for cell fractionation.[29-31] Monoclonal antibodies produced in this way were suitable for radioimmunoassays and for neuropharmacology,[32] as blood group reagents,[33] and for large-scale purification of natural products.[34] We also extended the hybrid myeloma technology to a second species—the rat[35]—and to the production of bi-specific immunoglobulins (hybrid-hybridomas).[36]

Table 2. Selected list of monoclonal antibodies derived in our laboratory.

Hybridoma	Antigen	Purpose and use	Selected references
R3/13 R2/10P R2/10S	Rat MHC	Reagents for tissue typing Synergistic effects	*Galfré* et al. (1977) [27] *Howard* et al. (1979) [60]
W3/13 W3/25	Rat T-cell markers	Analysis of cell surface antigens	*Williams* et al. (1977) [29]
H6/31	Mouse IgD allotype	Standard allotype reagent	*Pearson* et al. (1977) [61]
W6/32 W6/1 W6/34 and others	HLA-A, B, C Blood group A Controlled by chromosome 11	Tools for genetic analysis and biochemical studies	*Barnstable* et al. (1978) [62]
M1/69, M1/70	Mac-1 and other mouse leukocyte surface antigens	Novel mouse leukocyte differentiation antigens	*Springer* et al. (1978, 1979) [63, 64]
M1/22	Forssman	Embryonic development	*Stern* et al. (1978) [30]
H9/25	Alloantigen on killer and plaque-forming cells		*Takei* et al. (1980) [65]
NA1/34	Subpopulation of human thymocytes (CD1)	Define subpopulations of human lymphoid cells	*McMichael* et al. (1979) [66]
NC1/34	Substance P	Radioimmunoassay. Immunocytochemical localization of neurotransmitters. Internally labeled antibodies.	*Cuello* et al. (1979) [32, 67]
YC5/45	Serotonin	Dual localization at the EM level	
6D4 NB1/19	Blood group A Blood group B	Standard blood group reagents	*Voak* et al. (1980) [33, 68]
NK2	Human anti-interferon	Large scale protein purification	*Secher* and *Burke* (1980) [34]

Genetic Origin of Antibody Diversity

In the period 1970-1975, a considerable effort was being made to measure the number of germ-line genes coding for the variable regions of immunoglobulin chains. Our own

contributions started when we persuaded *Terry Rabbitts* to join us. After considerable effort and a lot more radioactivity we obtained results indicating that the number of germ line genes was not much higher than would be predicted from our understanding of subgroups, and this view was shared and reinforced by parallel work being conducted by others.[37,38] By 1976 this view was gaining general support.[39] But then the impact of the recombinant DNA revolution began to be very strongly felt. Within a few years, and largely through the work of *Tonegawa, Leder, Rabbitts, Hood, Baltimore,* and others, a coherent picture of the arrangement and rearrangement of immunoglobulin genes and their involvement in the generation of diversity began to emerge.[40] The precursors of the antibody-producing cells do not express an immunoglobulin, but during their differentiation into pre-B cells and B cells, they express first the heavy chain and then the light chain (Fig. 6). The first antibody produced is membrane bound and this functions as the receptor molecule, which receives antigenic signals. Triggered cells divide and differentiate to antibody-producing cells and memory cells.

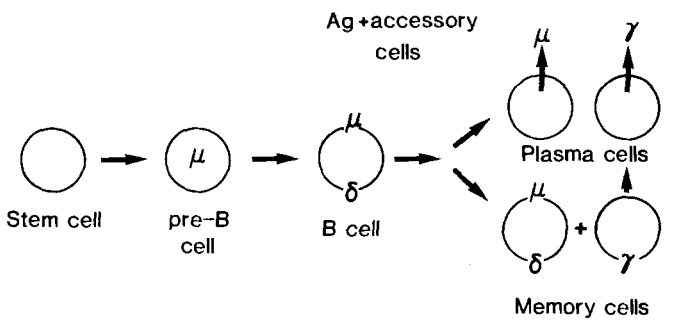


Fig. 6. Differentiation of B cells.

These events at the cellular level are correlated with changes in the DNA structure (Fig. 7). The germ-line DNA contains the V- and C-genes on different DNA fragments, as predicted. But in addition, there are further fragmentations, and only some of them are shown in Figure 7. Light and heavy chains can only be transcribed and translated when certain fragments (any one of the V and J in light chains; V, D, and J in heavy chains) are integrated by a deletion mechanism. During this process of integration, enormous diversity is generated.

To theorize about the genetic origin of antibody diversity was a "must" among molecular immunologists for quite a number of years. How do those theories contrast with the reality of today? The hard experimental facts made possible by the methodological advances in molecular biology show that, while none of them was right, most of them contained at least a grain of truth. There were two major currents of opinion. One consisted of germ-line theories whereby all the diversity was inherited as genes present in the germ line. The other included somatic diversification theories, whereby somatic processes were responsible for the generation of diversity, starting from a small number of germ-line genes. As it turns out, the genetic mechanisms responsible for the generation of diversity include a little bit of everything (Table 3). There are between

Table 3. Mechanisms that generate antibody diversity.

1. Germ line: multiple V-gene segments
2. Combinatorial: a) Different combinations of V-(D)-J
   b) Different combinations of V_H and V_L
3. Junctional: variation at V-J, V-D, and D-J boundaries
4. Somatic point mutation: nucleotide substitutions throughout the V region

50 and 300 gene fragments in the germ line encoding the light or the heavy chains. The number varies from species to species. So there is a considerable germ-line contribution. Recombination and gene conversion are probably important genetic events in the evolution and maintenance of that germ-line gene pool. We still do not know whether these events are significant as somatic generators of diver-

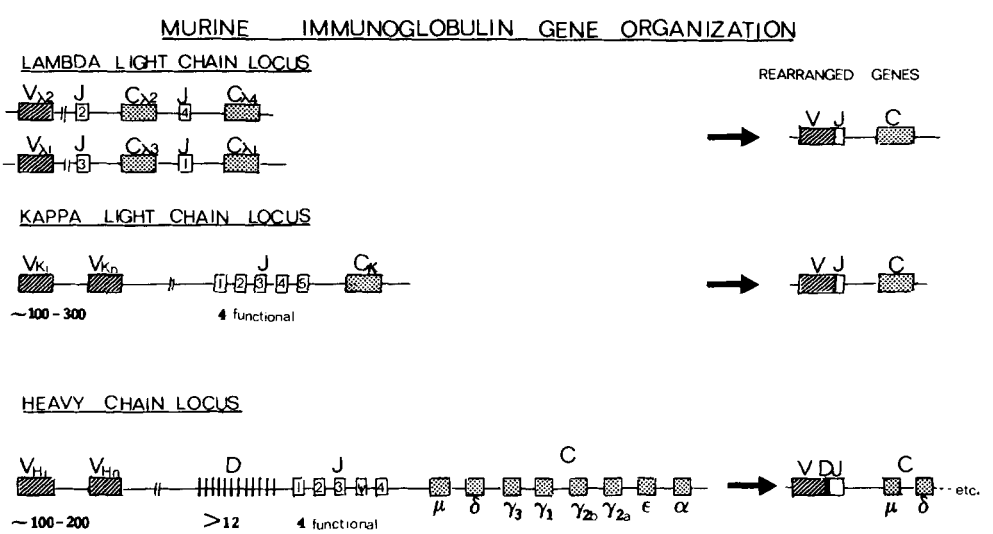


Fig. 7. Genetic arrangement of immunoglobulin genes in the germ line. During differentiation into pre-B cells and B cells large deletions of DNA lead to the integration of fragments (rearranged genes). Further proliferation leads to somatic mutation of the integrated gene and this is of major importance in the maturation of the response.

sity.[41] As shown in Figure 7, the V-region is encoded by V, D, and J segments (heavy chain) and V and J segments (light chain). Their combinatorial integration into a single gene, although an important component of the generation of diversity, is not the critical mechanism predicted by the mini gene hypothesis.[42] Also important is the diversity generated during the joining process, and this contains an element of the errors and aberrations during repair predicted by other theories.[43] And then there are the somatic point mutations for which a mechanism remains to be elucidated. It may involve error-prone repair enzymes,[7] genetic hot-spots,[24] appropriate selection either by antigen[44] or by other network elements,[45] or quite possibly by a mixture of all or some of these. The instructional theories were largely forgotten as soon as the chemical diversity of antibodies was established.[46] Yet they also may contain a grain of truth. It has recently been proposed that peptide segments of the antigen which appear to be mobile are better immunogens, presumably because they adapt their structure to a predefined antibody structure.[47,48] It is also possible that to some extent the antibody combining site itself has a certain degree of mobility, which has a limited capacity to accommodate its own structure to that of the antigen. Of course dynamic adaptation has a price to pay in terms of affinity. Adaptability should not be confused with the generation of specificity. As I discuss below, an improved fit of binding to the ligand is the result of somatic mutation and antigenic selection.

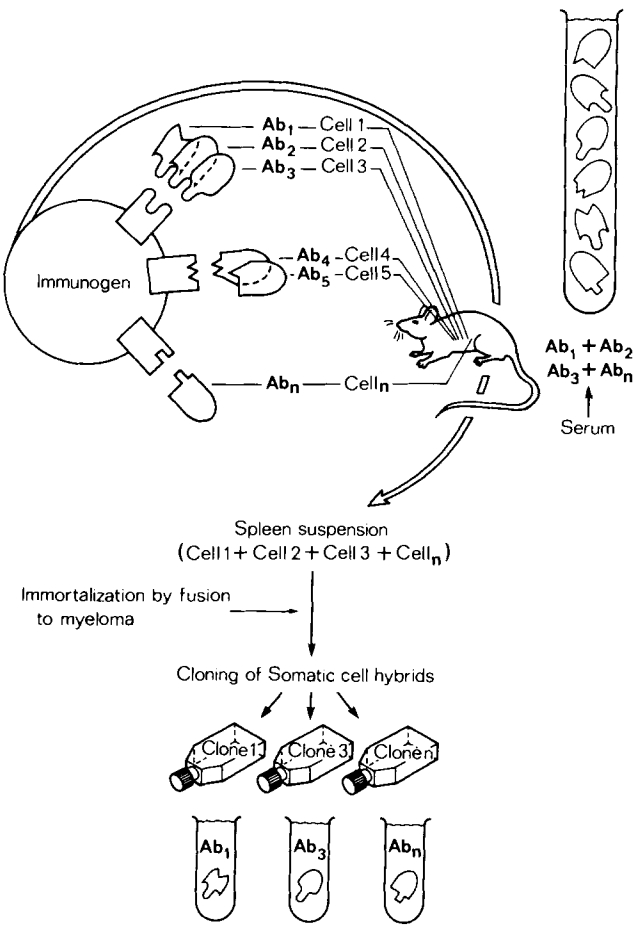


Fig. 8. The dissection of the immune response by the hybridoma technique. When an animal is injected with an immunogen the animal responds by producing an enormous diversity of antibody structures directed against different antigens, different determinants of a single antigen, and even different antibody structures directed against the same determinant. Once these are produced they are released into the circulation and it is next to impossible to separate all the individual components present in the serum. But each antibody is made by individual cells. The immortalization of specific antibody-producing cells by somatic cell fusion followed by cloning of the appropriate hybrid derivative allows permanent production of each of the antibodies in separate culture vessels. The cells can be injected into animals to develop myeloma-like tumors. The serum of the tumor-bearing animals contains large amounts of monoclonal antibody.

Molecular Analysis of an Immune Response Using Monoclonal Antibodies and mRNA Sequencing

Let us return to an animal that is being immunized with a certain substance. The immune system recognizes the substance as foreign, and the B cells are triggered to produce antibody (Fig. 8). The different antibodies are secreted and mixed in the serum. The individual antibody molecules are extremely similar and once mixed cannot be separated from each other. For this reason, and until the advent of the hybridoma technology, it was impossible to study the diversity of the antibody response to a given immunogen. The derivation of immortal cell hybrids solved this problem, because it affords individual antibodies separately produced, on culture vessels and as mouse myelomas. This permits dissection of the individual components of the antigen. Monoclonal antibodies prepared against hitherto undefined cellular components can themselves be used to identify the chemical nature of those components, to probe for their function, and later for use as reagents for diagnostic and therapeutic purposes. These are the fundamental properties behind the most important of the general applications of monoclonal antibodies. When we started to explore these applications, and until some years ago, it was possible to some extent to summarize the main results obtained.[49] In recent years their application to basic research, clinical biochemistry, medical therapy, and in industry has been so widespread that I do not intend even to attempt to discuss it any further here.

Different antibodies recognize different antigenic determinants of the immunogen, and the recognition of each determinant is complex in itself (Fig. 8). It has been known for a long time that even the simplest antigenic determinants are recognized by an unknown variety of antibody molecules. Monoclonal antibodies can be made pure and used to answer the old questions of how complex the collection of antibody molecules produced by the animal as a response to a particular antigen is, and how the individual molecules differ from each other. This brings me back to sequencing messenger RNA.

While in the late '70s the excitement about monoclonal antibodies and DNA recombinant methods was simmering, *Pamela Hamlyn* was quietly adapting *Sanger*'s fast DNA sequencing methods to the sequencing of light chain mRNA. Her eventual success[21] added to our capacity to derive cell lines secreting monoclonal antibodies to a predefined antigen, and to our ability to sequence quickly the

messenger RNA of the antibody molecule they produce. So, instead of asking the question "What is the nature of antibody diversity?", we were now in a position to ask the question "How do antibodies diversify during an immune response?" In other words, how, in real life in the animal, do all those genetic events capable of producing antibody diversity actually operate in response to an antigenic stimulus?

In collaboration with *Matti Kaartinen, Gillian Griffiths,* and *Claudia Berek,* we have been conducting a study of the response to the hapten phenyl oxazolone.[50,51] The essence of the experiment is described in Figure 9. The

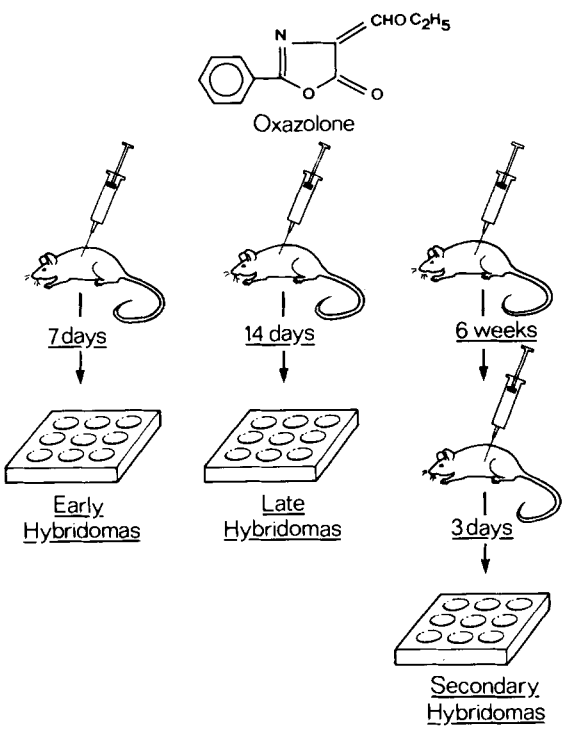


Fig. 9. Derivation of monoclonal antibodies at the onset and during the maturation of the response to oxazolone.

hapten conjugated to chicken serum albumin as carrier is injected into mice, and 7 days and 14 days later animals are sacrified, hybridomas are prepared, and a number of random clones isolated in each case. Other animals are left for a couple of months, and hybridomas of the secondary response are prepared.

Hybridomas prepared 7 days and 14 days after primary immunization are compared in Figure 10. Each point on the figure represents the avidity of each one of 32 monoclonal antibodies. The mixture of antibodies at each stage, as a first approximation, represents a cross section of the complexity of a typical antiserum. The average titers of the antibodies at both stages are not very different, although the day-14 average is slightly higher. This is as expected. The antibody titer of an antiserum, as well as its average avidity, increases during the course of an immunization. It is what we refer to as the maturation of the response. What distinguishes the results of the day 7 and day 14 is that while the day 7 results cluster around the average, the scatter at day 14 is much wider.

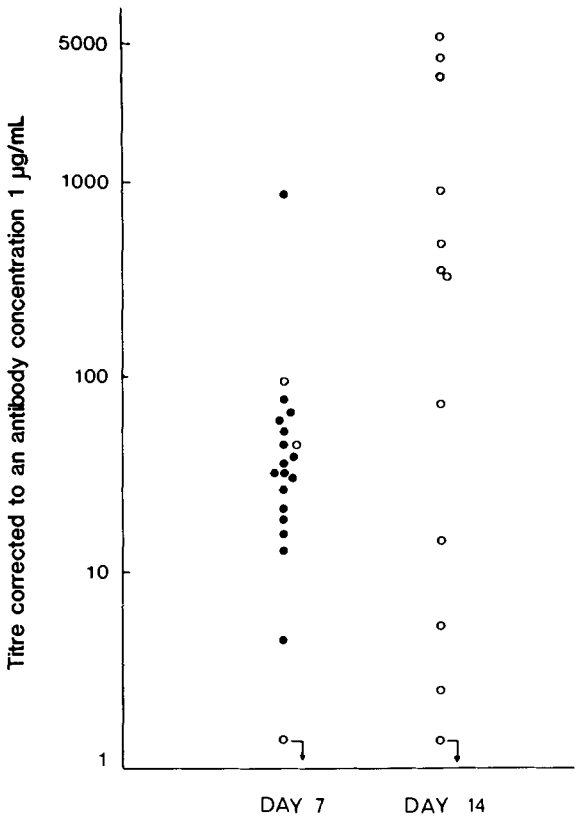


Fig. 10. Avidity of monoclonal antibodies 7 and 14 days after immunization. Haptenated phage inhibition (HPI) per µg of anti-phOx immunoglobulin from supernatants of IgG-secreting hybridomas. Those on the left were from day 7 and those on the right from day 14 fusions. Black circles represent oxazolone idiotype-positive IgG and open circles represent idiotype-negative IgG (taken from ref. [50]).

Since each monoclonal antibody was the product of an immortal hybridoma, we could go one step further and study the total amino acid sequence of each one of these monoclonal antibodies. Better still, we could study the sequence of the mRNA coding for each amino acid sequence. This not only provided more information, but was also technically simpler. To do so, RNA was prepared from the hybridoma cells and direct sequencing done on the impure messenger preparations, as shown in Figure 11. In this way, sequences of antibodies at different stages of the immune response could be compared.

What we have learned from this is that the majority of anti-oxazolone antibodies at day 7 express a single set of germ-line V-genes taken from the total pool of over 100 for each of the two chains (Fig. 12). This pair of term-line genes (which we refer to as V_H-Ox1 and V_k-Ox1) are at this stage expressed in their unmutated form. The few differences between them arise by junctional diversity—that is, the variations introduced during integration of the DNA fragments V, D, and J which make up the variable region of the antibodies. At day 14 the same germ-line genes V_H-Ox1 and V_k-Ox1 still seem to dominate the response. However, in sharp contrast to day 7, the day-14 antibodies express a small number of point mutations which are responsible for a significant increase in affinity for the same hapten. In other words, as the response matures, new somatic mutants appear in a seemingly endless variety.

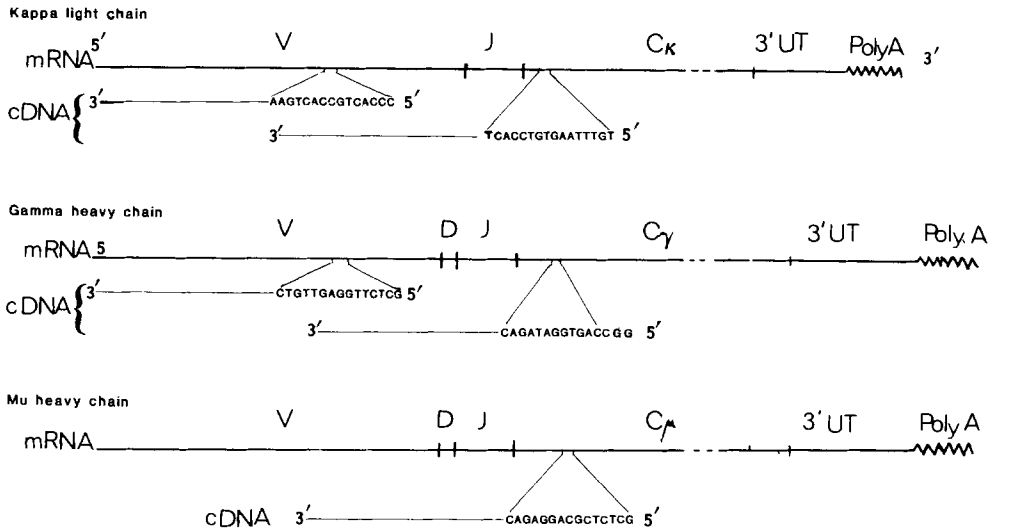


Fig. 11. mRNA sequencing strategy. Synthetic oligonucleotide primers designed to pair with defined bases within segments of mRNAs were used to initiate reverse transcription. Using dideoxynucleotides, specific stops in the cDNA can be generated and the nucleotide sequence determined by gel methods (taken from ref. [59]).

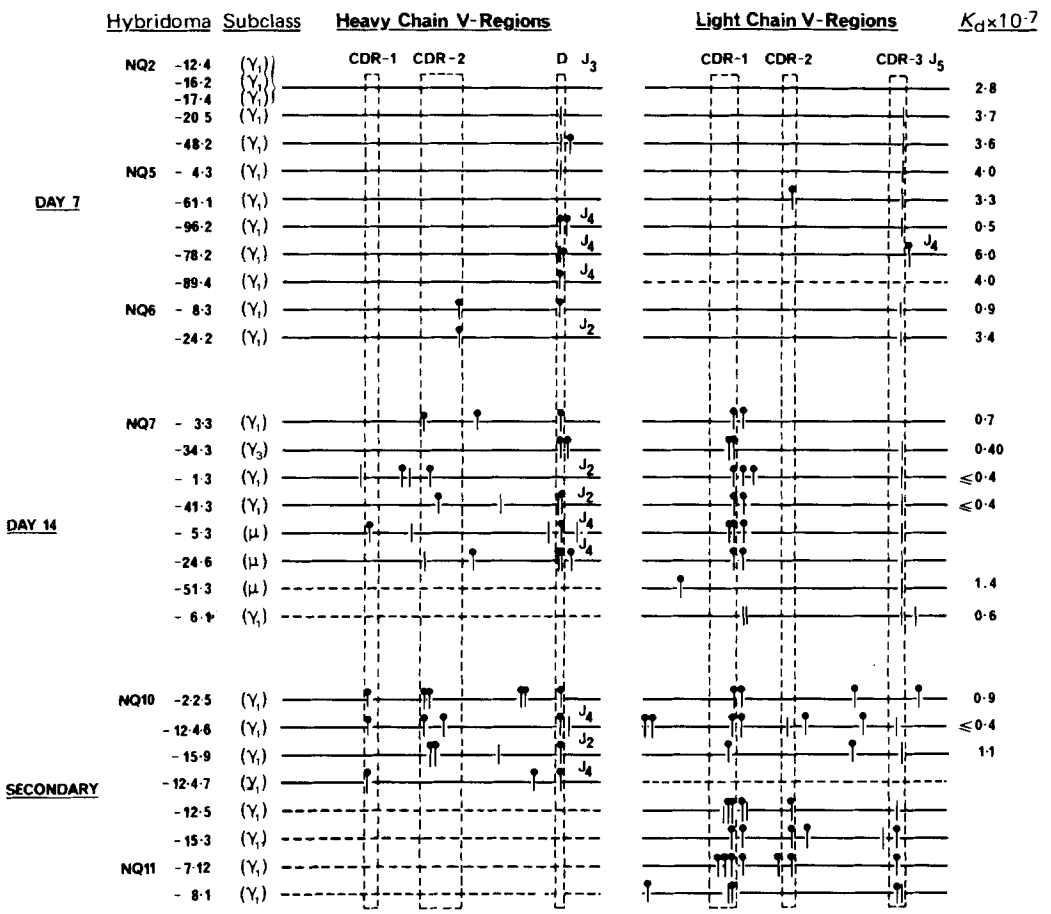


Fig. 12. Diagrammatic comparison of the mRNA sequences from anti-phOx-secreting hybridomas derived at different stages after immunization with Ox-CSA. Only sequences closely related to the prototype are shown. The variable region sequences of each hybridoma have been compared with the sequences of V_H-Oxl and V_k-Oxl, respectively. Unbroken horizontal lines denote identical sequences, broken lines represent extensive sequence differences. A black circle indicates that these changes predict an amino acid difference at this position. Complementary determining regions (CDR-1, -2, -3) have been marked as have the D and J regions. Where different J segments are observed these are represented accordingly. Dissociation constants determined hy fluorescence quenching (K_d) are shown on the right (taken from ref. [51]).

The antibodies obtained during the secondary response, expressing the germ-line gene combination characteristic of the primary response, show a further small increase in point mutations (Fig. 12). However, the most important feature of the secondary response is a shift towards other germ-line genes (see Table 4).

It appears therefore that the development and maturation of the immune response to oxazolone—which we take

Table 4. Expression of germ-line V-genes in the maturation of the response to oxazolone.

	V_HOxl-V_kOxl combination	Other combinations	V_HOxl-V_kOxl [%]
Day 7	11	4	73
Day 14	6	5	54
Secondary	4	18	18

as a model system—proceeds basically in three stages. In the first, the majority of the antibody reflects a very restricted choice from a vast repertoire of germ-line gene combinations, self-selected for their capacity to bind the antigen. In the second stage, cells expressing these combinations proliferate, and during this proliferation mutants arise which improve the affinity of the antibody for the antigen. In the third stage, as the first type of germ-line gene combinations and their mutants reach a certain limit of dissociation constants, new germ-line gene combinations and somatic mutants are selected for further improvements. Of course, the three stages are not absolutely separate and all three processes overlap to a certain extent. In many ways, the system behaves as a Darwinian system, where adaptation is an improvement in antigen binding. It remains to be seen to what extent other regulatory constraints are critical to the process.

From Monoclonal Antibodies to Antibody Engineering

The immortalization of antibody-producing cells not only allows the permanent supply of an antibody of a constant chemical structure but, more important, affords all the advantages that can be derived from the techniques of cell culture and somatic cell genetics. The most obvious is cell cloning, and this has been at the root of the explosion in the use of this technology. And yet the derivation of cell lines producing specific antibodies cannot go beyond the immortalization of what already exists. We select hybrids producing monoclonal antibodies of desired properties, but if the immunized animal does not make it, there is no way of immortalizing it. Fortunately we can go further.

Hybridomas are established cell lines and are therefore capable of other "in vitro" manipulations using somatic cell genetic and molecular engineering techniques. We are at the beginning of a new era of immunochemistry, namely, the production of "antibody based" molecules. The derivation of hybrid hybridomas is one example of the utilization of such methods for the biosynthesis of bi-specific antibodies.[36] Another example is the derivation of class switch mutant antibodies.[52]

Some years ago I discussed the eventual use of recombinant DNA techniques to make more drastic changes.[53] Recent developments have shown the feasibility and potential of the approach. Antibody genes have been put into suitable vectors, propagated, modified, and re-introduced into myeloma cells which will then secrete recombinant antibodies possessing novel properties. For instance, in my laboratory *Neuberger* has developed a cell line which secretes a mouse-human antibody molecule with a mouse anti-nitrophenacyl variable region and a human epsilon heavy chain constant region.[54] In another example, the Fc portion of the mouse antibody was replaced by staphylococcal nuclease.[55] A novel antibody was thus made which contains an antigen-specific Fab portion joined to an enzymatic effector function replacing the normal Fc portion.

More elaborate modifications will be made possible by the fast-developing techniques of site-directed mutagenesis. These will allow well-planned specific modifications of antibody combining sites. In this way we will be able to test the contribution of individual point mutations to the generation of high-affinity antibody during the process of the maturation of the response. This brings us back to the problems of the diversity of molecular recognition and the maturation of the immune response.

Exciting as these prospects are, they still require the basic starting genes taken from a hybridoma line. With them, we can introduce changes at the amino acid sequence level but with the exception of simple changes, the ultimate folding pattern and their effect on protein-ligand interaction cannot yet be reliably predicted. This will remain so for the time being. Total construction of antibody molecules to suit specific needs depends on a much better understanding of protein folding.

While selection is the strategy of the antibody response of an animal, the immunochemistry of the future will revert to an instructional approach where the antigen will tell us what antibody structure we should construct. Although this is not science fiction, we need to overcome the theoretical problems involved in the translation of one-dimensional reality into a valid three-dimensional prediction. Although the way ahead is full of pitfalls and difficulties, this is indeed an exhilarating prospect. There is no danger of a shortage of forthcoming excitement in the subject. Yet, as always, the highlights of tomorrow are the unpredictabilities of today.

The hybridoma technology was a by-product of basic research. Its success in practical applications is to a large extent the result of unexpected and unpredictable properties of the method. It thus represents another clear-cut example of the enormous practical impact of an investment in research which might not have been considered commercially worthwhile, or of immediate medical relevance. It resulted from esoteric speculations, for curiosity's sake, only motivated by a desire to understand nature. It is to the credit of the Medical Research Council in Britain to have fully appreciated the importance of basic research to advances in medicine. We are delighted to belong to the small, lucky group of those who are at the window-dressing end of the justification for the wisdom of that policy.

I learned what research was all about as a research student of Stoppani in Argentina, and then with Sanger in the Department of Biochemistry at Cambridge. I owe an enormous debt to the atmosphere of the Laboratory of Molecular Biology, where all the work I have described here was done, mostly under the Chairmanship of Max Perutz, and within the Division of Protein and Nucleic Acid Chemistry, of which Fred Sanger was the Head. From them, I always received an unspoken message which in my imagination I translated as "Do good experiments, and don't worry about the rest."

During my lecture I have tried to acknowledge those of my collaborators whose contributions were critical at specific stages of the work. In addition, so far unmentioned, is John Jarvis, my personal assistant for well over 20 years—only months less than my involvement with immunology. Since this prize mentions the discovery of the principles of the hybridoma technology, I would like to acknowledge specifically the importance of the contributions of Dick Cotton and David Secher, with whom preliminary work leading to that discovery was made, and my tissue culture assistant, Shirley Howe, who was directly involved not only in the preliminary work but also in some of the specific experiments conducted with Georges Kohler. I would also like to acknowledge other

collaborators who were concerned in our own contributions to the demonstration of the practical potential of the hybridoma technology in a variety of fields, particularly G. Galfré, A. R. Williams, and A. C. Cuello, and the technical assistance of Mr. B. W. Wright. The list of acknowledgements is certainly much longer, but I wouldn't like to end it without recording my indebtedness to my secretaries, Margaret Dowding and Judith Firth. Their handling of the press in the immediate period after the announcement of this prize ranks high among my memories of that exciting moment.

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Derivation and Diversification of Monoclonal Antibodies (Nobel Lecture)**

By Georges Köhler*

A mouse can make ten million different antibodies, each synthesized by its own B-lymphocyte. About 1000 different antibodies are able to recognize one single antigenic determinant. When a conventional mouse response to such a determinant is analyzed, only 5–10 different antibody species are seen, representing probably a random sample of the total repertoire. So even when appropriate absorptions or allogenic immunizations have confined the antibody heterogeneity to one single determinant, the sera obtained have four disadvantages: (1) the titers are low, (2) the antibodies, while specific for a single determinant, are nevertheless heterogeneous, (3) the supply is limited, and (4) the same combination of specific antibodies is impossible to reproduce in a new animal.

The method of lymphocyte fusion developed together with *C. Milstein,* MRC, Cambridge (England), provides a tool to overcome these limitations (Fig. 1). Mouse myeloma tumor cells are fused to spleen cells derived from a mouse which previously had been immunized with antigen. About 50% of the hybrid cells combine the hoped for parental traits: vigorous growth in tissue culture derived from the myeloma tumor cell and antibody production coming from the splenic B cell. A relatively high proportion of the hybridoma cells secrete antibody specific to the immunizing antigen.[1,2]

The advantages of this technique are:

1) Single specificity. Each hybrid produces only one antibody.
2) Unlimited supply of antibody. The hybrids are immortal like tumor cells, can be frozen, secrete 10–50 μg/mL antibody into the culture fluid, and upon injection into mice produce titers as high as 1–10 mg antibody per mL body fluid.
3) Impure antigens lead to pure antibody reagents. The monoclonal antibody by definition characterizes only one antigen of the many injected into the mouse.
4) All specificities can be rescued. The empirical observation seems to be that if an immune response can be elicited in the mouse also specific hybridomas can be derived.
5) Enrichment of specific hybridomas. Specific B cells are rare even in the spleen cell population of an immunized mouse. They are found to be enriched 10–100 fold in the corresponding hybridoma population.
6) Dominance of antibody secretion. B-hybridomas secrete a high level of antibodies, irrespective of whether or not the normal B cell was a high producer.
7) Antibodies become manipulable. The hybridoma cell lines can be mutated to produce antibodies not found in nature.
8) It is a general method. The only generalization so far was to apply cell fusion for the rescue of T-cell functions, where T-hybridoma lines secreting different lymphokines and exerting killer function or helper and suppressor activities have been generated.

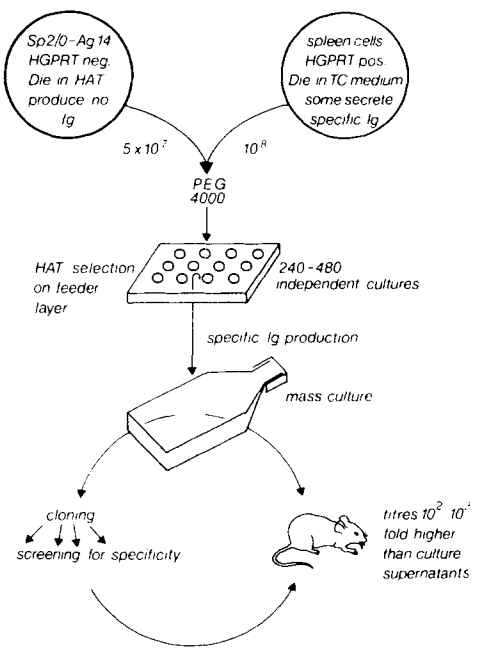


Fig. 1. The hybridoma technique. The fusion line Sp2/0-Ag14 comes itself from a hybridoma line and is devoid of endogenous immunoglobulin production [61]. HGPRT = hypoxanthine-guanine phosphoribosyltransferase, an enzyme necessary in DNA synthesis, when the normal pathway is blocked by aminopterin. HAT = hypoxanthine, aminopterin, thymidine [1, 62, 63]. PEG = polyethylene glycol.

Some selected applications are summarized in Table 1.

In the past, conventional sera have been used to define, purify, detect, quantify, map, modify, select, and localize antigen. Thus, with few exceptions,[18,19] the monoclonal antibodies have not led to applications unthought of previously. However, as pure chemicals of higher precision and unlimited supply, they are replacing the conventional sera and thereby contributing to a worldwide standardization of antibody-mediated reactions.

One of the great advantages of the hybridoma lines lies not only in the production of monoclonal antibodies but also in the availability of the machinery which produces

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them. One can diversify a single antibody molecule by selecting mutant molecules, by introducing new immunoglobulin heavy and light chains, and by cloning and mutating its genes by "reverse genetics" techniques and reintroducing them into cell lines or into the germ line of a mouse.

Table 1. Uses of monoclonal antibodies.

Use	Application	Success, example	Ref.
to *define* antigen	- on bacteria	classification	[3]
	viruses	becomes easier	[4]
	parasites		[5]
	- on cells	11 human T-cell antigens established	[6]
		histocompatibility antigen typing	[7]
		tumor antigens	[8, 11]
purify	- factors, hormones	5000-fold enrichment of interferon	[9]
	- cell membrane	200-fold enrichment of Ia antigen of rat	[10]
detect and *quantify*	- in crude mixtures	human chorionic-gonadotropin in pregnancy tests	[11]
map	- epitope characterization	7 determinants on mouse μ chain (constant region)	[12]
modify	- infectivity	sporozoite of *Plasmodium berghei*	[13]
	- toxicity	digoxin overdose	[14]
	- function	αLy2 suppresses T-cell killing	[15]
	- immunogenicity	α Rhesus factor	[16]
select	- α idiotype	enhancement and suppression of anti-NP immune response	[17]
	- mutations	histocompatibility antigen	[18]
		influenza A virus	[19]
localize	- in organs	nervous system of leech	[20]
	- in body	tumor imaging in humans	[21]

The variants give some insights into the structure-function relationships of immunoglobulin proteins, their RNA, and genes. The analysis of variants has also led to a more speculative hypothesis about the interaction of H and L chains in multigene families.

Diversification of Monoclonal Antibodies

Many investigators have generated variant forms of monoclonal antibodies (Table 2), with perhaps more interesting properties than the ones I will describe here. But this is a somewhat personal account of this development, and not meant to be a review. It is focused, where possible, on experiments using one hybridoma cell line, Sp6/HLGK. The line is derived from a Balb/c mouse immunized with trinitrophenyl-lipopolysaccharide (TNP-LPS). It secretes an immunoglobulin mu heavy chain associated with a kappa light chain of anti-TNP specificity (designated HL in Sp6 and equivalent hybridomas) together with a gamma and kappa chain derived from the fusion myeloma line X63-Ag8 (designated GK in Sp6 and equivalent hybridomas).[2]

Table 2. Mutations and alterations in cell lines producing monoclonal antibodies.

Selection	Mutation/alteration	Frequency	Ref.
loss of isotype	loss of H- or L-chain	$1/10^2$	[22]
	domain deletions	$1/10^3$	[23, 24]
	loss of λ-chain secretion due to point mutation	$>1/10^4$	[25, 26]
change in isoelectric focusing (IEF)	domain deletions frameshift, point mutation	$1/10^3$	[27]
cell sorter, positive selection for different isotype	change of isotype often associated with deletions	$\approx 1/10^5$-$1/10^7$	[28–30]
loss of idiotype, loss and gain of antigen binding	possible gene conversion point mutations	$1/10^2$-$1/10^3$	[31–33]
loss of lytic activity	deletions, frameshifts insertions	$1/10^3$-$1/10^4$	[34–36]
reverse genetics	chimaeric antibodies V_H-C_α		[37, 38]
	V_{mouse}-C_{human}		[39, 40]
	antibody-enzyme		[41]
secondary hybrids	monovalent antibodies		[41a]
	two specificities		[41b]
	complementation of specificity		[49]

Immunoglobulin Chain-Loss Variants Lead to the Heavy-Chain Toxicity Hypothesis

The first hybridomas all produced two immunoglobulins, the specific lymphocyte-derived one and the myeloma-derived one, and were therefore, like Sp6, of the HLGK-type. To obtain pure specific antibodies, sublines were selected which had lost the production of the nonspecific G and K chains of the myeloma fusion partner.[2,42] It was observed that heavy chains are more easily lost than light chains. The sequence of chain loss as exemplified with Sp6 was Sp6/HLGK→Sp6/HLK→Sp6/HL and not Sp6/HLGK→Sp6/HLG→Sp6/HL. This was reminiscent of results of *Coffino* and *Scharff*,[22,43] who, using the myeloma line MPC11, found that H-chain loss was observed at a rate of $1\text{-}2\times10^{-3}$ per cell and generation but L-chain loss was not observed even at a 100 times lower rate. After H-chain loss, however, L chains were lost at a rate similar to H chains.

To test the generality of the observation, a series of hybridoma lines were established making three, two, and one antibody and their chain-loss variants were monitored (Table 3[42]). L-chain loss was inhibited with increasing sever-

Table 3. H-Chain toxicity.

3H+3L	⟶	2H+3L / 3H+2L	≈ 2/1
2H+2L	⟶	1H+2L / 2H+1L	≈ 8/1
1H+1L	⟶	0H+1L / 1H+0L	≳ 100/1

2H+3L, 1H+2L, 0H+1L } L-loss as frequent as H-loss

ity only in those combinations resulting in an increasing excess of H-chain production. It is concluded that heavy chains not counterbalanced by enough light chains are toxic for the cells. Excess H-chain producers have a growth disadvantage and cannot be cloned out from the cell population. Additional support for the H-chain toxicity hypothesis came from the analysis of Sp6 variants. A subline (Sp6/HLk) was derived producing a variant K chain, which combined less efficiently with the H chain (this property is symbolized by the lower k in Sp6/HLk). The Sp6/HLk line lost L at a 1000 times lower frequency than the original Sp6/HLK line.[34,42] We concluded that the variant k could not substitute for the parental K chain to avoid toxic accumulation of free H chain. We have cloned the H- and L-chain genes of Sp6 and reintroduced them separately or physically linked into the Ig non-producing myeloma line X63Ag8.6.5.3 (Table 4). If production of free heavy chain is toxic for the cell, we would expect that μ-alone transformants are selected which produce lower amounts of μ when compared to (μ and κ) transformants. A 5- to 13-fold difference was observed between these two groups of transformants. On average, about 100 times less μ RNA or protein is found in the μ-alone transformants. This low amount is comparable to the amount of μ alone found in pre-B cells[44] and may no longer be toxic for the cells. In proteins consisting of two different subunits such as H and L in immunoglobulins, often one chain is produced in excess (L chains in Ig-producing cells). Potentially toxic effects of free light but not free heavy chains will therefore be selected against. In the multigene Ig-family with about 5000–10000 H and 250 L chains, elimination of cells producing H-L pairs with too low affinities to form antibody molecules may be an important control mechanism.

Table 4. Expression of cloned Sp6 μ and κ genes in X63Ag8.6.5.3 B-myeloma cells [a].

Gene	DNA Copy Number	RNA (% of Sp6 parent)		Protein (% of Sp6 parent)	
		μ	κ	μ	κ
κ	50 (41)	—	62 (10)	—	50 (4)
μ	7 (8)	1.3 (9)	—	1 (9)	—
μ+κ	5 (11)	6 (8)	4 (8)	13 (12)	13 (12)
$\frac{\mu+\kappa}{\mu}$	≈1	5		13	

[a] Data from *J. McCubrey*, unpublished. In parenthesis: the number of stable transformants analyzed.

Somatic mutants of H and L chains dominate late immune responses.[45,46] It is conceivable that mutations occurring in the variable regions of low-affinity H and L pairs enhance their pairing affinity. Such cells avoid elimination caused by free H-chain toxicity and contribute to the somatic diversification of antibody molecules. Scaling up Ig production or switching Ig-classes may induce new rounds of selections (Fig. 2). Preferential association of original H-L pairs in competition experiments[47,48] are easily explained by this intracellular selection mechanism.

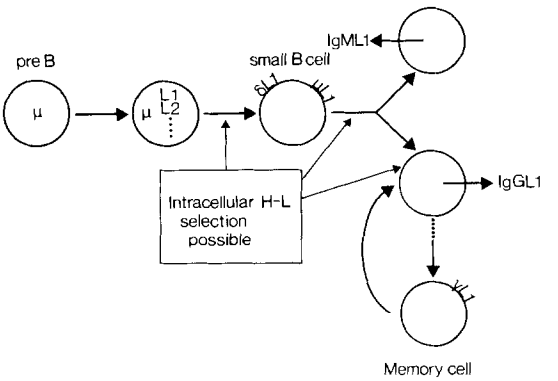


Fig. 2. Schematic representation of B-cell development. The points at which increased production of heavy chains or production of different heavy-chain isotypes might become toxic for the cells are indicated. Variable region mutations increasing heavy(H)- and light(L)-chain pairing affinities may avoid toxicity of free heavy chains and be enriched.

Arrays of Antibodies with One Specificity Generated by Secondary Fusions

The Sp6/HK and Sp6/LK lines (chain-loss derivatives of Sp6/HLGK) are no longer producing antibodies with anti-TNP specificity (a property confined to the HL combination). Both lines were fused to unimmunized mouse spleen cells stimulated for four days with the mitogen lipopolysaccharide. The resulting hybrids were screened for restoration of the original anti-TNP specificity.[49] In about every 100th hybridoma the anti-TNP activity of the Sp6/HK line was restored. In about every 2000th hybridoma the anti-TNP activity of the Sp6/LK line was restored, which was indistinguishable from values obtained with the line Sp2/0, which does not contribute any Ig chain. The generality of this observation was confirmed by using three other pairs of hybridomas of the HK- or L-type, with similar results. The HK-lines could easily be complemented, the L-lines gave "background" complementation. From these experiments the following conclusions were drawn:[49]

1) Around 40 light-chain variable-region genes contribute to the light-chain repertoire of the mouse.
2) Around 250 different light chains are found in unstimulated spleen cells, due to the combination of 40 V-region genes with 4 J (joining) segments and their early somatic diversification.
3) About 20–40 fold more heavy than light chains are expressed in early, unstimulated spleen lymphocytes.
4) A statistical analysis of the data leads to the generalization, that, could one screen through all heavy chains with a given light chain, one would find any given antibody specificity. Could one screen through all light chains with a given heavy chain, a given antibody specificity would only be found in every 20th case.

The above points have to be considered with caution, since they are based on limited numbers of hybridomas. Nevertheless, I think hybridomas have opened a new way to analyze the problem of antibody diversity, by analyzing H and L chains separately, thereby avoiding the enormous

heterogeneity created by the combination of heavy and light chains in antibody molecules. The Sp6 line has been diversified to 10 different sublines, each of which makes a different light chain, which together with the Sp6 heavy chain gives rise to the original anti-TNP specificity. Such lines will provide insights into the heavy- and light-chain variable-region interactions necessary to create a given antigenic combining site. A more practical aspect of such secondary arrays of antibodies with one specificity would be the isolation of low-affinity antibodies, which for certain antigen purification procedures may be advantageous.

Diversification by Mutant Selection

We have studied mutants of the Sp6 and PC 700 (IgM anti-phosphorylcholine (PC)) line. The selection method was simple. The hapten TNP or PC was covalently attached to the membranes of the cells. The cells were diluted and incubated in the presence of complement. Cells secreting wild type IgM preferentially bind their own antibody and are killed. Cells secreting less or less lytic IgM are enriched. Three to four selection rounds lead to an almost "pure" mutant-cell population. Table 5 summarizes

Table 5. Mutations affecting Sp6 immunoglobulin M.

Defect	Number	Description	Ref.
not determined, possibly point-mutations	2	10-fold lower affinity 200-fold reduced lytic activity	[34]
insertion	2	loss of L production or reduced L production	[36]
deletion	4	loss of Cμ1, Cμ2, Cμ3 [a]	[35]
frameshift	16	loss of *C*-terminal portions	[50]

[a] Found in the PC 700 system [52] only.

the mutants so far characterized for the Sp6 line. The deletion variants were used to map a panel of monoclonal antibodies.[12] Figure 3 shows the IgM structure of some of the deletion variants and the mapping of monoclonal antibodies to each of the five μ-domains. The monoclonal antibodies against eight-defined, non-cross-reacting determinants of mouse μ chains were used to define new IgM variants,[50] to map C1q binding to the area of binding of C2-23 monoclonal antibody (ref. [38], unpublished) and to define the quaternary structure of some of the IgM-mutants.[12]

Diversification by Reverse Genetics

The light-chain gene of Sp6 has been cloned and sequenced.[36] The Sp6 heavy-chain variable-region gene was placed into the V_κ-C_κ intron using the HindIII and XbaI restriction sites. After transfection into the X63Ag8.6.5.3 (X63/0) myeloma line,[51] a V_μ-C_κ chimaeric protein was revealed (Fig. 4). Fusing this line to Sp6/L (igm10) resulted in hybrids producing covalently linked dimers containing the V_κ-C_κ and the chimaeric V_μ-C_κ chain. Binding of the heavy-chain-dependent anti-idiotypic antibody 20-5

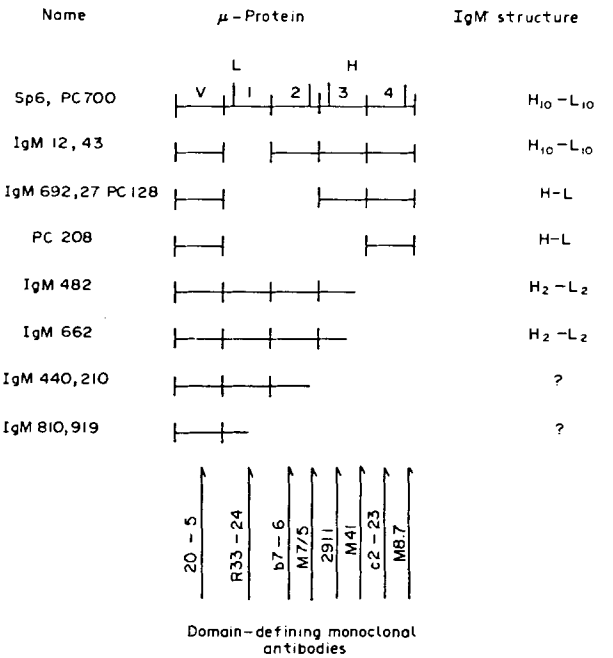


Fig. 3. Deletions in mouse μ chains. The wild-type μ-protein (Sp6 and PC700) is drawn in its domain structure and disulfide bridges to the light (L) or heavy (H) chains are indicated. The light chain of igm 12 and igm 43 is not covalently bound to μ, whereas it is in all other mutants with known IgM structure. The monoclonal rat anti-mouse μ-antibodies were selected from about 20 antibodies and define independent binding sites. The line 20-5 makes a mouse anti-idiotypic antibody reacting with Sp6 but not PC 700 IgM.

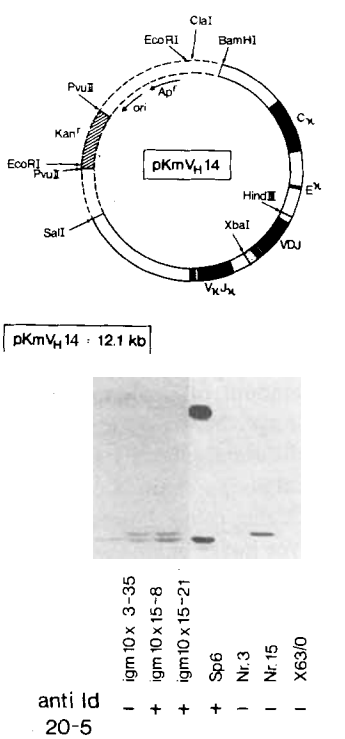


Fig. 4. Production of chimaeric antibodies. Top: The plasmid pK_mV_H14 carries the kanamycin-resistance gene (shaded), pBR322 sequences (dashed), and an insert of the Sp6 kappa gene from the BamHI to the SalI restriction sites. The Sp6 variable heavy-chain gene (VDJ) was inserted into the XbaI and the Hind3 restriction sites in front of the kappa enhancer element (E^κ). Bottom: SDS-gel electrophoreses under reducing conditions of products formed after transfection of pK_mV_H14 plasmid into X63/0 myeloma cells. Stably transformed lines No. 3 and No. 15 show a band with slightly slower mobility than the Sp6 light chain. Light-chain- and pK_mV_H14-directed production of V_HC_κ in (No. 15 × igm 10) hybrids 8 and 21 is observed. Only in these hybrids is the heavy-chain-dependent idiotype 20-5 restored.

was restored in these dimers. We could not measure antigen binding activity, because of the low anti-TNP affinity of the Sp6/IgM (10^{-4} M[34]). A similar chimaeric protein with antigen binding for arsonyl was however described.[37] Small, antigen-binding molecules lacking the heavy-chain constant-region determinants might be useful when only one binding site is required (to avoid modulation of cell surface antigens), and when a smaller molecule with fewer non-specific interactions (via Fc-receptors) and possibly a higher elimination rate is needed. Also such molecules might be less immunogenic. Since most therapeutically interesting antibodies are of mouse origin, the construction of chimaeric antibodies using human constant regions and mouse variable regions would be a solution, avoiding immunogenicity but keeping effector functions of the antibody. That this is possible has recently been shown with the Sp6 IgM.[39] The mouse heavy- and light-chain variable regions were placed in front of human μ- and κ-constant regions, respectively. Mouse-human chimaeric IgM was recovered from supernatants of a plasmid-carrying myeloma line. The IgM was pentameric and functional in terms of being able to lyse TNP-coupled sheep erythrocytes.

The Transgenic Mouse Model

So far three groups have introduced rearranged immunoglobulin genes into the germ line of the mouse. A μ and a κ gene alone as well as a combination of both genes derived from the Sp6 line have been used (Table 6).

Table 6. Immunoglobulin genes introduced into mouse germ line cells.

Gene (specificity)	Molecules injected	Zygotes implanted	Offspring (with transgene)	Number of copies per genome	Gene in germ line	Ref.
μ (NP)	50	284	13 (5)	17–140	3	[53]
κ_{21} (?)	440	197	11 (6)	20–200	6	[54–56]
μ, κ (TNP)	50	13	5 (1)	4	1	[57]

In the Sp6 case about 50 molecules of the heavy- and light-chain genes both cloned into a pBR322 plasmid vector ($pRHL_{TNP}$) were injected into fertilized eggs from Swiss albino mice. From 13 implanted zygotes, 5 offspring mice were obtained, one of them carrying the gene. Analysis of the germ-line transmission pattern indicated integration of 4 copies of the $pRHL_{TNP}$ plasmid into one autosomal chromosome.

Expression of Trans-Immunoglobulins

In all cases, along with germ-line transmission of the immunoglobulin genes, also expression of the respective chains was observed. Expression of κ_{21} chains was confined to the B-cell lineage excluding Abelson-virus-transformed pre-B cell lines.[65] Expression of μ_{NP} chains was observed in B- and in T-cells.[53] Other tissues, like kidney, brain, heart, lung and liver, did not transcribe the genes. By fluorescence analysis, the Sp6 μ_6 and κ_6 chains were expressed on the membrane of B- but not T-cells, although the μ_6 chain (κ_6 was not testable) was expressed in around one-quarter of Con-A-stimulated, splenic T cells. The Sp6 immunoglobulin was found as pentameric, functional IgM in the sera of the transgenic mice where it represented around one-fifth to one-third of the total IgM. It will be interesting to see whether such massive production of one specificity induces changes in idiotypic network interactions. Introducing antibodies with anti-self specificities into the germ line of the mouse may give some insight into how self-tolerance is achieved at the B-cell level. With the genes introduced so far, another immunological question, the one of allelic exclusion, was analyzed. How is it possible that B cells produce heavy and light chains from only one of the two homologous chromosomes, a prerequisite of effective clonal selection?

Influence of Transgenic μ and κ Chains on Allelic Exclusion

In order to create a functional heavy-chain gene, three spatially separated DNA segments, the variable region, the diversity, and the joining (V, D, J_H) segments have to juxtapose. To create a functional light-chain gene, a V_L and a J_L segment have to join. In roughly one-quarter of the B cells, allelic exclusion is achieved by having functionally rearranged VDJ_H^+ and VJ_L^+ units in one allele and non-functionally rearranged VDJ_H^- and VJ_L^- units in the other allele, which due to mistakes during the joining process are unable to produce the respective chains. In about 75% of the B cells, either the heavy- or the light-chain variable region or both have not been completely rearranged. In order to explain this finding a regulatory feedback mechanism of the immunoglobulin chains on the rearrangement process was postulated.[58]

To study the effect of rearranged and expressed immunoglobulin transgenes on the rearrangement process of endogenous Ig genes, a series of B-cell hybridomas were made and their endogenous heavy- and light-chain expression monitored. In Table 7 our results and those obtained from transgenic mice carrying a rearranged kappa gene

Table 7. Allelic exclusion in trans hybridomas.

κ_{21} [56]:	24 Hybrids			
	11	$H_{\kappa_{21}}$ - (germ line) [a]		
	2	H–L		
	7	$-\kappa_{21}$L		
	2	$-\kappa_{21}$ - (germ line) [a]		
	2	$-\kappa_{21}$ - (rearranged) [a]		
$\mu_6\kappa_6$ [57]:	11 Hybrids			
	3	$\mu_6\kappa_6$–HL		
	8	$\mu_6\kappa_6$–L [b]		
5 lines still have both H-encoding chromosomes	⟶ 10 alleles:	VDJ⁻	DJ	germ line
		1	8	1

[a] H = endogenous heavy chain; L = endogenous light chain; in parenthesis, light-chain gene configuration. [b] Heavy-chain gene configuration of 5 of the 8 H-minus hybrids is shown.

alone[56,57] are summarized (results from the μ-alone transgenic mice are not yet available). Of 24 hybridomas derived from κ_{21} transgenic mice, none expressed a heavy

chain with two light chains. In seven cases where no heavy chain production is observed, two light chains, the endogeneous and the transgenic one are expressed. These results are compatible with a negative feedback mechanism of H-L molecules on the light-chain gene rearranging process.

Expressing the transgenic μ_6 and κ_6 chains should therefore inhibit endogeneous light-chain gene rearrangement, which in none of the eleven hybridomas was observed. However, the trans-κ_6 chain was expressed at one-tenth the level of the endogeneous light chains whereas the μ_6 chain was made in excess. Thus, low amounts of μ_6-κ_6 molecules in an excess of free μ_6 chains are not a feedback signal to stop light-chain gene rearrangement. This observation is well in agreement with the exceptional light-chain double producers found in myeloma cell lines such as S107 where one of the kappa light chains was unable to combine with the alpha heavy chain,[59] or such as in the MOPC315 line where a truncated λ_1 chain unable to bind to its heavy chain is found together with a functional λ_2 light chain.[60] A high proportion (8/11) of hybridomas derived from the $\mu_6\kappa_6$-expressing mouse did not express a second endogenous heavy chain. Five of these lines still retained both heavy-chain-encoding chromosomes. Only in one of the ten heavy-chain alleles was a complete (though inactive) VDJ_H^- unit found. One allele apparently was frozen in the germ-line configuration and eight stopped rearrangement at the immature DJ_H state. Thus again, the result is compatible with a (leaky) feedback regulation of the heavy-chain gene rearrangement process by the mu chain itself. Whether also the light chains are involved in this process has to be clarified by analyzing pre-B cell lines. Other interpretations, however, such as different cellular selection processes in transgenic versus normal mice are possible. Nevertheless, the power of the transgene approach to study immunological phenomena is clearly demonstrated.

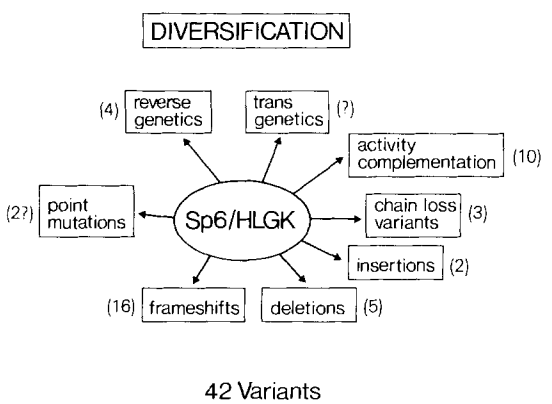


Fig. 5. Summary of Sp6 variants.

Let me now go back to the general theme of this paper and ask whether or not diversification of our Sp6 antibody could be achieved by having introduced its genes into the mouse. At the moment one can only speculate. A somatic mutation mechanism operates on immunoglobulin light- and heavy-chain genes at an approximate rate of 10^{-3} per base and generation.[45,46] It seems possible that the introduced genes will profit from this mechanism and that we will generate a whole series of somatically mutated Sp6 IgM molecules. Figure 5 summarizes the variants obtained so far from the Sp6 line using different techniques and underlines my belief that a single monoclonal antibody will only be the starting point of a variety of man-made secondary antibodies, each manufactured to fulfill a special requirement.

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Dinuclear Complexes with Predictable Magnetic Properties

By Olivier Kahn*

When two paramagnetic transition metal ions are present in the same molecular entity, the magnetic properties can be totally different from the sum of the magnetic properties of each ion surrounded by its nearest neighbors. These new properties depend on the nature and the magnitude of the interaction between the metal ions through the bridging ligands. If both ions have an unpaired electron (e.g. Cu^{2+} ions), then the molecular state of lowest energy is either a spin singlet or a spin triplet. In the former case, the interaction is said to be antiferromagnetic, in the latter case ferromagnetic. The nature and the order of magnitude of the interaction can be engineered by judiciously choosing the interacting metal ions and the bridging and terminal ligands, and, thus, by the symmetry and the delocalization of the orbitals centered on the metal ions and occupied by the unpaired electrons (magnetic orbitals). The first success in this "molecular engineering" of bimetallic compounds was in the synthesis of a $Cu^{2+}VO^{2+}$ heterobimetallic complex in which the interaction is purely ferromagnetic. The same strategy could be utilized for designing molecular ferromagnets, one of the major challenges in the area of molecular materials. Another striking result is the possibility of tuning the magnitude of the interaction through a given bridging network by modifying the nature of the terminal ligands, which, in some way, play the role of "adjusting screws". By careful selection of the bridging and terminal ligands, a very large antiferromagnetic interaction can be achieved, even if the metal ions are far away from each other. Some sulfur-containing bridges are especially suitable in this respect.

1. Introduction

Since the beginning of this century, and following the pioneering work of *Werner*, an enormous amount of relevant information has been collected concerning the physical and chemical properties of transition metal complexes. In particular, the magnetic properties of these systems have been well documented, and are rather well understood today.[1-7] In this respect, the main points deserving attention are the following:

(1) When all the thermally populated states are spin and orbital singlets, the complex is diamagnetic with temperature-independent, weakly negative magnetic susceptibility. When one of these states has an angular momentum, the complex is paramagnetic. Its magnetic susceptibility is positive and generally increases upon cooling.

(2) When the ground state has a spin momentum S without first order orbital momentum and is largely separated in energy from the first excited states, the molar magnetic susceptibility, χ_M, follows the Curie law, except perhaps at very low temperature.

$$\chi_M = (N\beta^2 g^2/3kT)S(S+1) \quad (1)$$

In Equation (1), N is the Avogadro number, β the Bohr magneton, k the Boltzmann constant, and g the Zeemann factor. χ_M is almost always very weakly anisotropic. Thus, for example, all the monomeric copper(II) complexes obey the relationship given in Equation (1), with $S=1/2$; indeed, Cu^{2+}, with d^9 configuration, has one unpaired electron. When S is larger than 1/2, at very low temperature, χ_M may substantially deviate from the values given by Equation (1) and become anisotropic owing to the zero field splitting of the magnetic ground state. This is the case, for instance, for octahedral nickel(II) complexes.[8]

(3) When the ground state has an orbital momentum or is close in energy to a state with an orbital momentum, the magnetic susceptibility no longer obeys the Curie law (1) and may be strongly anisotropic. This occurs, for instance, in the case of octahedral cobalt(II) complexes with $^4T_{1g}$ ground state.

(4) Finally, in the case of some complexes with ions like Fe^{2+}, Fe^{3+}, or Co^{2+}, the ground state may be either high spin or low spin or even may undergo high spin-low spin transitions.[9] This is the only case where the magnetic behavior of a monomeric complex of known structure cannot be estimated a priori. A small modification of the environment of a given ion may drastically modify the magnetic properties.[10]

To summarize, one can say that so far as the magnetic properties of isolated monomeric complexes are concerned, the only problem deserving new thorough investigation is that of high spin-low spin duality.

For one or two decades, the inorganic chemist has been more and more interested in polynuclear compounds. When the metal ions are not isolated from one another, these systems can acquire new physical properties or a new reactivity. Thus, the magnetic properties of a polynuclear complex are, in general, totally different from the sum of the magnetic properties of each metal center surrounded by its nearest neighbors.[11-12] It was for a long time consid-

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ered impossible to estimate a priori the magnetic properties of a polynuclear complex, since such complexes can be extremely sensitive to very small structural modifications. The main aim of this review article is to present evidence of the fact that the situation is quite different today. It is possible, from a small number of basic concepts, to predict the nature of the transition ions and of the terminal and bridging ligands which must be utilized and the whole geometry which has to be achieved in order to obtain compounds with certain magnetic properties. In other words, we are attempting to lay the foundations of a molecular engineering of magnetic polynuclear systems.[12-13]

The studies on magnetic polynuclear complexes started in 1952, when *Bleaney* and *Bowers* demonstrated that the magnetic and ESR properties of copper(II) acetate were due to the dimeric nature of the molecule.[14] These authors established a theoretical expression for the magnetic susceptibility of such a system as a function of the temperature and the energy parameter J characterizing the interaction between the Cu^{2+} ions inside the same molecular entity (see Section 2). By the end of the sixties, numerous polynuclear complexes had been synthesized, whose parameters J were determined by comparing the observed magnetic data with the theoretical laws.[15-17] More and more researchers then attempted to rationalize the sign and the value of J in the light of structural data. This allowed correlations between structural and magnetic properties to be made, and constituted quite an important step toward an understanding of the mechanism of interaction between metal centers.[12] The most elegant of these correlations was established by *Hatfield* and *Hodgson* who showed that the magnitude of the interaction in planar dihydroxo-bridged copper(II) dimeric complexes depends on the CuOCu bridging angle.[18-19] Other correlations concerning di-μ-chlorocopper(II) dimers[20-22] and di-μ-hydroxochromium(III) dimers[23-25] were also established. Despite their undoubted interest, however, such correlations cannot be regarded as actual contributions to the molecular engineering mentioned above. Indeed, except maybe in very few cases, it seems extremely difficult to control the value of the structural parameters during the synthetic process. Thus, in di-μ-hydroxocopper(II) dimers,[18] the value of the CuOCu angle, which plays a key role regarding the sign and value of J, depends in an almost unforeseeable fashion on the terminal ligands and on the counterion. Our first attempt to synthesize a new complex exhibiting definite magnetic properties dates back to the late seventies when we prepared a $Cu^{2+}VO^{2+}$ bimetallic complex in which the interaction is purely ferromagnetic (see Section 4).[26,27] The present paper is divided up as follows: In the next section, we shall recall very briefly the basic principles of the electronic structure and the magnetic properties of polynuclear complexes, then we shall present some fundamental concepts concerning the mechanism of the interactions. In some way, these concepts are our tools for designing new systems having desired magnetic properties. Then, in the sections to follow, we shall present several examples selected from the work carried out in our group. Namely, we shall outline the strategy leading to a purely ferromagnetic interaction. This outline will be kept rather brief since this facet of our work has already been reviewed elsewhere.[28] We shall then focus our attention on bimetallic complexes with bisbidentate extended ligands. The first ab initio calculations concerning complexes of this kind will also be presented. Finally, we shall give some insights into the ESR spectroscopic properties of this class of compounds before discussing the vast perspectives of this area of coupled systems.

This review has been written with the hope that it will be read by a large audience of chemists, and not just by those who are already active in this field. Accordingly, the reader does not need to have any previous knowledge of the subject. All the concepts and formulas used will be explained in detail.

The electronic structure of the coupled polynuclear systems has attracted the attention of a very large number of research workers.[12] The main reason is probably that the phenomenon of interaction between metal centers lies at the crossover point of two widely separated areas, namely the physics of the magnetic materials and the role of polynuclear reaction sites in biological processes.[29] This paper is intended to convince the reader that there are still many activities in this field and that important new developments may be expected in the near future.

2. Electronic Structure and Magnetic Properties of Dinuclear Complexes

Let us consider the simplest case of a dinuclear copper(II) complex, denoted A-B, having spins $S_A = S_B = 1/2$. The interaction between the metal centers gives rise to a molecular spin singlet ($S = 0$) and a molecular spin triplet ($S = 1$) with a singlet-triplet (S-T) energy gap, conventionally denoted by J. When the ground state is the singlet state ($J < 0$), the interaction is said to be antiferromagnetic. When the triplet state is the lowest ($J > 0$), the interaction is said to be ferromagnetic. The situation concerning the triplet state is, however, more complicated owing to the second order spin-orbit coupling. The three components of the $S = 1$ state may be split in the zero field, so that the spectrum of the low lying states in A-B is as shown in Figure 1, where the effects are arranged according to decreasing magnitude.

Generally, the absolute value of J is much larger than D and E and the spectrum in Figure 1 may be described in

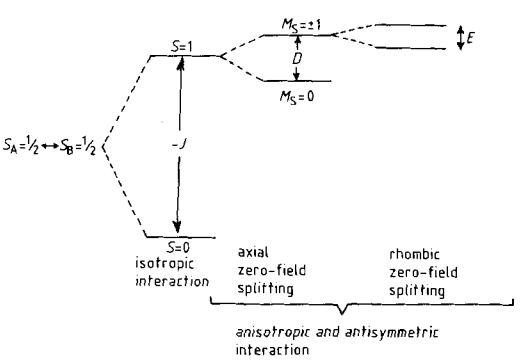


Fig. 1. Spectrum of the low lying states in a dinuclear copper(II) complex A-B.

quite a simple form by the Hamiltonian operator [Eq. (2)], in which only the local spin operators $\hat{S}_A$ and $\hat{S}_B$ occur:[30,31]

$$\mathcal{H} = -J\hat{S}_A \cdot \hat{S}_B + \hat{S}_A \cdot D \cdot \hat{S}_B + \vec{d} \cdot \hat{S}_A \cdot \hat{S}_B \quad (2)$$

J is a scalar, D a tensor, and $\vec{d}$ a vector. The first term in Equation (2) leads to the S-T splitting, the second term splits the triplet state, and the last term, which vanishes when the complex is symmetrical, couples the singlet and triplet states. This Hamiltonian operator is easy to handle; however, it does not provide any information about the mechanism of the phenomenon. Indeed, the first term, J, is related to the electrostatic interactions between the electrons of the system. Therefore, the only way to obtain information on the mechanism of the interaction is to work with the original electrostatic Hamiltonian (cf. next section).

We now want to establish the theoretical expression for the molar magnetic susceptibility of A-B. In a magnetic field H, one mole of any compound acquires a molar magnetic moment M_M given by

$$M_M = \chi_M H \quad (3)$$

where χ_M is the molar magnetic susceptibility. In classical mechanics, the magnetic moment is related to the free energy of the system by

$$M = -\partial E/\partial H \quad (4)$$

The expression for one mole of a quantized system with discrete energy levels changes to

$$M = \frac{N \sum_n (-\partial E_n/\partial H) \exp(-E_n/kT)}{\sum_n \exp(-E_n/kT)} \quad (5)$$

with summation over all thermally populated states. In A-B, n is 4 and the E_n's are:

$$E_1 = -g\beta H; \quad E_2 = 0; \quad E_3 = g\beta H; \quad E_4 = J \quad (6)$$

where E_1-E_3 refer to the triplet state taken as origin and E_4 to the singlet state. D and E have been neglected with regard to J. Substituting Equation (6) in Equation (5) gives[14]

$$\chi_M = \frac{2N\beta^2 g^2}{kT} [3 + \exp(-J/kT)]^{-1} \quad (7)$$

if we assume that H/kT is small. When the complex A-B is dissymmetrical, a very small additional term arising from the coupling of the $M_S = 0$ components of the singlet and the triplet occurs in the expression of χ_M.[28,32] This term is negligible when $|J|$ is larger than a few wave numbers. In the case of antiferromagnetic interaction, χ_M exhibits a maximum on changing the temperature T. The smaller the maximum susceptibility and the further this maximum is displaced toward high temperatures, the larger is the stabilization of the singlet state. In the case of ferromagnetic interaction, χ_M increases upon cooling down faster than $1/T$. The best way to demonstrate a ferromagnetic interaction is to plot the product $\chi_M T$ versus T.[33,34] For $J = 0$, $\chi_M T$ is constant and equal to $N\beta^2 g^2/2k$. For $J < 0$, $\chi_M T$ decreases upon cooling and tends to zero (or more exactly toward a value close to zero, owing to the presence of monomeric impurities). For $J > 0$, $\chi_M T$ increases upon cooling and reaches a plateau with $\chi_M T = 2N\beta^2 g^2/3k$, corresponding to the temperature range where only the ground triplet state is populated. At very low temperature, say below 10 K, $\chi_M T$ can deviate from this plateau owing to very small effects like zero field splitting of the ground state or intermolecular interactions, which, in most cases, couple the molecular triplet states in an antiferromagnetic fashion.[35] Moreover, whatever care is taken in the purification of the samples, a coupled dinuclear complex always contains a small amount ρ of uncoupled species, the magnetic susceptibility of which obeys the Curie law. This uncoupled species may be either an actual monomeric impurity, or merely defects at the surface of the microcrystallites. To account for this effect, the experimental susceptibility χ_M^{exp} is expressed as

$$\chi_M^{exp} = \chi_M(1-\rho) + \rho \cdot C/T \quad (8)$$

where C is the Curie constant of the uncoupled species. J is then determined by least squares fitting of the experimental data. Actual examples of ferromagnetic or antiferromagnetic behavior will be given in Sections 4–8.

3. Basic Concepts

Let us consider again the dinuclear copper(II) complex A-B where A (or B) now symbolizes one of the metal ions surrounded by its ligands. A and B are therefore monomeric fragments. Some of the ligands are common to A and B; they constitute the bridging zone. In the fragment A (or B), we have an unpaired electron which occupies the highest molecular orbital Φ_A (or Φ_B) for this fragment. These semi-localized orbitals Φ_A and Φ_B are defined as the magnetic orbitals. From the ground state configuration $\Phi_A\Phi_B$ with one unpaired electron in A and the other in B, two low lying states arise: a spin singlet state and a spin triplet state, separated by J. To a first approximation, the orbital parts of the wave functions that are suitable for describing these low lying states are given by[36]

$$\Psi_{S \atop T} = [2(1 \pm S^2)]^{-1/2} [\Phi_A(1)\Phi_B(2) \pm \Phi_A(2)\Phi_B(1)] \quad (9)$$

where the + sign holds for the singlet and the − sign for the triplet. S is the overlap integral between the magnetic orbitals.

$$S = \langle \Phi_A(1) | \Phi_B(1) \rangle \quad (10)$$

Above the ground state configuration $\Phi_A\Phi_B$, there are metal-metal charge transfer configurations $\Phi_A\Phi_A$ and $\Phi_B\Phi_B$ with the two electrons in the same fragment. These excited configurations form two spin singlet excited states, which, in principle, may interact with and stabilize the

low-lying singlet state. In fact, these excited configurations of the $Cu^{+}Cu^{3+}$ type are very high in energy and, so far, have never been unambiguously detected, so that it is reasonable to assume that this second order stabilization of the low-lying singlet state is generally a very small effect, which, in a qualitative approach, may be neglected.

The electrostatic (non-phenomenological) Hamiltonian for this problem is

$$\mathscr{H} = h(1) + h(2) + r_{12}^{-1} \tag{11}$$

where only the two electrons in Φ_A and Φ_B are taken into account. h(i) is a one-electron Hamiltonian containing the kinetic energy of the electron i and the potential energy exerted by the nuclei and the other electrons in A–B, which are assumed to be passive. r_{12} is the distance between the two magnetic electrons. The energies of the low-lying states are[37]

$$E_{S \atop T} = (\alpha_A + \alpha_B \pm 2\beta S + 2k \pm 2j)/(1 \pm S^2) \tag{12}$$

where again + holds for the singlet and − for the triplet. The integrals in Equation (12) are defined as

$$\begin{aligned} \alpha_A &= \langle \Phi_A(1) | h(1) | \Phi_A(1) \rangle \\ \beta &= \langle \Phi_A(1) | h(1) | \Phi_B(1) \rangle \\ k &= \langle \Phi_A(1)\Phi_B(2) | r_{12}^{-1} | \Phi_A(1)\Phi_B(2) \rangle \\ j &= \langle \Phi_A(1)\Phi_B(2) | r_{12}^{-1} | \Phi_A(2)\Phi_B(1) \rangle \end{aligned} \tag{13}$$

The S-T energy gap, J, may be expanded in increasing powers of S.

$$J = 2j + 4tS + \text{terms in } S^2 \ldots \tag{14}$$

with

$$t = \beta - [(\alpha_A + \alpha_B)/2] \cdot S \tag{15}$$

If J is small enough for the two low-lying states to be thermally populated, then the upper limit for $|J|$ is about 0.1 eV (800 cm^{-1}). In other words, the interaction in A–B is weak, compared for instance to the metal-metal bond in organometallic complexes. It follows that the overlap integrals S will also remain small, so we can limit the expansion of J in Equation (14) to the term linear in S.[38,39] At the same level of approximation, J may also be expressed by[39,40]

$$J = 2j - 2S(\Delta^2 - \delta^2)^{1/2} \tag{16}$$

where Δ is the difference in energy between the two singly occupied molecular orbitals γ_1 and γ_2 for the triplet state of A–B, built from the magnetic orbitals Φ_A and Φ_B. δ is the energy difference between these magnetic orbitals as specified in Figure 2. If the fragments A and B in A–B are related by a symmetry operation, Φ_A and Φ_B have the same energy and δ is zero.

In Equations (14) and (16), the first term, $2j$, is always positive. This term stabilizes the triplet state and represents the ferromagnetic contribution J_F. Each of the second terms are negative or zero. They stabilize the singlet state and represent the antiferromagnetic contribution J_{AF}. In the Wolfsberg-Helmholtz approximation,[41] the one-electron transfer integral t is assumed to be proportional to S, so that J_{AF} becomes proportional to S^2. Therefore, we can say that the S-T splitting results from a competition

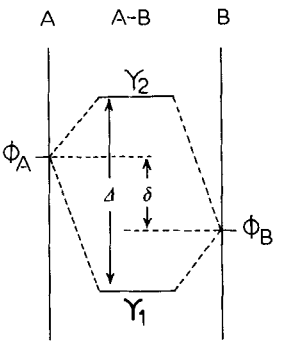


Fig. 2. Relative energies of the magnetic orbitals Φ_A, Φ_B and molecular orbitals γ_1, γ_2 built from these magnetic orbitals in a dissymmetrical dinuclear copper(II) complex.

between two antagonist terms, the one, the ferromagnetic contribution, is proportional to the two-electron exchange integral between the magnetic orbitals, the other, the antiferromagnetic contribution, is proportional to the square of the overlap integral of the magnetic orbitals. Both terms depend on the overlap density, ρ(i), in the bridging network:[42]

$$\rho(\mathrm{i}) = \Phi_A(\mathrm{i})\Phi_B(\mathrm{i}) \tag{17}$$

j is the self-repulsion of the overlap density. The zones of strong overlap density, irrespective of their sign, will give the main contributions to j. As for S, it is the integral of the overlap density, so that J_{AF} will depend on the balance between the positive and negative zones of overlap density. When positive and negative zones compensate exactly, S is zero. The magnetic orbitals are then said to be orthogonal and the interaction is ferromagnetic. In this case, the more pronounced the extrema of ρ(i), the greater is the stabilization of the triplet state (see Section 4).

Finally, we shall discuss the problem of the possible magnitudes of j and S when the two metal centers are bridged by extended ligands. In such cases, each magnetic orbital is delocalized over a large number of bridge atoms. Consequently, the overlap density is spread over the whole bridge without any pronounced maximum (Fig. 3, right). In contrast, the maximum of the overlap density in the case of a monoatomic bridge may be very pronounced (Fig. 3, left). It follows that, in the case of extended bridges, the overlap integral $S = \int_{space} \rho(\mathrm{i})\, d\tau$; may eventually be large if the magnetic orbitals are properly oriented to give an overlap density of the same sign over the whole bridging network, but the self-repulsion of the overlap density

$$j = \int_{space} \frac{\rho(\mathrm{i})\rho(\mathrm{j})}{r_{ij}}\, d\tau_i\, d\tau_j$$

remains weak. In other words, it can be expected that the main factor governing the magnitude of the interaction in dinuclear complexes with extended bridges will be the overlap of the magnetic orbitals, which favors the antiferromagnetic interaction. Of course, such a topological approach is purely qualitative and is open to criticism. In Section 6 an example will be shown in which the ferromagnetic component J_F is actually very small when the metal centers are bridged by an extended ligand.

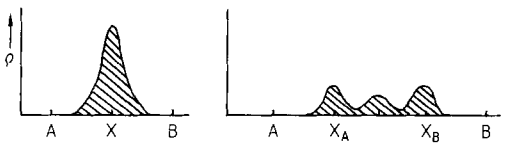


Fig. 3. Schematic representation of the overlap density ρ in the case of monoatomic bridges (left) and extended bridges (right).

4. The Symmetry of the Magnetic Orbitals and Nature of the Interaction

Quite a spectacular way of demonstrating the influence of the symmetry of the magnetic orbitals on the nature of the interaction is to compare the two complexes $[CuVO(fsa)_2en \cdot CH_3OH]$ **1** and $[Cu_2(fsa)_2en \cdot CH_3OH]$ **2**, where $(fsa)_2en^{4-}$ is the dinucleating ligand derived from *N,N'*-bis(4-carboxy-3-hydroxybenzyl)ethylenediamine.[27,43] In **1** and **2** (Figs. 4 and 5, respectively) the inner coordination site of the ligand is occupied by a Cu^{2+} ion. It is coordinated in a square pyramidal fashion by the nitrogen atoms and the phenolic oxygen atoms of the $(fsa)_2en^{4-}$ ligand in the basal plane and by the CH_3OH ligand at the apex. The outer coordination site is occupied by a VO^{2+} ion in square pyramidal surroundings (**1**) or by a Cu^{2+} ion in planar surroundings (**2**). The plane containing the metal ions, perpendicular to the plane of the dinucleating ligand, is almost a mirror plane.

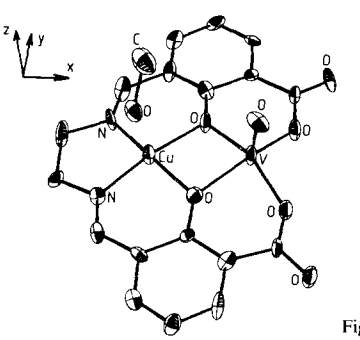


Fig. 4. Crystal structure of **1**.

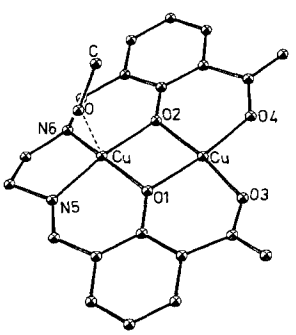


Fig. 5. Crystal structure of **2**.

In a 4+1 environment, the most destabilized orbital occupied by the unpaired electron of Cu^{2+} is of the d_{xy}-type. It points from the metal toward the four nearest neighbors in an antibonding fashion (Fig. 6). The unpaired electron of the VO^{2+} ion (configuration d^1) occupies a $d_{x^2-y^2}$ type orbital, pointing along the bisectrices of OVO angles involving the phenolic and carboxylic oxygen atoms. Consequently, the magnetic orbitals Φ_{Cu} in $Cu^{2+}VO^{2+}$ and $Cu^{2+}Cu^{2+}$ complexes are antisymmetric with regard to the mirror-plane, while the magnetic orbital Φ_{VO} is symmetric with regard to the mirror-plane. Thus, the overlap integral $\langle\Phi_{Cu}|\Phi_{VO}\rangle$ in $Cu^{2+}VO^{2+}$ is equal to zero. The magnetic susceptibilities (Fig. 7) confirm that the interaction is actually ferromagnetic with a triplet ground state 118 cm^{-1} below the singlet state. In contrast, the overlap integral $\langle\Phi_{Cu}|\Phi_{Cu}\rangle$ in $Cu^{2+}Cu^{2+}$ is different from zero. The antiferromagnetic contribution J_{AF} in the expression for J becomes preponderant and the singlet state is now the lowest with a S-T gap of -650 cm^{-1}. This comparison between the $Cu^{2+}VO^{2+}$ and $Cu^{2+}Cu^{2+}$ pairs is shown schematically in Figure 8.

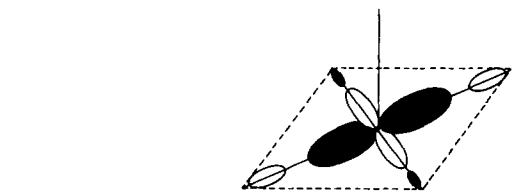


Fig. 6. Singly occupied orbital of a Cu^{2+} ion in a square pyramidal environment.

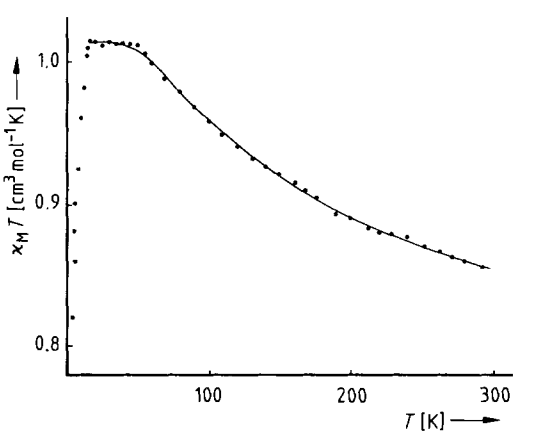


Fig. 7. Experimental (···) and theoretical (—) temperature dependence of $\chi_M T$ for **1**.

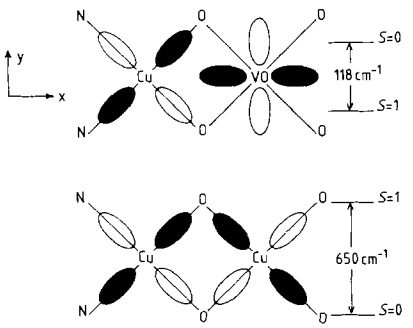


Fig. 8. Symmetries of the magnetic orbitals and the nature of the interaction in 1 (above) and 2 (below).

The symmetry of the magnetic orbitals Φ_{Cu} and Φ_{VO} in the $Cu^{2+}VO^{2+}$ complex **1** imposes the ferromagnetic nature on the interaction; their shape enables a qualitative understanding of why $J=2j$ is relatively large. Figure 9 shows in detail the two magnetic orbitals in the bridging network and Figure 10 gives two representations of the overlap density in the plane of the macrocycle. The overlap density exhibits two strongly positive lobes in one of the bridges and two strongly negative lobes in the other. Positive and negative lobes cancel exactly and the overlap integral is zero. However, the strong values of the extrema of the overlap density in each bridge lead to a significant self-repulsion of the overlap density, and hence to a large stabilization $2j$ of the triplet state.

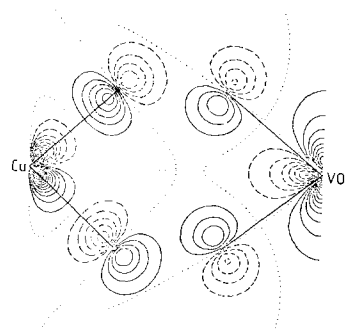


Fig. 9. Magnetic orbitals Φ_{Cu} and Φ_{VO} in the bridge of **1**.

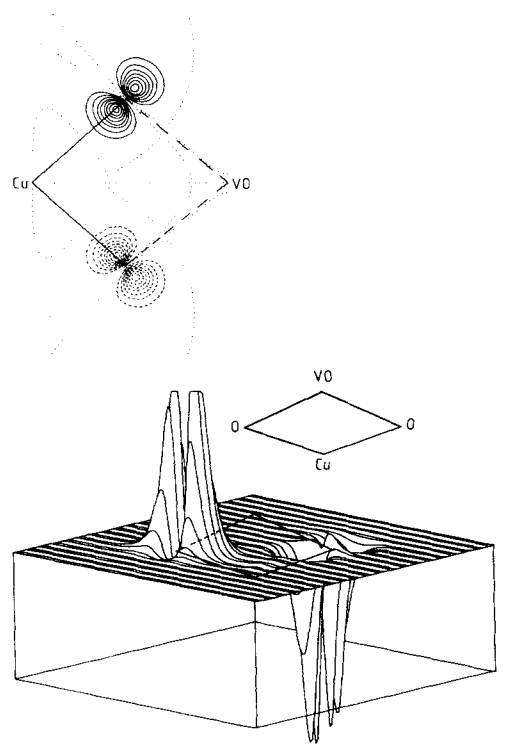
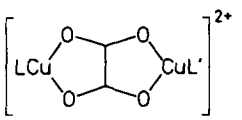
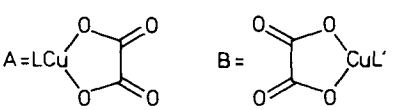


Fig. 10. Overlap density in the bridge of **1**. Isovalue map (top); relief map (bottom).

5. Magnetic Orbitals in Dinuclear Copper(II) Complexes with Extended Ligands

In this and the following sections, attention will be focused on complexes in which two Cu^{2+} ions are bridged by ligands of the type $C_2X_2Y_2^{2-}$, where the X and Y atoms bound to the metal ions may be oxygen, nitrogen, or sulfur. A highly symmetrical ligand of this kind is the oxalate ion $C_2O_4^{2-}$, which forms complexes with L and L′ as neutral terminal ligands. In dinuclear complexes of this kind, we can define the two monomeric fragments A and B considered in Section 3 as





Very often, these monomeric fragments can actually be synthesized. $[LCu(C_2O_4)CuL]^{2+}$ complexes are therefore particularly good candidates for application of the basic concepts introduced in Section 3.[44]

Owing to the Jahn-Teller effect the coordination sphere of a Cu^{2+} ion in a fragment A (or B) is remarkably flexible.[45,46] Hence, the environment of the Cu^{2+} ion will be strongly influenced by the nature of the L or L′ ligand. The Cu^{2+} ion most often adopts a coordination 4 or 4+1 or 4+2 with four nearest neighbors in the basal plane and eventually one or two next nearest neighbors in apical position. The orbital which the unpaired electron occupies is shown in Figure 6. When the symmetry of the coordination sphere is such that the xz plane is no longer a mirror plane, there is a mixing of the d_{xy} and d_{z^2} metal orbitals. The unpaired electron is then described by a $d_{xy}+\lambda d_{z^2}$-type orbital which is slightly delocalized toward the eventual apical sites. In a 4+1 coordination, the environment of the metal is not necessarily rigorously square pyramidal, it may adopt some trigonal bipyramidal character with a singly occupied orbital delocalized toward all five ligands. The

orientation of the singly occupied orbital for an intermediate case between the square pyramid and the trigonal bipyramid as well as for a pure trigonal bipyramid is shown in Figure 11.

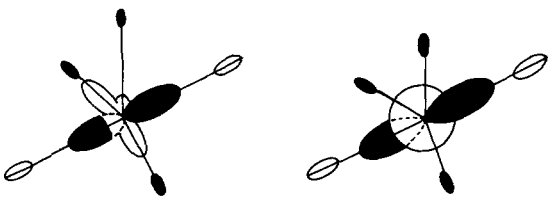
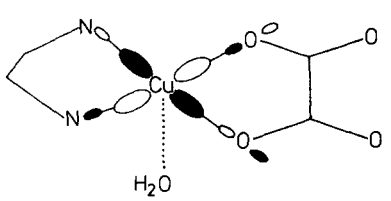


Fig. 11. Singly occupied orbital of a Cu^{2+} ion in an environment intermediate between square pyramidal and trigonal bipyramidal (left) and of a Cu^{2+} ion in a pure trigonal bipyramidal environment (right).

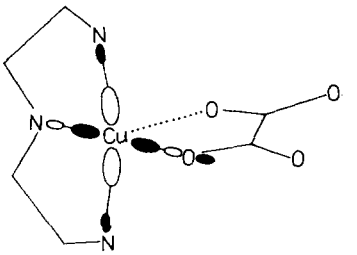
In order to decide whether oxygen or nitrogen takes over the role of nearest neighbors one must, if conclusions cannot be drawn from simple theoretical considerations, resort to the examination of a large number of structural data. Almost without exception, the Cu^{2+} ion first chooses the nitrogen atoms as nearest neighbors, then eventually completes its basal plane with oxygen atoms. If this finding is taken as a rule, then one is in a position to influence the orientation of the magnetic orbital in a $LCu(C_2O_4)$ fragment by appropriate selection of L. For example, if one wants the magnetic orbital to lie in the plane of the oxalato group, then a diamine is chosen for L. For instance, in the mononuclear complex $[(tmen)Cu(C_2O_4)\cdot 4H_2O]$ **3**, with tmen = *N,N,N',N'*-tetramethylethylenediamine, the four nearest neighbors of the Cu^{2+} ion are the two nitrogen atoms of tmen and two oxygen atoms of the oxalato group. They lie in the base of the square pyramid, with a water molecule occupying an apical position.[47] The unpaired electron is then described by the orbital shown in Scheme 1.



Scheme 1. Magnetic orbital of **3**.

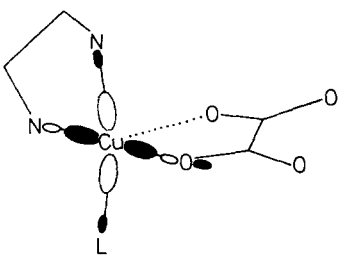
If, on the other hand, it is desired that the magnetic orbital lie in a plane perpendicular to the plane of the oxalato group, then a triamine is chosen for L. Thus, in $[(dien)Cu(C_2O_4)\cdot 4H_2O]$ **4** (dien = diethylenetriamine), the four nearest neighbors are the three nitrogen atoms of dien and only one of the oxygen atoms of the oxalato ligand, with another oxygen atom occupying the apical position.[48] It follows that the unpaired electron is now described by an orbital as shown in Scheme 2.

An alternative way of achieving the same orientation of the magnetic orbital as that depicted in Scheme 2 is to start



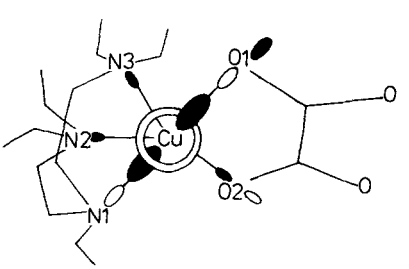
Scheme 2. Magnetic orbital of **4**.

from $[(tmen)Cu(C_2O_4)\cdot 4H_2O]$ **3** and to incorporate a new monodentate nitrogen-containing ligand L which reverses the orientation of the orbital in complex **5** (Scheme 3).



Scheme 3. Magnetic orbital of **5**.

In the case of 4 + 1 coordination, the environment of the Cu^{2+} ion may acquire some trigonal bipyramidal character. The bulkier the ligands bound to the metal, e.g. on replacing dien in **4** by *N,N,N',N'*-pentamethyldiethylenetriamine (pmedien) and by *N,N,N',N'*-pentaethyldiethylenetriamine ($[LCu(C_2O_4)\cdot 4H_2O]$ **6**; L = pmedien, petdien), the more pronounced the distortion from the square pyramidal toward the trigonal bipyramidal character of the N_3O_2 coordination,[49] whereby the admixture of the d_{z^2} metal orbital in the singly occupied orbital progressively increases. In the hypothetical borderline case of a pure trigonal bipyramidal symmetry with N1CuO1 as trigonal axis and N2N3O2 as equatorial plane, the magnetic orbital can be represented as in Scheme 4.



Scheme 4. Magnetic orbital of **6**.

How can the relative magnitudes of the interactions in dinuclear μ-oxalatocopper(II) complexes be predicted

from the orientations of the orbitals in **3** to **6**?[50] **3** represents the monomeric fragments of the complex $[(tmen)(H_2O)Cu(C_2O_4)Cu(H_2O)(tmen)](ClO_4)_2 \cdot 1.25\,H_2O$ **7**,[50] and the orbital shown in Scheme 1 may be regarded as one of the two magnetic orbitals of the dinuclear system. These magnetic orbitals are suitably oriented for interaction on both sides of the bridge, since the σ orbitals of the oxygen atoms bound to the same carbon atom of the oxalato bridge overlap each other. **4** represents the monomeric fragments of $[(dien)Cu(C_2O_4)Cu(dien)]^{2+}$[51] and, as above, the orbital shown in Scheme 2 may be considered as one of the two magnetic orbitals of the dinuclear complex. The two short Cu–O bonds must be in the *trans* position with respect to the C–C bond of the oxalato ligand. It follows that the two magnetic orbitals are unfavorably oriented for interaction and, in the absence of d_{z^2} admixture, the overlap integral may be assumed to be zero. In the case where the CuN_3O_2 coordination sphere acquires some trigonal bipyramidal character, owing to the admixture of the d_{z^2} orbital and the associated delocalization of the spin density on the apical site, the overlap integral between magnetic orbitals is no longer zero. Such a situation may be expected in $[(pmedien)Cu(C_2O_4)Cu(pmedien)]^{2+}$ and, to a greater extent, in $[(petdien)Cu(C_2O_4)Cu(petdien)]^{2+}$.[49] In $[(tmen)(L)Cu(C_2O_4)Cu(L)(tmen)]^{2+}$, owing to the orientation of the magnetic orbital being as shown in Scheme 3, the overlap integral is again zero or close to zero, depending on eventual trigonal bipyramidal distortion.

Because of the relative orientation of the magnetic orbitals of the dissymmetrical dinuclear complex $[(dien)Cu(C_2O_4)Cu(tmen)]^{2+}$ (Schemes 1 and 2), the overlapping takes place only on one side of the bridge. Consequently, the overlap integral is approximatively half of what it is in $[(tmen)(H_2O)Cu(C_2O_4)Cu(H_2O)(tmen)]^{2+}$. Replacement of dien by pmedien, and then by petdien, leads to increased trigonal bipyramidal coordination, but the magnitude of the overlap nevertheless remains smaller than in $[(tmen)(H_2O)Cu(C_2O_4)Cu(H_2O)(tmen)]^{2+}$.

To sum up, our predictions concerning the relative magnitudes of the interactions in a series of μ-oxalatocopper(II) complexes are:

(1) In $[(tmen)(H_2O)Cu(C_2O_4)Cu(H_2O)(tmen)]^{2+}$, in spite of the large separation between the metal centers, the interaction is expected to be strongly antiferromagnetic.

(2) The antiferromagnetic interaction is expected to be negligible in $[(dien)Cu(C_2O_4)Cu(dien)]^{2+}$ and to increase slightly on varying the tridentate terminal ligands in the series dien < pmedien < petdien.

(3) Similarly, the interaction is expected to be negligible or very small in $[(tmen)(L)Cu(C_2O_4)Cu(L)(tmen)]^{2+}$, where L is a nitrogen-containing monodentate ligand.

(4) In the complex $[(dien)Cu(C_2O_4)Cu(tmen)]^{2+}$, the interaction should be about a quarter of what it is in $[(tmen)(H_2O)Cu(C_2O_4)Cu(H_2O)(tmen)]^{2+}$ since the ratio of the overlap integrals is close to 1/2. The magnitude of the interaction is expected to increase in the hypothetical complexes in which dien is replaced by pmedien, then by petdien.

6. Structures and Magnetic Properties of μ-Oxalatocopper(II) Complexes

Most of the complexes considered in the previous Section have actually been synthesized. Generally, their crystal structures have also been refined. In all cases, the temperature-dependence of their magnetic properties have been investigated, and the S-T energy gaps are accurately known.

The synthesis of symmetrical complexes is straightforward and is carried out according to the following reaction scheme.

$$2Cu^{2+} + 2L + C_2O_4^{2-} \longrightarrow [LCu(C_2O_4)CuL]^{2+}$$

Dissymmetrical complexes, $[LCu(C_2O_4)CuL']^{2+}$, are prepared in two steps. First, a monomeric fragment is obtained according to the following reaction:

$$Cu^{2+} + L + C_2O_4^{2-} \longrightarrow LCu(C_2O_4)$$

Then, this fragment is used as a ligand:

$$LCu(C_2O_4) + Cu^{2+} + L' \longrightarrow [LCu(C_2O_4)CuL']^{2+}$$

The compound $[(tmen)(H_2O)Cu(C_2O_4)Cu(H_2O)(tmen)](ClO_4)_2 \cdot 1.25\,H_2O$, **7**, contains centrosymmetrical dinuclear cations in which the Cu^{2+} ions have a square pyramidal environment with a water molecule in the apical position (Fig. 12). The $Cu(C_2O_4)Cu$ network has a flattened chair configuration, the Cu···Cu separation being 5.15 Å. The magnetic properties of **7** (see Fig. 16) are characteristic for a strong antiferromagnetic interaction with maximal magnetic susceptibility at 300 K. The S-T energy gap was found to be $J = -385.4\ cm^{-1}$.

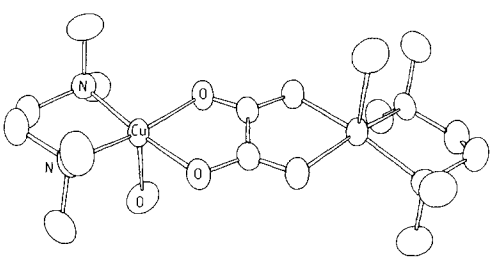


Fig. 12. Structure of the dinuclear cation $[(tmen)(H_2O)Cu(C_2O_4)Cu(H_2O)(tmen)]^{2+}$ in the crystal of **7**.

The compounds $[LCu(C_2O_4)CuL]^{2+}$, where L is a tridentate ligand, have been synthesized by *Waters* et al.,[51] by *Hendrickson* et al.,[49,52,53] and by *Sletten*.[54] When L = dien, the environment of the metal ions is square pyramidal; the basal plane is perpendicular to the plane of the bridge. In the perchlorate $[(dien)Cu(C_2O_4)Cu(dien)]^{2+}$ **8**[51] the Cu···Cu separation is 5.43 Å (Fig. 13). Down to 4.2 K, the temperature-dependence of the magnetic susceptibility obeys the Curie law for two uncoupled Cu^{2+} ions. J is very close to zero. As expected, replacement of

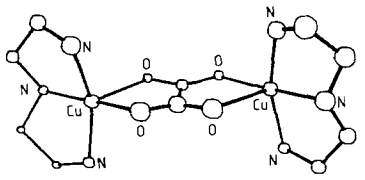


Fig. 13. Structure of the dinuclear cation $[(dien)Cu(C_2O_4)Cu(dien)]^{2+}$ in the crystal of **8**.

dien by pmedien and petdien, progressively increases the trigonal bipyramidal character, as well as the S-T energy gap. When the counterion is the perchlorate, J is $-4.5\ cm^{-1}$ for the pmedien derivative and -20 cm for the petdien derivative.[52] For a given dinuclear cation, J also depends on the counterion. For instance, for $[(petdien)Cu(C_2O_4)Cu(petdien)](BPh_4)_2$, J is as large as $-75.8\ cm^{-1}$. The dinuclear complex cation $[(tmen)(L)Cu(C_2O_4)Cu(L)(tmen)]^{2+}$, with L = 2-methylimidazole (2-Melm), which could be isolated as the PF_6^- salt **9**, is centrosymmetric (Fig. 14). Each Cu^{2+} ion is coordinated in a distorted square pyramidal fashion, the distortion introducing some trigonal bipyramidal character. The basal plane contains the two nitrogen atoms of tmen, one of the nitrogen atoms of 2-Melm, and one of the oxygen atoms of the oxalato bridge; the other oxalato oxygen atom occupies the apical position. The $Cu(C_2O_4)Cu$ network has a flattened chair configuration with a Cu···Cu separation of 5.43 Å. The magnetic susceptibility of **9** exhibits a maximum at 10.8 K; this corresponds to a S-T splitting of $-13.8\ cm^{-1}$.

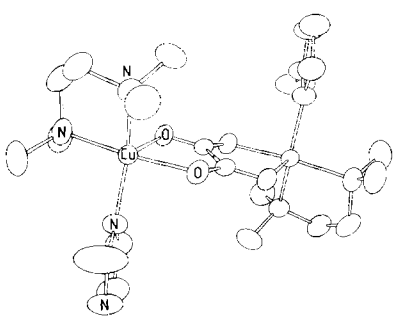


Fig. 14. Structure of the dinuclear cation $[(tmen)(2\text{-}Melm)Cu(C_2O_4)Cu(2\text{-}Melm)(tmen)]^{2+}$ in the crystal of **9**.

Only one dissymmetrical complex has been synthesized so far in the series $[LCu(C_2O_4)CuL']^{2+}$, namely $[(dien)Cu(C_2O_4)Cu(H_2O)_2(tmen)](ClO_4)_2$, **10**. The structure of the dinuclear cation is given in Figure 15. On the tmen side, the Cu^{2+} ion is in a 4+2 environment. The four nearest neighbors are the nitrogen atoms of tmen and two oxygen atoms of the oxalato bridge; the two apical positions are occupied by water molecules. On the dien side, the Cu^{2+} ion is again in a 4+2 environment. The four nearest neighbors are the three nitrogen atoms of dien and an oxygen atom of the bridge. They occupy the basal corners of a square pyramid whose apex is occupied by a second oxygen atom of the oxalato group. An oxygen atom belonging to the bridge of a neighboring dinuclear cation occupies the second apical site 2.75 Å from the metal. The magnetic susceptibility of **10** with a maximum at 62 K corresponds to a S-T splitting of $-75.5\ cm^{-1}$. The magnetic susceptibility curves of **7**, **9**, and **10** are shown in Figure 16.

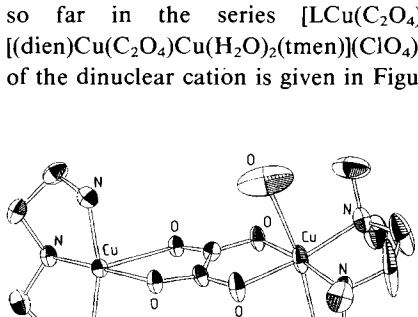


Fig. 15. Structure of the dinuclear cation $[(dien)Cu(C_2O_4)Cu(H_2O)_2(tmen)]^{2+}$ in the crystal of **10**.

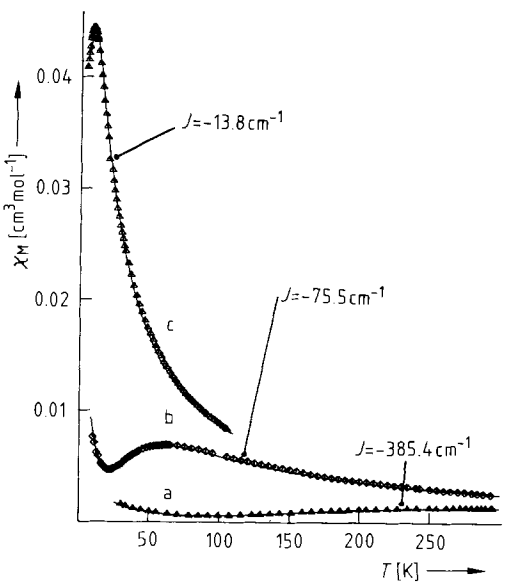


Fig. 16. Magnetic susceptibilities of 7(a), **9** (c), and **10** (b). (▲) experimental data; (—) calculated curves.

Let us now compare the experimentally determined S-T splittings with the predictions made in the previous section: As expected, owing to the favorable orientation of the magnetic orbitals, **7** exhibits a strong antiferromagnetic interaction. Again, as expected, the interaction in **8** is negligible, but increases with increasing trigonal bipyramidal character of the coordination spheres. By coordination of the 2-Melm ligand to the metal ion in **9**, we succeeded in reversing the orientation of the magnetic orbitals and in drastically diminishing the magnitude of the interaction. Finally, in **10** the S-T splitting is about five times smaller than in **7**, whereas we predicted a ratio of four. The essence of this discussion is summarized in Figure 17, where the relative orientations of the magnetic orbitals in **7**, **8**, and **10** are shown.

The monomeric fragments which are taken into consideration in the theoretical model presented in Section 3 do actually exist. In $[(bpy)(H_2O)Cu(C_2O_4)Cu(H_2O)(bpy)][(bpy)Cu(C_2O_4)](NO_3)_2$, **11** (bpy = 2,2'-bipyridyl), the binuclear complex and the monomeric fragment coexist in the same crystal lattice.[55] In the dinuclear cation, bpy plays

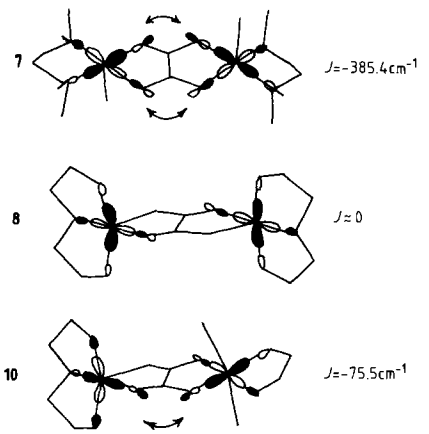


Fig. 17. Relative orientations of the magnetic orbitals in **7**, **8**, and **10**.

much the same role as tmen in **7**. Like the monomeric unit, it is almost planar (Fig. 18). The magnetic orbitals are also favorably oriented to give a strong antiferromagnetic interaction. The magnetic susceptibility of **11** corresponds to that of the monomeric fragment, which obeys the Curie law, and that of the dinuclear complex with a S-T energy gap of $-385.9\ cm^{-1}$ (equal to the value found in **7**).

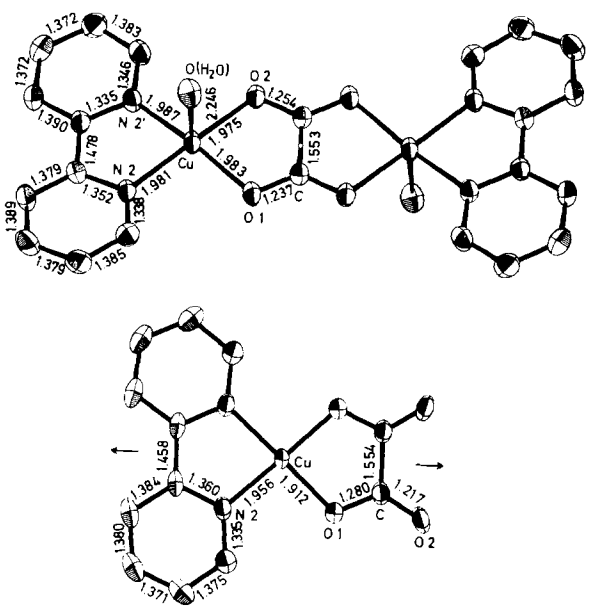


Fig. 18. Structure of the dinuclear cation $[(bpy)(H_2O)Cu(C_2O_4)\text{-}Cu(H_2O)(bpy)]^{2+}$ and of the neutral mononuclear unit $[(bpy)Cu(C_2O_4)]$ in the crystal of **11**. Distances [Å]. The arrows denote a twofold axis of symmetry.

All our predictions in the previous Section on the magnitude of the interaction were based on the assumption that the ferromagnetic contribution $J_F = 2j$ is very weak when the metal ions are bridged by extended ligands. This assumption is substantiated by the magnetic behavior of the compound $[(tmen)(H_2O)Cu(C_2O_4)VO(H_2O)(C_2O_4)]$, **12**, the most likely structure of which is shown in Figure 19.[56] A Cu^{2+} ion and a VO^{2+} ion are bridged by oxalate. The magnetic orbitals of Cu^{2+} and VO^{2+} (Scheme 1 and Fig. 9, respectively) are, as in the case of $[CuVO(fsa)_2en \cdot CH_3OH]$, **1**, orthogonal, and the antiferromagnetic contribution vanishes. Therefore, the interaction should be ferromagnetic with a triplet ground state. From the magnetic and ESR data, it is found that J is in the range 0.3–1 cm^{-1}. The ferromagnetic contribution of the oxalato bridge is effectively negligible.

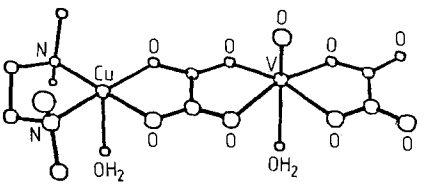
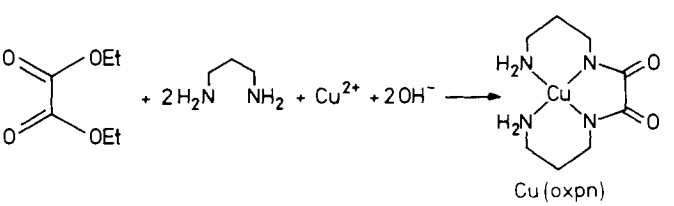


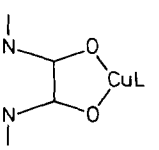
Fig. 19. Crystal structure of **12**.

7. Tunable Interaction in μ-Oxamidocopper(II) Complexes

The concepts developed in Section 3 have been applied to another series of dinuclear copper(II) complexes where the metal ions are bridged by an oxamide derivative. The monomeric fragment Cu(oxpn) can be synthesized according to the following reaction:[57]



The metal center has square planar coordination, so that the unpaired electron occupies an orbital pointing toward the nitrogen atoms, similarly to that shown in Scheme 1. The other monomeric fragment, of the type



may be modified by changing L.

For very large interactions, a nitrogen-containing bidentate ligand, bpy, is chosen for L. The structure of the dinuclear cation $[Cu(oxpn)Cu(bpy)](ClO_4)_2$, **13**, is essentially planar with very weak interactions between the Cu^{2+} and the perchlorate ions (Fig. 20). The $Cu \cdots Cu$ separation is 5.19 Å. The S-T gap is as large as $-439.7\ cm^{-1}$. We shall see in the next section why the antiferromagnetic interaction is even larger than in **7**.

To minimize the interaction, a nonbulky nitrogen-containing tridentate ligand must be chosen for L; dien would appear to be particularly promising for this purpose; unfortunately, however, all attempts to synthesize $[Cu(oxpn)Cu(dien)](ClO_4)_2$ failed. Instead, $[Cu(oxpn)Cu(pmedien)](ClO_4)_2$, **14**, was prepared, whose crystal structure has not yet been refined. On the pmedien side, the Cu^{2+} ion is most likely in a distorted square planar environment with the three nitrogen atoms of pmedien and an oxygen atom of oxpn in the basal plane, the other oxygen atom of oxpn occupying the apical position. The S-T energy gap is only $-82.8\ cm^{-1}$.

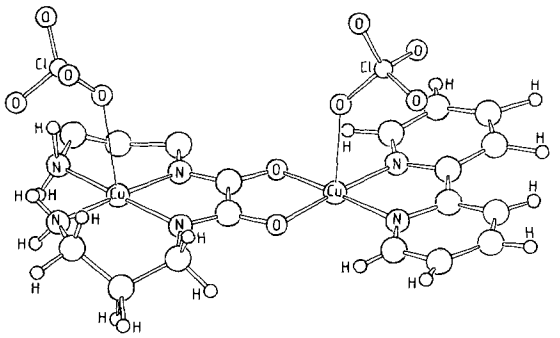


Fig. 20. Structure of the dinuclear cation $[Cu(oxpn)Cu(bpy)]^{2+}$ in the crystal of **13**.

For an interaction of intermediate magnitude, a bulky nitrogen-containing tridentate ligand can be chosen for L so as to enhance the trigonal bipyramidal character. This has been achieved with L = petdien, in the compound $[Cu(oxpn)Cu(petdien)](ClO_4)_2$, **15**. The environment of one of the Cu^{2+} ions is planar, that of the other, on the petdien side, is in an environment intermediate between a square pyramid and a trigonal bipyramid (Fig. 21). A square pyramidal description places the three nitrogen atoms of petdien and an oxygen atom of the bridge in the basal plane, the other oxygen atom of the bridge being in the apical position. A trigonal bipyramidal description, on the other hand, places the central nitrogen atom of petdien and an oxygen atom of the bridge along the trigonal axis and the three other atoms around the metal in the equatorial plane. The Cu···Cu separation is 5.25 Å. The S-T gap J, with a value of $-242.0\ cm^{-1}$, lies between the values for **13** and **14**. The magnetic susceptibilities of **13**, **14** and **15** are compared in Figure 22.[58]

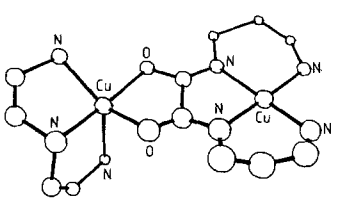


Fig. 21. Structure of the dinuclear cation $[Cu(oxpn)Cu(petdien)]^{2+}$ in the crystal of **15**.

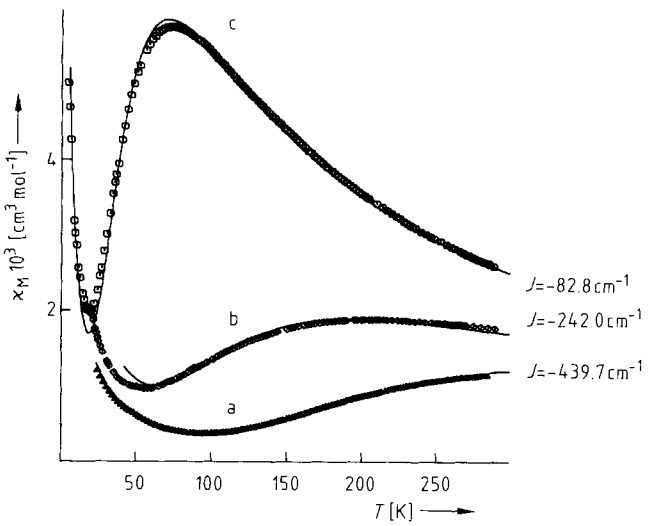


Fig. 22. Magnetic susceptibilities of **13** (a), **14** (c), and **15** (b). (□, △) experimental data; (—) calculated curves.

8. Maximization of the Interaction Through a Bis-Bidentate $C_2X_2Y_2$ Bridge

Despite a separation of 5.15 Å between the metal centers in the dinuclear copper complex **7**, the interaction is very strong ($J = -385.4\ cm^{-1}$). The questions posed then are: Is it possible to do better? Is it possible to achieve a larger interaction between two metal ions that are separated as much as or more than in **7**? The answer is in the affirmative, for we have already mentioned the compound **13** in which the metal-metal distance is much the same as in **7** and the S-T splitting is equal to $-439.7\ cm^{-1}$.

The strong interaction in **7** is due to the relative orientation of the magnetic orbitals and to their delocalization from the metal toward the oxygen atoms of the bridge bound to the metal. Both the orientation and the delocalization of the magnetic orbitals favor their overlapping, and thus the antiferromagnetic interaction. Consequently, there are in principle two ways in which to enhance this interaction: either by improving the orientation of the magnetic orbitals or by increasing their delocalization. The possibilities of the former way are very limited since the magnetic orbitals are already located in the plane containing the bridging network, and, moreover, point to each other. One can only improve the planarity of the dinuclear cation, by weakening the apical copper-water bond which pulls the metal from the basal plane. For instance, in **7**, the metal is displaced from the N_2O_2 basal plane toward the apical water molecule by 0.16 Å. It has been found, however, that displacement of the apical water molecules has almost no effect on the magnitude of the interaction. Is it, on the other hand, possible to increase the delocalization? Here, the answer is quite positive. By replacing the oxygen atoms of the oxalato bridge by less electronegative atoms, one can diminish the energy gap between the metal orbital and the ligand orbitals. In the monomeric fragment, the metal orbital-ligand orbital interaction is strengthened, giving rise to a low energy bonding molecular orbital with en-

hanced metal character and a high-energy antibonding molecular orbital with enhanced ligand character, the magnetic orbital (Fig. 23).

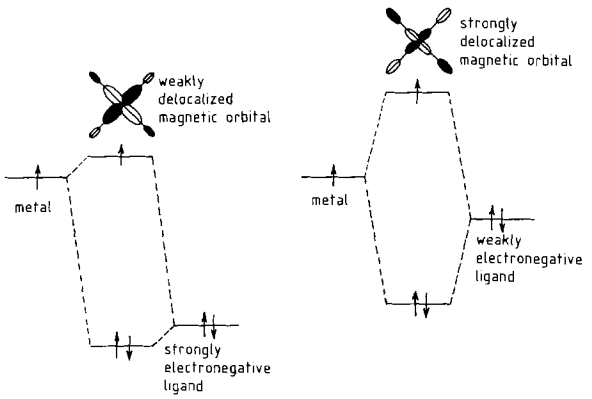


Fig. 23. Electronegativity of the ligands and delocalization of the magnetic orbitals.

This strategy for increasing the interaction has been tested by replacing the oxalato bridge in **7** by an oxamido bridge.[59,60] The compound $[(tmen)(H_2O)Cu(C_2O_2N_2H_2)Cu(H_2O)(tmen)](ClO_4)_2$ **16** was obtained. Each Cu^{2+} ion in the dinuclear cation is coordinated in a square pyramidal fashion with the two nitrogen atoms of tmen, a nitrogen atom, and an oxygen atom of the oxamido bridge in the basal plane (Fig. 24). A water molecule occupies the

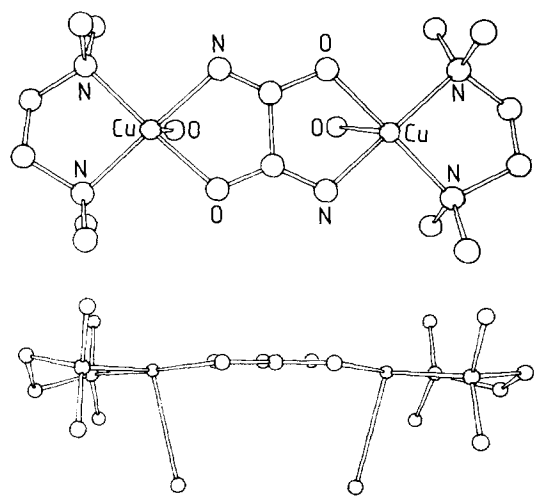


Fig. 24. Structure of the dinuclear cation $[(tmen)(H_2O)Cu(C_2O_2N_2H_2)Cu(H_2O)(tmen)]^{2+}$ in the crystal of **16**.

apical position. Surprisingly, the two water molecules are on the same side of the molecular plane, so the $Cu(C_2O_2N_2H_2)Cu$ network has a flattened boat configuration with a Cu···Cu separation of 5.17 Å. The maximum of the magnetic susceptibility occurs well above room temperature, which is consistent with a very large S-T energy gap. J was found to be equal to $-581\ cm^{-1}$. A value of J lying between those for **7** and **16** might be expected for the compound $[(tmen)Cu(C_2O_3NH)Cu(tmen)](PF_6)(NO_3)\cdot H_2O$, **17**, where the Cu^{2+} ions are bridged by the oxamato ligand $O_2C-C(O)NH^{2-}$; Indeed, a value of $J = -425\ cm^{-1}$ was found. The magnetic susceptibilities of **7**, **16**, and **17** are compared in Figure 25.[59,60]

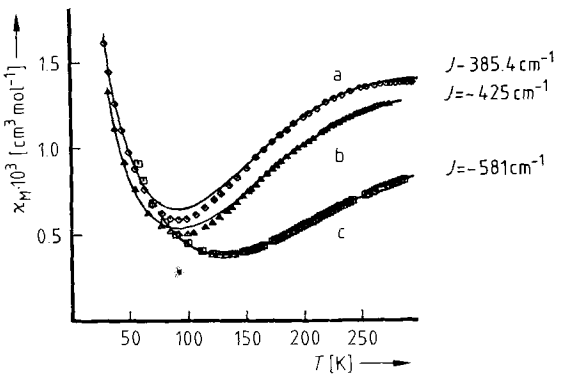
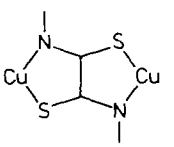


Fig. 25. Magnetic susceptibilities of **7** (a), **16** (c) and **17** (b). (◇, △, □) experimental data; (—) calculated curves.

What kind of X or Y atoms in the bridges $C_2X_2Y_2^{2-}$ could lead to even further improvement of the interaction? Sulfur is less electronegative. The tetrathiooxalate ion $C_2S_4^{2-}$[61] has not as yet been employed for the bridging of metal centers. On the other hand, the chemistry of dithiooxamide derivatives with a bridging network has been studied extensively in the past few years.[62-66].



Only a few examples can be cited here. The compound $[Cu_2\{S_2C_2(NCH_2CH_2OH)_2\}(H_2O)_2]_2(SO_4)_2$ **18** has been prepared from *N,N'*-bis(2-hydroxyethyl)dithiooxamide.[62] The dinuclear complex cation is almost planar. The Cu···Cu separation is 5.61 Å, i.e. 0.46 Å larger than in **7** and 0.42 Å larger than in **16**. In spite of this much larger metal-metal separation, the S-T energy gap $J = -594\ cm^{-1}$

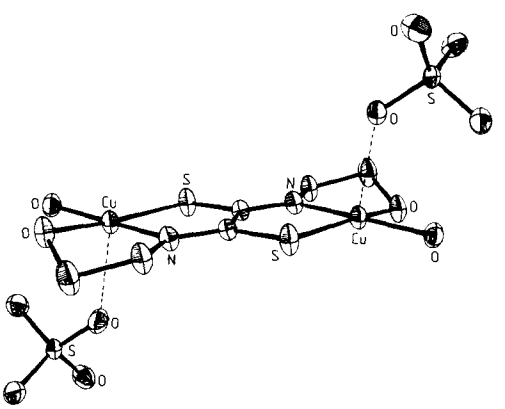


Fig. 26. Crystal structure of **18**.

in **18** is increased considerably compared to that in **7** and slightly increased compared to that in **16**. In other compounds with the same bridging network, J may even be more negative. This is the case, for example, in $[Cu_2\{C_2S_2[NCH(CH_2CH_2SCH_3)COOCH_3]_2\}Br_2]$, **19**, the structure of which is shown in Figure 27. The $CuS_2C_2N_2Cu$ network resembles very closely the network found in **18**, in that the corresponding bond lengths deviate less than 0.03 Å from each other and the Cu···Cu separation is 5.67 Å.[66] The S-T energy gap deduced from the magnetic properties is $J=-730\ cm^{-1}$. In **19**, the environment of each Cu^{2+} ion is far from being a pure square pyramid with a basal plane almost coplanar with the bridging network. Indeed, in **19**, the sulfur atom S2 of the methionine group is displaced by more than 2 Å from the N-S1-Br plane, S1 being the sulfur atom of the bridge (see Fig. 27). This distortion is, however, not sufficient to reverse the orientation of the magnetic orbital, which remains delocalized toward the nitrogen and sulfur atoms of the bridge.

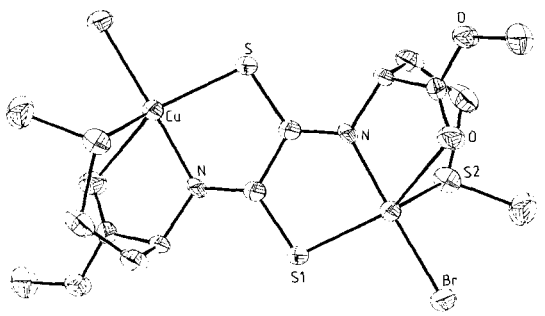


Fig. 27. Crystal structure of **19**.

In **19**, the delocalization is, as in **18**, particularly significant, because of the small energy difference between the 3d metal orbitals and the sulfur valence orbitals. Another way of expressing this is to say that the 3s and 3p valence orbitals of the sulfur are quite diffuse, which favors both the delocalization of the magnetic orbitals as well as overlapping of the orbitals of the S- and N-bridging atoms bound to the same carbon atom. It is interesting to note that all attempts to achieve a reversal of the magnetic orbital and thus a drastic decrease in the interaction in μ-dithiooxamidocopper(II) complexes have been unsuccessful. Such an orbital reversal would require significant lengthening of the Cu-S (dithiooxamide) bond length. Apparently, the affinity of the Cu^{2+} ion for the sulfur atoms of the dithiooxamide is too pronounced.

9. Ab Initio Calculation of the S-T Energy Gap in Complexes 7 and 18

In Section 3 we have defined the magnetic orbitals Φ_A and Φ_B as the singly occupied molecular orbitals for the monomeric fragments. Generally, the magnetic orbitals are not orthogonal; in fact, we have seen that the overlap between them is the key factor governing the magnitude of the antiferromagnetic interaction. This approach is justified by its heuristic character, and a strategy could be proposed for obtaining a purely ferromagnetic interaction and for tuning the magnitude of the antiferromagnetic interaction through extended bridges of the type $C_2X_2Y_2^{2-}$ in the range $-730\ cm^{-1}<J<0$. Probably its main advantage is its simplicity; it uses a language familiar to the inorganic chemist, for whom the overlap between orbitals is considered the cornerstone of the chemical bond. However, this approach is apparently not appropriate for quantitative theoretical calculations, owing to the difficulty arising from the non-orthogonality of the magnetic orbitals. In 1959, *Anderson* proposed a model using orthogonalized magnetic orbitals as basis set for extended lattices,[67] and, in 1975, *Hay, Thiebault,* and *Hoffmann*[68] presented its molecular variant. A brief formulation of this model is given here for the case of a symmetrical dinuclear copper(II) complex A-B. First, a molecular orbital calculation for the triplet state of lowest energy is performed. The two singly occupied molecular orbitals are γ_1 and γ_2 (cf. Fig. 2) and the two orthogonalized magnetic orbitals Φ'_A and Φ'_B are obtained according to:

$$\Phi'_A=\sqrt{2}/2(\gamma_1+\gamma_2)$$
$$\Phi'_B=\sqrt{2}/2(\gamma_1-\gamma_2) \qquad (18)$$

Φ'_A and Φ'_B are not perfectly localized in the A and B monomeric fragments, respectively. Due to the orthogonalization, Φ'_A has a residual contribution in B, outside the bridging region between A and B. The larger the overlap integrals $S=\langle\Phi'_A|\Phi'_B\rangle$, the more important is this residual contribution. From the ground configuration with one unpaired electron per magnetic orbital a singlet and a triplet state arise. From the excited configuration with the two electrons in the same magnetic orbital, two singlet states arise. One of them interacts with the low lying singlet state and stabilizes it. J is then calculated by a perturbational treatment and found to be

$$J=2j'-\Delta^2/U \qquad (19)$$

where Δ, as already mentioned, is the energy difference between γ_1 and γ_2, and U the energy difference between the configurations of the excited state and the ground state.

$$U=\langle\Phi'_A(1)\Phi'_A(2)|r_{12}^{-1}|\Phi'_A(1)\Phi'_A(2)\rangle$$
$$-\langle\Phi'_A(1)\Phi'_B(2)|r_{12}^{-1}|\Phi'_A(1)\Phi'_B(2)\rangle \qquad (20)$$

j' is given by:

$$j'=\langle\Phi'_A(1)\Phi'_B(2)|r_{12}^{-1}|\Phi'_A(2)\Phi'_B(1)\rangle \qquad (21)$$

Two calculations of this kind have been performed, one for compound **7**,[69] the other for compound **18**.[70]

The values of j', Δ and U are given in Table 1 together with the J values derived from Equation (19) and the final J value obtained from an extended configuration interaction (see below). The electronic isodensity curves $[(\Phi'_A)^2=\text{const.}]$ of **7** and **18** are shown in Figure 28.

Table 1. Ab initio calculation of the S-T splitting J [cm^{-1}] in the oxalato complex **7** and the dithiooxamido complex **18**.

	7	**18**
j'	360	192
Δ	7572	6694
U	126600	87800
J from Eq. (19)	270	−124
Additional contribution to J	−565	−434
Final J value	−295	−558
Experimental J value	−385.4	−594

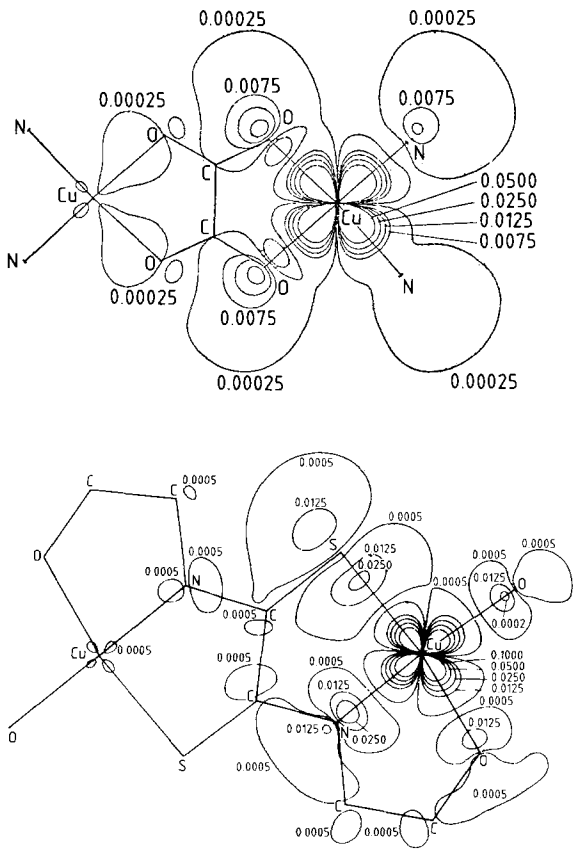


Fig. 28. Electronic isodensity curves [$(\Phi'_A)^2$ = constant] of the orthogonalized magnetic orbitals in **7** (top) and **18** (bottom). Electron density [eÅ^{-3}].

The following conclusions can be drawn from Figure 28 and Table 1:

(1) As expected, the magnetic orbital is less concentrated on the metal for the dithiooxamido complex than for the oxalato complex.

(2) j', which stabilizes the triplet state, is larger in **7** than in **18**; both Δ and U are larger in **7**, but Δ^2/U, which stabilizes the singlet state, is more important in the dithiooxamido complex **18**.

(3) The S-T splittings deduced from Equation (19) deviate widely from the experimentally determined values. J at this level of approximation has even the wrong sign for **7**. At first sight, this result is discouraging. Both *de Loth* et al.[71] and later *Charlot* et al.[69] showed great foresight in having searched for the mechanism which, beyond the formalism of *Anderson* and Equation (19), effects stabilization of the singlet state. Equation (19) is based implicitly on a configuration interaction limited to the two configurations $|\gamma_1\bar{\gamma}_1|$ and $|\gamma_2\bar{\gamma}_2|$ for the singlet state and on the only configuration $|\gamma_1\gamma_2|$ for the triplet state. To go beyond this formalism necessitates a more extended configuration interaction being carried out. By using a perturbational approach of the configuration interaction problem,[69-71] additional negative contributions of $-565\ cm^{-1}$ for **7** and $-434\ cm^{-1}$ for **18** were found, so that J was finally calculated as $-295\ cm^{-1}$ for the oxalato complex and $-558\ cm^{-1}$ for the dithiooxamido complex. The agreement between theory and experiment now appears quite satisfactory. In the latter case, in fact, this agreement is probably somewhat fortuitous.

This kind of sophisticated calculation raises problems for the chemist engaged in the challenge of designing polynuclear systems with predictable magnetic properties. It is extremely difficult to visualize the additional contributions arising from the configuration interaction, and it is even more difficult to predict their sign and their relative magnitude. In some way, these calculations resemble a "black box" which apparently is able to reproduce roughly the experimental data. This black box does not, at the present time, appear suitable enough for providing really useful information on the strategy to follow for a given interaction. Moreover, a further complication should be noted: the definition of the orthogonalized magnetic orbitals in Equation (18) is valid only when the dinuclear system is symmetrical. Dissymmetric complexes have so far never been treated according to *Anderson*'s formalism.

10. Anisotropic and Antisymmetric Interactions, and ESR Spectra

In addition to the S-T splitting, which is by far the main phenomenon, the interaction between two local doublet states may also lead to a splitting within the triplet state which is generally detectable in ESR spectroscopy. It may also lead to a coupling between singlet and triplet states (see Fig. 1).[72,73] This problem will now be briefly discussed in the light of the results established in the previous sections. The basic scheme of an ESR spectrum for a triplet state split in zero field is reproduced in Figure 29,

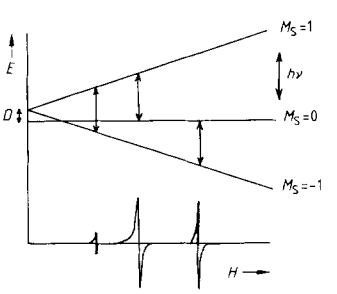


Fig. 29. Zero field splitting and ESR spectrum for a triplet state.

where the magnetic field is assumed to be parallel to the z axis of the axial symmetry. This spectrum exhibits two allowed transitions $\Delta M_S = \pm 1$, the separation of which depends on the axial zero field splitting parameter D, and a forbidden transition $\Delta M_S = 2$ at half field.

The zero field splitting within the triplet state has two origins, namely the dipolar interaction between magnetic dipoles, which varies roughly as d^{-3} (d being the distance between the metal centers) and the sum of the anisotropic and antisymmetric interactions.[74,75] In the case of symmetrical systems, for which the antisymmetric interaction is zero, the anisotropic interaction is due to the combined effect of the local spin-orbit coupling and of the interaction itself. To find appropriate expressions for the zero field splitting parameters, we must replace the magnetic orbitals Φ_A and Φ_B as defined in Section 3 by new orbitals which take into account the coupling between local ground state and excited states through the spin-orbit coupling.[72] The calculation of the relative energies of the low lying states becomes tedious, and, generally, the final expressions are very complicated. Since the aim of this paper is merely to present the general philosophy of the problem, only the simple case of a symmetrical copper(II) complex like **7** will be described here. The axial zero field splitting parameter D may then be approximated by

$$D \simeq \frac{1}{32}(\Delta g_z)^2 J_{xy,x^2-y^2} \tag{22}$$

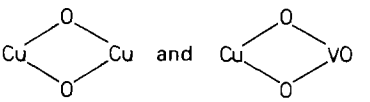
Δg_z is the deviation of the component g_z of the Zeeman factor for the monomeric fragment referred to $g_e = 2.0023$. This deviation comes from the second-order effect of the spin-orbit coupling. J_{xy,x^2-y^2} is the magnitude of the interaction between the xy-type ground state of an ion and the x^2-y^2 type excited state of the other ion, this interaction being assumed to be much larger than the other interactions between ground state and excited state. The important point in Equation (22) is that the interaction to be taken into account is not the interaction between the local ground states characterized by the S-T splitting J. In other words, it is in principle possible to deduce from D an order of magnitude for the interaction between the ground state of an ion and the excited state of the other ion.[35] This information cannot be derived from the magnetic data.

In the case of compound **7**, D is too small to be detected from the ESR spectrum.[56] This value of D, close to zero, is surprising at first sight, since interaction between the local ground states is large, with $J = -385.4\ cm^{-1}$. In fact, if the dipolar interaction between two metal ions separated by 5.15 Å is clearly negligible, the anisotropic interaction which involves the xy- and x^2-y^2-type orbitals located in the plane of the oxalato bridge can hardly be expected to be negligible. An interaction of the type J_{xy,x^2-y^2} through an oxalato bridge has already been described (cf. Section 6). It occurs between the local ground states of the Cu^{2+} and VO^{2+} ions in [(tmen)(H_2O)Cu(C_2O_4)VO(H_2O)(C_2O_4)], **12**. Symbolically, we may therefore write

$$\underset{\text{in [CuCu]}}{D} \approx \tfrac{1}{32}(\Delta g_z)^2 \cdot \underset{\text{in [Cu–] in [CuVO]}}{J} \tag{23}$$

where [CuCu] and [CuVO] denote the dinuclear complexes **7** and **12**, respectively, and [Cu–] denotes the monomeric fragment **3**. J in [CuVO], **12**, was found to be close to zero, which explains why D in [CuCu], **7**, is also close to zero. In all the other complexes with an extended bridge and exhibiting a strong antiferromagnetic interaction (for instance **13**, **16**, **18** and **19**), D was also found to be close to zero.[76]

A similar comparison between $Cu^{2+}Cu^{2+}$ pairs and $Cu^{2+}VO^{2+}$ pairs can be carried out with the networks:



In **1**, the ferromagnetic interaction is large with $J = 118\ cm^{-1}$. *Gatteschi* and co-workers extensively investigated the ESR spectra of doubly bridged hydroxocopper(II) dimers.[77,78] They found that, whatever the sign and the value of the S-T energy gap between the low lying states may be, D is much larger than what would be expected if only the dipolar interaction were operative. In fact, in these doubly hydroxo-bridged dimers, the anisotropic interaction is significant owing to the strong ferromagnetic interaction between the ground state of an ion and the x^2-y^2 excited state of the other. This interaction has the same orbital character as that occurring between the local ground states in **1**.

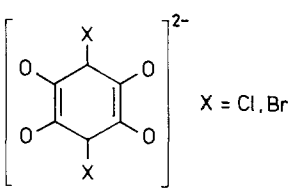
For dissymmetrical complexes, there is an additional contribution to the zero field splitting within the triplet state, namely for the antisymmetric interaction. In fact, the origin of this new contribution is the same as that of the anisotropic interaction, namely the synergic effect of the spin-orbit coupling and of the interaction.[79] The antisymmetric interaction is a first order term in $\Delta g J_{ij}$ instead of $(\Delta g)^2 J_{ij}$, which vanishes when the two monomeric fragments are related by a symmetry center. The antisymmetric interaction not only contributes to the zero field splitting, but also mixes the singlet and the triplet states. This mixing effect has been detected in many extended lattices. It leads to weak ferromagnetism.[79,80] The singlet-triplet interaction in dinuclear copper(II) complexes has not yet been detected. Dissymmetrical complexes like **10** and **15** are potentially suitable candidates for observing this phenomenon for the first time.

11. Conclusion and Outlook

The inorganic chemist also can be likened to Prometheus: He can transform matter, not only for pleasure or to prove his power, but in order to design new systems exhibiting desired physical or chemical properties. Such an ambition, when dealing with the magnetic properties of polynuclear systems, necessitates going many times through the steps of a cycle. These steps are: (i) the synthesis of a new compound, which one thinks will exhibit given magnetic properties; (ii) the determination of its crystal and molecular structure; (iii) the investigation of its magnetic properties and of its ESR spectrum, and—on the basis of these data—the determination of the nature and the relative energies of the low lying energy states; (iv) lastly, and not least, conceptual reflections on the real (non phenomenological) mechanism of the observed phenomena,

so that it is possible in the following cycle to synthesize a novel compound whose magnetic properties will be even closer to what is expected. In the last few years, we have shown that by working according to this scheme, it is actually possible to impose the nature and the order of magnitude on the interaction between the two magnetic centers of a dinuclear compound. The first success achieved in this way was the design of ferromagnetically coupled complexes, using the strategy of orthogonality of the magnetic orbitals. One of the greatest challenges in the sector of molecular materials is the synthesis of molecular ferromagnets, in which a ferromagnetic order would occur up to as high a critical temperature as possible. With spin moments there is no one- or two-dimensional magnetic order. Consequently, in the design of molecular ferromagnets three-dimensional ferromagnetic interactions between neighboring magnetic centers must be realized. This can be most effectively achieved by orthogonality of the magnetic orbitals. For instance, a chromium(III)-nickel(II) lattice is well suited for ferromagnetic behavior. Thus, there are three unpaired electrons occupying the three $t_{2g}(d_{xy}, d_{yz}, d_{zx})$ orbitals around a Cr^{3+} ion in an octahedral environment, and around a Ni^{2+} ion, also in octahedral surroundings, there are two unpaired electrons occupying the two $e_g(d_{z^2}, d_{x^2-y^2})$ orbitals. Since the overlap integrals $\langle t_{2g} | e_g \rangle$ are zero,[81] the ground state of such a Cr(III)-Ni(II) system should exhibit parallel spins of respectively 3/2 for chromium(III) and 1 for nickel(II). This orthogonality of the magnetic orbitals could also be realized with organic radicals such as nitroxide.[82] Several groups over the world are engaged in the search for the first molecular ferromagnet with a Curie temperature that is not too low.

Another challenge is the design of coupled systems with strong interactions between distant metal centers. The efficiency of the dithiooxamido-bridge in this respect has already been mentioned; significant interactions can also occur between more distant metal ions. For instance, through the chloranilato and the bromanilato bridges,



X = Cl, Br

singlet-triplet energy gaps of about -24 cm^{-1} were recently found.[83, 84]

Is there a limit beyond which no interaction is detectable? Our feeling (and it is still only a feeling) is that this limit, if it does exist, has not yet been reached. The synthesis of novel bridging ligands which are especially efficient at transmitting electronic effects over long distances is certainly a field of research deserving further development. An understanding of the mechanism of the interaction and skilful organic synthesis are invaluable tools in this sector. Useful information can also be gleaned from natural processes. In some biological systems the electronic information is apparently transmitted over distances as large as 10 Å or more.[85]

The ability to tune the interaction through a given bridging network by 'playing' on the nature of the terminal ligands L and L' is a noteworthy achievement in the area of molecular magnetism. Two examples of this achievement were given. The strategy used could, of course, be extended; a key factor is the synthesis of dissymmetrical complexes with $L \neq L'$, which provide two "adjusting screws" for tuning the interaction. In fact, at the moment the main difficulty lies in the synthesis of the complex; not all of the desired dissymmetrical systems could be prepared, probably because of the high strain that would be involved with some complexes.

Despite all the results obtained so far, the field of molecular magnetism is still largely open. Many problems remain unsolved or must first be specified:

(1) Compared to isotropic interactions very little is known about anisotropic interactions, and even less is known about antisymmetric interactions. Demonstration of the singlet-triplet interaction in dissymmetrical complexes would constitute a great step forward.

(2) The concept of magnetic orbitals and of overlap density between magnetic orbitals can only be visualized by carrying out polarized neutron diffraction studies and obtaining spin density maps. The few investigations of this kind that have already been reported in the literature are far from satisfactory.[86]

(3) So far, the influence of the molecular vibrations on the magnetic properties has been completely neglected. Two effects could be expected, namely a temperature-dependence of the energy gaps between low lying states[87] and phase transitions with drastic modification of the interactions. This latter effect has only recently been observed,[88] and absolutely deserves further investigation.

Finally, the challenge presented by the design of molecular ferromagnets should be emphasized once again. Today, the strategy to follow is known. The problem, and it is not an easy problem, is the application of this strategy in three-dimensional space. It is also conceivable that the magnitude of the interaction could be tuned by L, L' adjusting screws. In any case such systems represent quite important milestones on the way to molecular electronics.

The work presented in this paper is the result of a collective adventure initiated by my co-workers and myself. Together, we reflected on the basic concepts, we imagined the strategies, we chose the systems to be investigated, we performed the syntheses and the physical measurements. We then analyzed the results. I wish to express my deepest gratitude to M. F. Charlot, J. J. Girerd, Y. Journaux, M. Julve, I. Morgenstern, R. Veit and M. Verdaguer, and would also like to thank my colleagues involved in the structural aspects of this work, namely J. Galy, A. Gleizes, J. Gouteron, J. Jaud, S. and Y. Jeannin, A. Michalowicz and J. Sletten. The work was financially supported by the CNRS, the Université de Paris Sud, and the SNEA.

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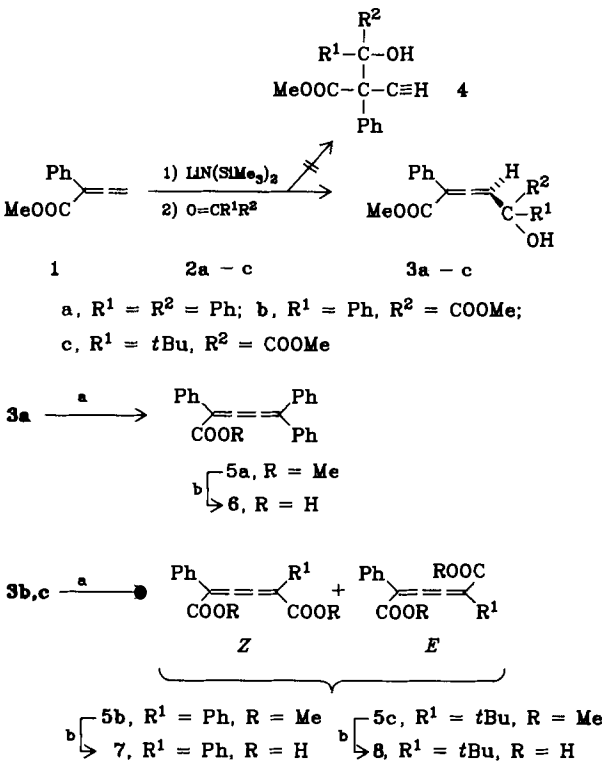
Synthesis of 1,2,3-Butatrienecarboxylic Acids**

By *Franz W. Nader** and *Claus-Dieter Wacker*

Owing to their bond system, the cumulenes represent a separate entity in the class of unsaturated compounds. Whereas numerous derivatives of the allenes have been prepared and investigated,[1] in the butatriene series only very few derivatives with functional groups have been reported,[2] among them no butatrienecarboxylic acids. Since we were interested, inter alia, in the solid state chemistry of such butatrienes and their complexes with amides,[3] we decided to search for a general entry to this class of compounds.

The conventional methods of butatriene synthesis[4] such as dehydrohalogenations (of 2-halogenobutadienecarboxylic acid derivatives) with bases,[5] dehalogenations (of 2,3-dihalogenodienecarboxylic acid derivatives[5]) with Zn or other reducing agents, and 1,4-elimination reactions (on 1,4-dihydroxy-2-butynecarboxylic acid derivatives[6]) with $SnCl_2$, P_2I_4 etc., failed. Finally, a successful strategy proved to be that based on the concept of constructing the butatriene system stepwise from homologous allene derivatives[7] (Scheme 1).

As starting material we used the 1-phenylallenyl ester **1**, which was formed in 75–79% yield by Wittig reaction of (α-methoxycarbonylbenzylidene)triphenylphosphane[8] with acetyl chloride using the method of *Lang* and *Hansen*.[9] Reaction of **1** with equimolar amounts[10] of lithium hexamethyldisilylamide at −78 °C afforded the mesomerically stabilized anion, which reacted with benzophenone **2a** and the keto esters **2b** and **2c** to give the allene alcohols **3a–c**.[11] The isomeric alkynols **4**[12] are not formed, obviously for steric reasons. The *p*-toluenesulfinyl residue proved to be a suitable leaving group for the subsequent 1,2-elimination. In the preparation of the sulfinyl ester of **3a**, elimination and formation of the desired butatrienecarboxylate **5a** already occurs at $T < -20$ °C. The *p*-toluenesulfinyl esters could therefore not be isolated and characterized. The extreme easiness of this elimination[13] enabled a one-pot variant of the reaction sequence **1** → **5**, thus circumventing the high losses in yield during purification of the alcohols **3**:[11] a solution of *p*-toluenesulfinyl chloride in THF was added dropwise at −78 °C to the reaction mixture containing the lithium alkoxides of **3** which had previously been treated with an equimolar amount of triethylamine; finally, the mixture was allowed to warm to room temperature.



Scheme 1. a) *p*-$MeC_6H_4S(O)Cl$, NEt_3, $T = -78$ °C. b) KOH/[18]crown-6, H_2O/THF (phase transfer catalysis).

Purification by column chromatography furnished intense yellow crystals (m.p. 94–95 °C) of **5a** in 31% yield (referred to **1** and with maximally 50% conversion of **2a**). Slow crystallization at −20 °C yielded a second, orange-colored modification of **5a** (m.p. 112–113 °C). Both crystal forms are storable in the dark, but are photolabile.

In an analogous way the keto ester **2b** affords a *Z/E* mixture of the butatriene diester **5b**. Treatment of the reaction mixture with ethanol leads to crystallization of isomerically pure *E*-**5b** (no cumulene band in the IR spectrum; strong butatriene band at 2040 cm^{-1} in the Raman spectrum) in 52% yield. Crystalline *E*-**5b** can be stored at room temperature, even when exposed to light; in solution at room temperature, the *Z/E* equilibrium already observed by *Kuhn* et al.[14] with unsymmetrically substituted butatrienes is established. From the second fraction obtained on column chromatographic separation of such an equilibrium mixture at −20 °C, *Z*-**5b** can be isolated as an orange colored powder, the *Z*-stereochemistry of which follows from the IR butatriene band observed at 2033 cm^{-1}. *Z*-**5b** is thermolabile and photoactive, but can be stored for long periods of time at −78 °C when not exposed to light. The equilibrium constant for the isomerization *E*-**5b** ⇌ *Z*-**5b** was determined ^{1}H-NMR spectroscopi-

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cally:[15] The *E*-isomer (with $K = 1.9$, in $CDCl_3$) is favored.

The keto ester **2c** furnishes the *Z*/*E* mixture of the butatrienediester **5c**. In contrast to **5b**, **5c** is configurationally stable at room temperature. Consequently, the isomers could be separated by conventional column chromatography. *E*-**5c** and *Z*-**5c** were obtained in 33% and 9% yield, respectively, in each case as pale yellow, crystalline and stable compounds (m.p. 87–88 °C and 71–73 °C, respectively). All the butatriene derivatives **5** prepared were characterized by accurate analytical and spectroscopic data.

The esters **5** can be converted into the carboxylic acids **6**–**8**. Since they have a pronounced tendency to undergo nucleophilic addition,[6] protic conditions had to be avoided. The hydrolysis was carried out with [18]crown-6 as phase transfer catalyst of the THF/KOH system. **5a** thus furnished the acid **6** in 83% yield as an orange-yellow crystalline substance. *E*- and *Z*-**5c** yielded the isomerically pure dicarboxylic acids *E*- and *Z*-**8**, respectively, in 65% yield as bright-yellow crystals. In contrast, *E*-**5b** forms a *Z*/*E* mixture of the dicarboxylic acids **7**, from which isomerically pure, orange-colored *E*-**7** precipitates in 71% yield upon crystallization. *Z*-**7**, on the other hand, could—due to sparing solubility—only be obtained by a very tedious chromatographic separation.

Upon determination of the melting points, still in the crystalline state, *Z*-**7** and *Z*-**8** rearranged into the *E*-isomers.

The dicarboxylic acids *E*- and *Z*-**7**, like their esters **5b**, have different ^{1}H-NMR spectra;[16] the equilibrium constant *K*, with a value of 2.9 (in $[D_6]$DMSO) in favor of the *E* isomer, is significantly higher than in the case of **5b**.

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[10] An excess of metalating agent leads to dimetalation, which causes substantial losses in yield.
[11] According to ^{1}H-NMR spectra the reaction mixtures contain ca. 50% **3a**, 75–80% **3b**, and 75% **3c**. The chromatographic purification afforded **3a** in only 30–35% yield as a readily decomposable oil. **3b** and **3c** (diastereomeric mixtures) were isolated in 40 and 45% yield, respectively, as viscous yellowish oils that decompose at room temperature. **3a**–**c** are characterized by accurate analytical and spectroscopic data.
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[15] ^{1}H NMR (300 MHz, $CDCl_3$): *E*-**5b**: $\delta = 3.94$ (s, 6H, OCH_3), 7.33–7.47 (m, 6H aromatic), 7.92–8.03 (m, 4H, *o*-H); *Z*-**5b**: $\delta = 3.95$ (s, 6H, OCH_3), 7.34–7.48 (m, 6H, aromatic), 7.76–7.88 (m, 4H, *o*-H).
[16] ^{1}H-NMR (90 MHz, $[D_6]$DMSO): *E*-**7**: $\delta = 7.34$–7.61 (m, 6H aromatic), 7.77–8.05 (m, 4H, *o*-H); *Z*-**7**: $\delta = 7.33$–7.55 (m, 6H aromatic), 7.64–7.81 (m, 4H, *o*-H).

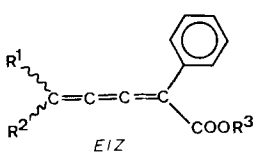
On the Thermal Behavior of Butatrienecarboxylic Acid Derivatives: Crystal and Molecular Structure of a [4]Radialene Tetracarboxylic Ester**

By *Franz W. Nader,* Claus-Dieter Wacker, Hermann Irngartinger, Ursula Huber-Patz, Rainer Jahn,* and *Hans Rodewald*

The cycloaddition reactions of cumulenes are of special interest, both from the preparative as well as the mechanistic point of view. The thermal behavior of numerous allene derivatives has been studied in detail.[1] Some relatively stable butatrienes have been thermally converted, via [2+2]-cycloaddition at the central cumulene bond, into [4]radialenes.[2–4] One exception so far is the unsubstituted butatriene, which already reacts thermally at 0 °C—sometimes explosively. The [4+4]-cycloaddition product 1,5-cyclooctadiyne could be isolated in 2% yield from the reaction mixture.[5]

The synthesis of the stable, crystalline butatrienecarboxylic acid derivatives **1**–**3** in isomerically pure form[6] enabled, inter alia, the investigation of its thermal behavior in the crystalline state and in solution.

The esters *Z*-**2a** and *E*-**2a** and the carboxylic acids *Z*-**2b** and *E*-**2b** were investigated.[7] The two *Z*-isomers were converted almost completely into the *E*-forms in the solid state, already slowly at room temperature, but much faster on heating (*Z*-**2a**: no longer detectable in the ^{1}H-NMR spectrum after two days at 70–75 °C).



1, $R^1 = R^2 = C_6H_5$, $R^3 = CH_3$

2a, $R^1 = C_6H_5$, $R^2 = COOCH_3$, $R^3 = CH_3$
2b $= COOH$ $= H$

3a, $R^1 = C(CH_3)_3$, $R^2 = COOCH_3$, $R^3 = CH_3$
3b $= COOH$ $= H$

Crystals of the carboxylic acid *E*-**2b** proved to be stable up to 110–120 °C; at 140–150 °C, a black viscous mass is slowly formed (after ca. 14 days), from which no well-defined products could be isolated. On the other hand, crystals of the ester *E*-**2a** underwent complete reaction within 5 days without any observable melting during conversion. Aside from a small amount of polymeric material (< 5%), only a bright yellow substance was formed, which, after column chromatographic separation of the polymeric material, could be isolated in crystalline form[9] in 75% yield.[8, 9] Its mass spectrum was consistent with a dimeric structure [*m/z* 625 ($M - CH_3$), CI(CH_4): *m/z* 641 ($M + 1$)]. The absence of a cumulene band in the IR spectrum indicated presence of a [4]radialene, which is consistent with the ^{13}C-NMR data.[9] Complete elucidation of the structure was accomplished by X-ray diffraction[10] (Fig. 1).

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Surprisingly, the results of this analysis revealed that the species formed was not the [4]radialene **4**, as would have been expected from the configuration of the starting compound *E*-**2a**, but its (1*Z*,2*Z*,3*Z*,4*Z*) diastereomer[11] **5**.

In the [4]radialene **5** the four-membered ring is considerably more puckered (puckering angle 142.6(4)°) than in any of the previously reported [4]radialenes.[12] The torsion angles of the four-membered ring are on average 26.3(2)°

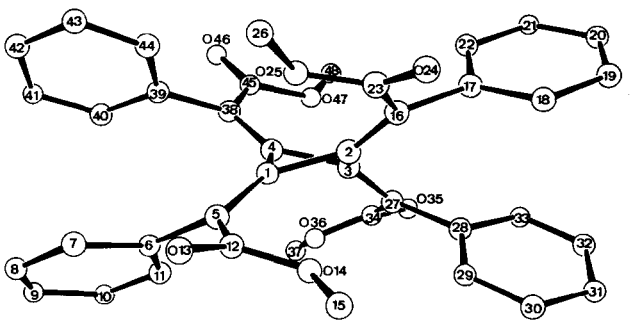
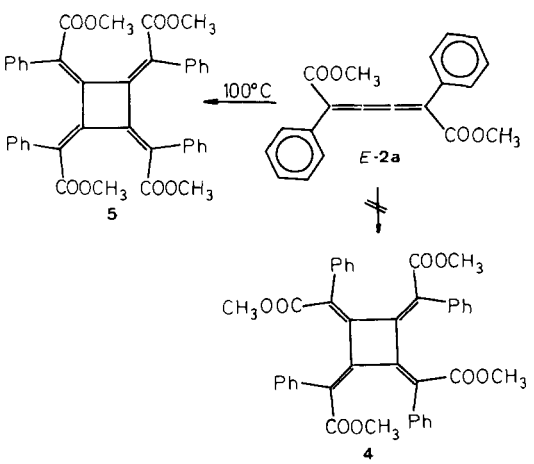


Fig. 1. Crystal structure of **5**. Selected bond lengths [Å] and angles [°]: C1-C2 1.494(4), C2-C3 1.498(4), C3-C4 1.499(4), C1-C4 1.494(4), C1-C5 1.336(4), C2-C16 1.334(4), C3-C27 1.342(3), C4-C38 1.336(4); averaged values: C_{Ph}-C_{sp^2} 1.484(8), C_{sp^2}-COOMe 1.485(12), (C-C)$_{aromat.}$ 1.377(11), C=O 1.197(9), C_{sp^2}-O 1.322(4), O-CH_3 1.449(6); C1-C2-C3 86.6(2), C2-C3-C4 87.1(2), C1-C4-C3 86.5(2), C2-C1-C4 87.4(2), C2-C1-C5 137.4(3), C4-C1-C5 132.2(3), C1-C2-C16 138.0(2), C3-C2-C16 132.3(3), C2-C3-C27 131.8(3), C4-C3-C27 137.6(3), C3-C4-C38 138.3(3), C1-C4-C38 131.2(2), C1-C5-C6 121.7(3), C1-C5-C12 120.2(3), C6-C5-C12 118.1(3), C2-C16-C23 121.3(3), C2-C16-C17 121.5(2), C17-C16-C23 117.0(3), C3-C27-C28 121.3(3), C3-C27-C34 120.9(3), C28-C27-C34 117.6(2), C4-C38-C39 120.4(3), C4-C38-C45 123.4(3), C39-C38-C45 116.0(3).

(internal) and 65.6(5)° (external). In addition to the puckering, the radialene double bonds are inclined at 13.8° to the plane of the three attendant carbon atoms of the four-membered ring. Due to steric hindrance of neighboring substituents the radialene double bonds are twisted. The angles of twist are between 12.6° and 18.3° on the "ester side" and between −5.2° and −11.1° on the "phenyl



side". The phenyl and ester groups are twisted counter to each other relative to the double bonds (46.5° to 67.7° and −2.6° to −47.9°, respectively), such that no regular propeller arrangement results.

Within the limits of experimental error, the bond lengths in the four-membered ring are equal (1.496(4) Å), as are also the lengths (1.337(4) Å) of the double bonds, and in each case they lie in the expected range (see Fig. 1).

The high stereospecificity of the solid state reaction is indicative of a crystal lattice control, whereby the stereochemical result requires that both molecules have to assume a *Z*-type rotational form during the course of the dimerization (possibly via a diradical mechanism), since the radialene **5** is made up of two *Z*-configurated butatriene units.

Compared to the solid-state reaction, the corresponding reaction in solution (boiling toluene) proceeds very inhomogeneously. Aside from 20% monomer (*E*/*Z* mixture), only ca. 32% of the dimer **5** could be detected (by ^{1}H-NMR spectroscopy) after five days. The remaining product was an inseparable mixture, which presumably contained the isomeric [4]radialenes[8] such as **4**.

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(*E*)-**2a**, 98066-47-8; (*Z*)-**2a**, 98066-46-7; (*E*)-**2b**, 98066-49-0; (*Z*)-**2b**, 98066-48-9; **5**, 98195-46-1; toluene, 108-88-3.

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[7] The uncatalyzed thermolyses of butatrienes usually require temperatures in excess of 100°C, a reason for having initially ruled out the lower melting compounds **1** (m.p. 94–95°C), *Z*-**3a** (m.p. 71–73°C), and *E*-**3a** (m.p. 87–88°C) as candidates for solid-state reactions.

[8] The substance is stable in the solid state; in solution, however, novel compounds are formed, which, on grounds of the similar ^{1}H-NMR and ^{13}C-NMR spectra, are presumably isomers. The solution contains only ca. 80% of the original product after two days, thus explaining the losses observed on chromatographic purification.

[9] Lemon-yellow crystals from CH_2Cl_2/methanol at −15°C, m.p. 213–216°C; ^{1}H-NMR (90 MHz, $CDCl_3$): $\delta = 3.72$ (s, 12H, OCH_3), 6.84–7.26 (m, 20H, aromatic); ^{13}C-NMR (22.63 MHz, $CDCl_3$): $\delta = 52.11$ (q, OCH_3), 123.80 (s, olefinic C), 127.76/129.10 (d, aromatic CH), 134.54 (s, aromatic C1), 142.36 (s, olefinic C), 166.77 (s, C=O); UV (cyclohexane): $\lambda_{max} = 259$ (log$\varepsilon = 4.3$), 374 nm (4.17). $C_{40}H_{32}O_8$ (640.7); calc. C 74.99%, H 5.03%; found: C 74.97%, H 5.24%.

[10] Crystal dimensions $0.5 \times 0.4 \times 0.4$ mm^3 (from CH_2Cl_2). $a = 20.996(3)$, $b = 10.283(3)$, $c = 32.572(5)$ Å, $\beta = 106.51(1)°$; C2/c; $Z = 8$; $\rho_{calc} = 1.262$ g cm^{-1}. $Mo_{K\alpha}$ radiation, Enraf Nonius CAD4 diffractometer, graphite monochromator; $\sin\theta/\lambda = 0.55$ Å^{-1}; 4826 independent reflections (2497 observed, $I \geq 3\sigma(I)$); $R = 0.040$. Further details of the crystal structure investigation are available on request from the Fachinformationszentrum Energie, Physik, Mathematik GmbH, D-7514 Eggenstein-Leopoldshafen 2, on quoting the depository number CSD-51502, the names of the authors, and the full citation of the journal.

[11] In the case of the radialenes described here, four *cis-trans* isomers are possible. Owing to the equivalence of the ring atoms, the usual *Z*/*E* convention fails. Even recourse to the more recently recommended sequence rule 3 (V. Prelog, G. Helmchen, Section 5.3.1 in *Angew. Chem. 94* (1982) 614; *Angew. Chem. Int. Ed. Engl. 24* (1985) 567) does not provide unambiguous descriptors for this problem. An invariant designation of the isomers is achieved, however, if the stereochemistry of the butatrienes on which the [4]radialenes are based is taken into consideration. In **5**, this is likewise the *Z*-butatriene for the 1,2, the 2,3, the 3,4 and the 4,1 bonds. **4** is correspondingly built up of *E*-units, and therefore has the descriptors 1*E*,2*E*,3*E*,4*E*. The two remaining isomers, each of which are formed from one *Z*- and one *E*-butatriene, are to be designated as 1*Z*,2*Z*,3*E*,4*E* and 1*Z*,2*E*,3*Z*,4*E*, respectively.

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Misinterpretation of CC Bonding through Unusually Large $^2J_{CC}$ Values—a Caveat for the Use of INADEQUATE-^{13}C-NMR Spectroscopy**

By *Hans Bauer, Joachim Buddrus,* Wolfgang Auf der Heide,* and *Wolfgang Kimpenhaus*

Dedicated to Professor Robert Kosfeld on the occasion of his 60th birthday

Recourse is increasingly being made to ^{13}C-^{13}C couplings for the structural elucidation of organic compounds;[1-6] thereby, double quantum coherence NMR spectroscopy with the INADEQUATE pulse sequence has proven especially helpful.[7] One presupposes that a CC coupling above a certain value arises from a CC bonding. It now emerges, however, that this does not always hold true.

The one-dimensional INADEQUATE-^{13}C-NMR spectrum of 3-butoxy-2,4,4-trichlorocyclobutenone **2d** shows, in addition to the expected ^{13}C-^{13}C couplings, an inexplicably large coupling between C-2 and C-4 (64.1 Hz) (Fig. 1); this value is typical for couplings between directly bonded C-atoms. Since there is no doubt about the structure,[8] this value can only be reconciled with a coupling over two bonds. $^2J_{CC}$ values[9] are generally not greater than 5 Hz; and even in exceptional cases, for instance the coupling in ketones via the carbonyl group, the values do not exceed 20 Hz. We have therefore investigated further compounds exhibiting the structural characteristics of **2d**.

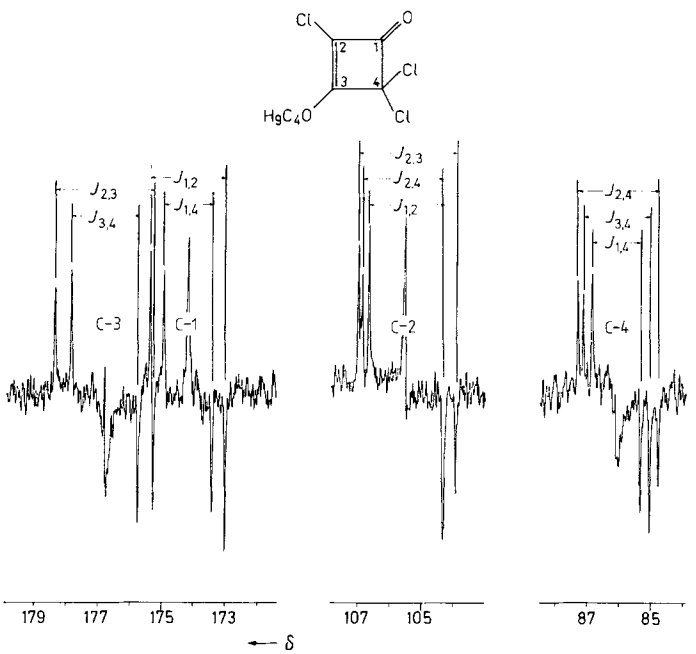
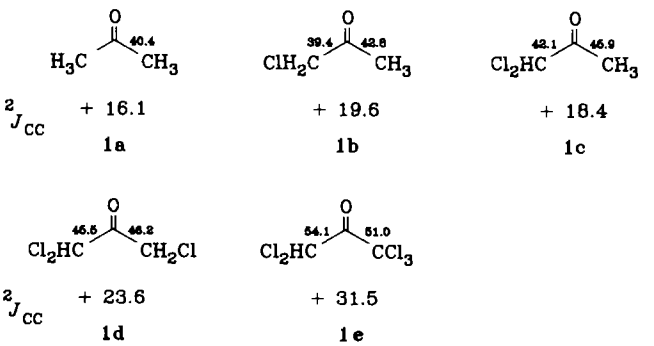


Fig. 1. INADEQUATE-^{13}C-NMR spectrum of **2d** at 25 MHz (three sections). Solution: 1.5 g of **2d** and ca. 10 mg of Cr(acac)$_3$ (relaxation reagent) in 1 mL of C_6D_6. Recording conditions: 3000 Hz, 16 K. The delay τ in the pulse sequence [7] corresponds to $J_{CC}=58$ Hz. 35404 scans with 5 s repetition time.

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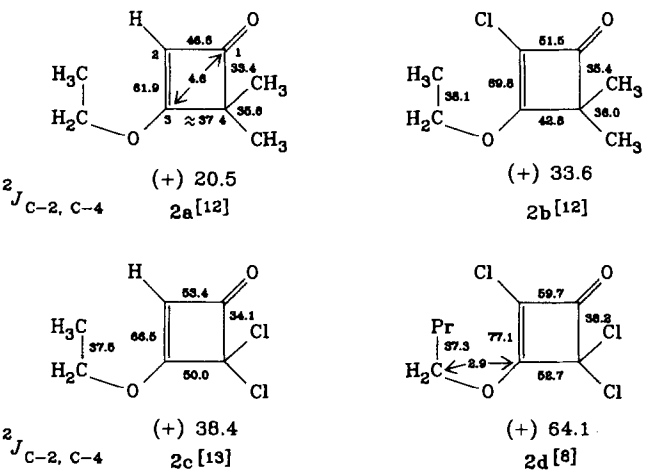
[**] We thank Herr *H. Herzog*, Dortmund, for his help in preparing and measuring the NMR spectra of some of the compounds; thanks are also due to Priv.-Doz. Dr. *K. Roth*, Berlin, for some helpful discussions.

In the case of acetone, **1a**, and the chlorinated derivatives **1b**-**1e** (Scheme 1) $^2J_{CC}$ increases from +16.1 Hz in **1a**[10] to 31.5 Hz in **1e**. The positive signs of **1b**-**1e** follow from the steady increase in the absolute values, an increase being interrupted only in the case of **1c**. The substituent effect of a chlorine atom on $^2J_{CC}$ is on average ca. ±2.5 Hz.



Scheme 1. $^1J_{CC}$ and $^2J_{CC}$ in Hz. For ^{13}C chemical shifts see [11].

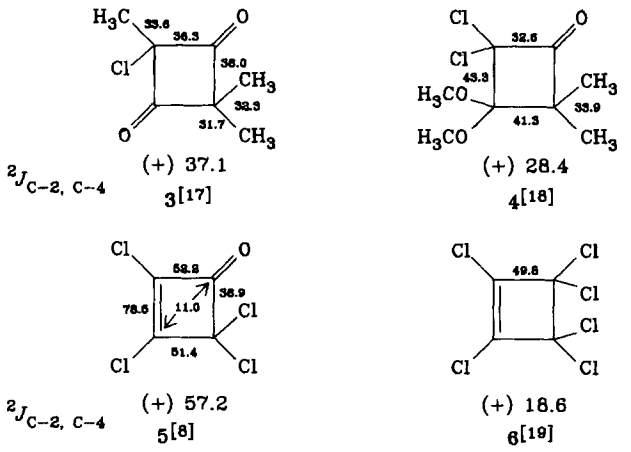
In the 3-alkoxycyclobutenone series **2a**-**2d** (Scheme 2) $^2J_{C\text{-}2,C\text{-}4}$ increases from (+)20.5 Hz in **2a** to (+)64.1 Hz in **2d**. The signs are most likely also positive, since the influence of the chlorine atoms should be the same as in the case of the acetone compounds. A comparison of the values for **2a** and **2b** and for **2c** and **2d** shows that the substituent effect of the chlorine atoms on $^2J_{CC}$ is, in these instances, respectively, ca. 13 and 26 Hz, i.e. distinctly greater than in the acetone series.



Scheme 2. $^1J_{CC}$ and $^2J_{CC}$ in Hz. For ^{13}C chemical shifts see [14].

The coupling constants $^2J_{C\text{-}2,C\text{-}4}$ of **2a**-**2d** result, in each case, from the contributions of two couplings (via the C-2/C-1/C-4 and C-2/C-3/C-4 bonds).[15,16] For comparison, the compounds **3**-**6** were investigated (Scheme 3).

The coupling constant $^2J_{C\text{-}2,C\text{-}4}$ in **3**, which has two identical coupling pathways, in each case via a carbonyl group, is 37.1 Hz; each coupling contributes 18.5 Hz to the total coupling. Since the corresponding coupling constant in **2b**-**2d**, and also in **4** and **5**, is considerably larger, a substantial portion of the same sign of the coupling must arise from the coupling via the CC double bond; this coupling also exists in **6**, so the coupling constant of 18.6 Hz is not surprising.



Scheme 3. $^1J_{CC}$ and $^2J_{CC}$ in Hz. For ^{13}C chemical shift see [20].

As yet, there is no explanation for the unusually large $^2J_{CC}$ values sometimes observed in chlorinated ketones. Regardless of this they indicate that care must be taken in determining the CC connectivities of unknown compounds via ^{13}C-^{13}C couplings: *not every coupling constant that is greater than ca. 25 Hz is an indication of CC bonding.*

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1a, 67-64-1; **1b**, 78-95-5; **1c**, 513-88-2; **1d**, 921-03-9; **1e**, 1768-31-6; **2a**, 4313-48-8; **2b**, 98303-51-6; **2c**, 37873-58-8; **2d**, 2892-59-3; **3**, 56513-93-0; **4**, 78550-00-2; **5**, 3200-96-2; **6**, 6130-82-1.

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[14] ^{13}C chemical shifts (in $CDCl_3$) (C-1, C-2, C-3, C-4, further C-atoms): **2a**: 192.9, 102.0, 190.0, 59.3, 19.0 ($2CH_3$), 68.9 (OCH_2), 13.6 (CH_3); **2b**: 190.8, 92.8, 184.9, 58.8, 19.2 ($2CH_3$), 70.4 (OCH_2), 15.2 (CH_3); **2c**: 178.4, 110.0, 182.4, 87.6, 72.0 (OCH_2), 14.4 (CH_3); **2d**: 173.4, 104.8, 176.1 (*t*, $J_{C,H}$ = 2.9 Hz), 85.4, 75.2 (OCH_2).
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[20] ^{13}C chemical shifts (in $CDCl_3$) (C-1, C-2, C-3, C-4): **3**: 204.8, 75.8, 204.8, 70.5, 21.0 (CCl-CH_3), 18.7 ($2CH_3$); **4**: 200.9, 88.7, 103.2, 64.2, 53.2 ($2OCH_3$), 20.4 ($2CH_3$); **5** and **6** see G. E. Hawkes, R. A. Smith, J. D. Roberts, *J. Org. Chem. 39* (1974) 1276.

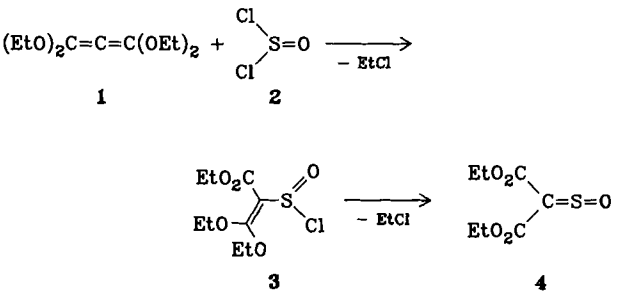
Diethyl Thioxomalonate *S*-Oxide; a Sulfine as Reactive Intermediate**

By *Rolf W. Saalfrank** and *Walter Rost*

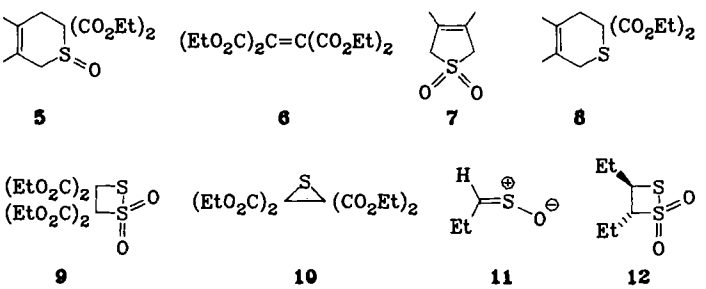
Dedicated to Professor Hans Jürgen Bestmann on the occasion of his 60th birthday

1,3-Bis(dialkylamino)-1,3-diethoxyallenes—malonamide dianion equivalents—react with disubstituted malonyl chlorides to give allene-1,1-dicarboxamides.[1] By the choice of appropriate combinations of substituents, this transallenation[2] has wide scope. Tetraethoxyallene—a malonic ester dianion equivalent—reacts with phosgene and thiophosgene to give bis(ethoxycarbonyl)ketene and bis(ethoxycarbonyl)thioketene, respectively.[3]

We have now been able to generate diethyl thioxomalonate *S*-oxide **4** as an intermediate by reaction of tetraethoxyallene **1**[4] with thionyl chloride **2**. The ketene acetal **3**, formed in the first step with elimination of ethyl chloride, spontaneously eliminates ethyl chloride again to afford the heteroallene **4**.



4 can be trapped with 2,3-dimethyl-1,3-butadiene in a Diels-Alder reaction, forming diethyl 3,6-dihydro-4,5-dimethyl-2*H*-thiopyran-2,2-dicarboxylate 1-oxide **5** (42% yield).[7,8] Surprisingly, tetraethyl ethylenetetracarboxylate **6** (31%), 2,5-dihydro-3,4-dimethylthiophene 1,1-dioxide **7** (21%), and diethyl 3,6-dihydro-4,5-dimethyl-2*H*-thiopyran-2,2-dicarboxylate **8** (22%) are also formed (Table 1). We assume that the dimerization of **4** to tetraethyl 1,2-dithietane-3,3,4,4-tetracarboxylate 1,1-dioxide **9**[9] competes with the trapping of **4** by 2,3-dimethyl-1,3-butadiene. By elimination of sulfur dioxide, **9** affords the intermediate tetraethyl thiiranetetracarboxylate **10**, which finally eliminates sulfur[11] to give the olefin **6**. The intermediacy of **9** and its



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decomposition explain in a simple manner the product **7**, which is formed in a cheleotropic reaction from 2,3-dimethyl-1,3-butadiene and the sulfur dioxide already present.[12] The formation of **8** has not yet been unequivocally explained. **8** is probably formed by reduction of **5** by the elemental sulfur that was formed earlier.[13] The intermediacy of **9** is supported, moreover, by the fact that the lachrymatory factor of onions, *Z*-thiopropionaldehyde *S*-oxide **11**, dimerizes to the stable *E*-3,4-diethyl-1,2-dithietane 1,1-dioxide **12**.[10] Furthermore, it was possible to demonstrate the existence of **9** in the crude product by mass spectroscopy [*m/z* 412 (M^+)]. All attempts to obtain pure **9** have been unsuccessful and have led exclusively to **6**. When the reaction of **1** and **2** is carried out in the absence of a trapping agent for sulfine, **6** is again the only product isolated in pure form.

Table 1. Physical data for the compounds **5**, **6**, **7**, **8**, and **15**.

5: IR (film): $\nu = 1730$ cm^{-1} (C=O); ^{13}C-NMR ($CDCl_3$): $\delta = 13.92$ and 13.98 (CH_3), 19.26 and 20.32 (CH_3), 28.15 and 51.57 (CH_2), 62.55 and 63.07 (OCH_2), 70.53 (C_q), 116.33 and 125.43 (C=), 165.36 and 165.75 (C=O); b.p. = 117 °C/0.1 torr

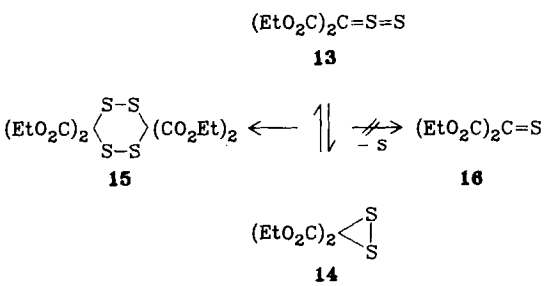
6: IR (KBr): $\nu = 1735$ cm^{-1} (C=O); ^{13}C-NMR ($CDCl_3$): $\delta = 13.83$ (4CH_3), 62.52 (4OCH_2), 135.35 (2C=), 162.29 (4C=O); m.p. = 56 °C

7: IR (KBr): $\nu = 1300$ and 1110 cm^{-1} (SO_2); ^{13}C-NMR ($CDCl_3$): $\delta = 14.56$ (2CH_3), 60.61 (2CH_2), 125.50 (2C=); m.p. = 135 °C

8: IR (film): $\nu = 1725$ cm^{-1} (C=O); ^{13}C-NMR ($CDCl_3$): $\delta = 13.89$ (2CH_3), 19.05 and 19.96 (2CH_3), 30.76 and 37.68 (CH_2), 56.67 (C_q), 62.09 (2OCH_2), 122.83 and 125.31 (C=), 168.66 (2C=O); b.p. = 97 °C/0.1 torr

15: IR (KBr): $\nu = 1720$ (C=O); ^{13}C-NMR ($CDCl_3$): $\delta = 13.92$ (4CH_3), 62.52 (2C_q), 63.77 (4CH_2), 165.84 (4C=O); m.p. = 56 °C

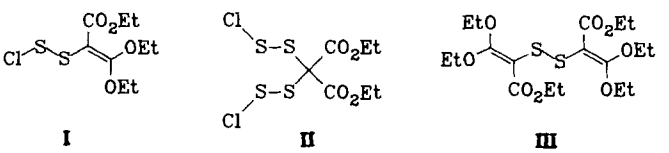
If tetraethoxyallene **1** is reacted with disulfur dichloride[14] instead of with thionyl chloride **2**, no diethyl thioxomalonate *S*-sulfide **13** can be trapped with 2,3-dimethyl-1,3-butadiene. (**13** possibly exists in equilibrium with the isomeric diethyl dithiiranedicarboxylate **14**[15, 16].) Instead, tetraethyl 1,2,4,5-tetrathiane-3,3,6,6-tetracarboxylate **15**[17] is isolated in 83% yield (Table 1). We assume that **15** is formed by dimerization of the isomers **13**/**14**.[18] Apparently, **13** and/or **14** do not eliminate sulfur, since no diethyl thioxomalonate **16** or its dimer can be detected.[15, 19]



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1, 85152-89-2; **2**, 7719-09-7 **4**, 98194-64-0; **5**, 96745-90-3; **6**, 6174-95-4; **7**, 18214-56-7; **8**, 66950-00-3; **15**, 98194-65-1; 2,3-dimethyl-1,3-butadiene, 513-81-5; toluene, 108-88-3, sulfur dichloride, 10545-99-0.

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[11] Cf. S. S. Bhattacharjee, H. Ila, H. Junjappa, *Synthesis 1984*, 249.
[12] H. J. Backer, J. Strating, C. M. H. Cool, *Recl. Trav. Chim. Pays-Bas 58* (1939) 778.
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[16] A. Senning, *Angew. Chem. 91* (1979) 1006; *Angew. Chem. Int. Ed. Engl. 18* (1979) 941.
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Do $Cp(CO)_2Mn$ Fragments Stabilize Radicals?**

By *Renate Gross* and *Wolfgang Kaim**

$Cp(CO)_2Mn$ fragments [Cp = η^5-C_5H_5(Cp^0), η^5-C_5H_4Me (Cp^1), η^5-C_5Me_5(Cp^5)] can stabilize diamagnetic, unstable molecules.[1] Three recent studies were concerned with the formation of radical complexes involving these metal fragments,[2–4] and although each of the complexes described has one unpaired electron, they differ significantly in the distribution of spin. For anionic, binuclear coordination compounds of pyrazine, the unpaired electron was shown by ESR spectroscopy to be localized largely in the π-system of the heterocyclic ligand;[3] for the complexes $[Cp(CO)_2(L)Mn]$ (L = NH(*m*-$C_6H_4CH_3$),[2] S*t*Bu, and SePh[4]), only a large ^{55}Mn coupling constant was ob-

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served. We report here on the ESR spectroscopic distinction between genuine radical complexes and those compounds that must be described as low-spin Mn^{II} systems.

We were able to obtain the radical anions of 4-cyanopyridine **1**, 4,4'-bipyridine **2**, and terephthalonitrile **3** with coordinated $Cp^{1}(CO)_2Mn^{I}$ fragments[5] analogously to the preparation of pyrazine radical complexes.[3] At room temperature, $\mathbf{1}^{\odot\ominus}$ forms an N^1-coordinated[5b] mononuclear radical complex (Fig. 1). $\mathbf{2}^{\odot\ominus}$ and $\mathbf{3}^{\odot\ominus}$ yield binuclear complexes, even though the neutral ligand **3** only affords the mononuclear complexes $[Cp(CO)_2(\mathbf{3})Mn]$;[5c] this is due to the increased basicity of reduced ligands.[6] In all these cases, the ESR data (Table 1) indicate that radical complexes are present, i.e., the spin distribution is little changed compared with that in the free radical anions[7] and the g factors are only slightly smaller than $g_{electron} = 2.0023$.[3]

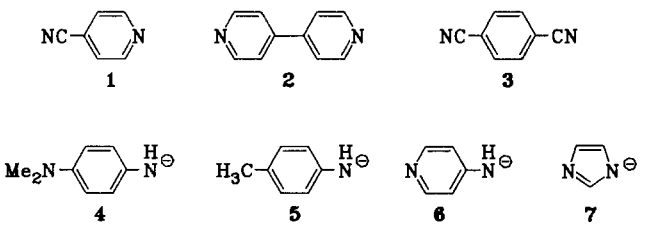


Table 1. ESR data of paramagnetic $Cp(CO)_2Mn$ complexes [a].

Compound	g	$a(^{55}Mn)$	$a(^{14}N)$	$a(^{1}H)$
Radical anion complexes [b]				
$[(pyrazine^{\odot\ominus})\{Cp^{1}(CO)_2Mn\}_2]$ [3]	1.9997	0.750	0.863	0.226 (4 H)
$[Cp^{1}(CO)_2(\mathbf{1}^{\odot\ominus})Mn]$	2.0005	0.655	0.725	0.211 (2 H, 1 N)
				0.154 (2 H)
$[(\mathbf{2}^{\odot\ominus})\{Cp^{1}(CO)_2Mn\}_2]$	2.0011	0.463	0.463	0.207 (4 H)
				0.050 (4 H)
$[(\mathbf{3}^{\odot\ominus})\{Cp^{1}(CO)_2Mn\}_2]$	2.0001	0.457	0.283	0.154 (4 H)
Mn^{II} systems				
$[Cp^{1}(CO)_2(\mathbf{4})Mn]$	2.0086	4.24	[c]	
$[Cp^{0}(CO)_2(m\text{-}C_7H_7NH)Mn]$ [2]	2.0114	5.0	—	—
$[Cp^{5}(CO)_2(\mathbf{5})Mn]$	2.014	5.09	—	—
$[Cp^{1}(CO)_2(\mathbf{6})Mn]$	2.022	5.5	—	—
$[Cp^{1}(CO)_2(7)Mn]$	2.035	6.1	—	—
$[Cp^{5}(CO)_2(t\text{BuS})Mn]$ [4]	2.031	5.14	—	—
$[Cp^{0}(CO)_2(\text{PhSe})Mn]$ [4]	2.069	4.61	—	—

[a] Coupling constants a [mT]. [b] In THF, counterion $K^{\oplus}$. Coupling constants determined by computer simulation. [c] Insufficiently resolved super-hyperfine coupling.

The complexes of $Cp(CO)_2Mn$ fragments with the deprotonated amine ligands **4**–**7**,[8] prepared according to the method of *Sellmann, Müller* et al.,[2] and the corresponding sulfur and selenium systems[4] show much larger ^{55}Mn coupling constants than do radical complexes (Fig. 1), exhibit no detectable interaction of the unpaired electron with the coordinated ligands, except for the special case $[Cp^{1}(CO)_2(\mathbf{4})Mn]$,[9] and have isotropic g factors that are significantly larger than $g_{electron}$ (Table 1). These results do not support their formulation as "radical complexes,"[2,4] but rather indicate the presence of low-spin manganese(II),[1,11] i.e., d^5 configuration of the metal. Further arguments in favor of this interpretation are provided by comparison with other cyclopentadienyl manganese(II) complexes: $[CpCl(D)_2Mn^{II}]$ (D = amine or phosphane) are high-spin complexes[10] and a high-spin/low-spin equilibrium is observed in the manganocenes, Cp_2Mn,[11] so that a low-spin complex is expected for $[Cp(CO)_2(L)Mn^{II}]$ with the strong ligands CO and L. Electrochemical investigations[3,12] show that the one-electron oxidation of $[Cp(CO)_2(L)Mn^{I}]$ is extremely facilitated by nucleophilic ligands L: the difference between $E_{ox} = +1.24$ V for L = CO and $E_{ox} = +0.09$ V for L = piperidine[12] suggests that the extremely strong nucleophiles $^{\ominus}NR_2$ and $^{\ominus}SR$ should effectively stabilize the oxidized state, that is, Mn^{II}; indeed, negative potentials relative to the saturated calomel electrode are found for $[Cp^{5}(CO)_2(L)Mn^{II/I}]$: $E = -0.87$ V (L = **5**[13]) and $E = -0.98$ V (L = $^{\ominus}S$*t*Bu[4]).

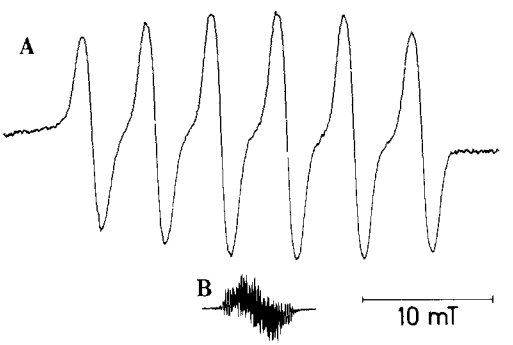


Fig. 1. The ESR spectra of $[Cp^{5}(CO)_2(\mathbf{5})Mn]$ (**A**) and $[Cp^{1}(CO)_2(\mathbf{1}^{\odot\ominus})Mn]$ (**B**) at room temperature in toluene and THF, respectively, illustrate the difference between localization of the unpaired electron on the metal and in the π-system of the radical ligand. In **A**, only a large ^{55}Mn coupling constant is observed ($I = 5/2$, 100% natural abundance), whereas spectrum **B** exhibits extensive hyperfine coupling of the numerous magnetically active nuclei of the radical ligand (486 theoretical lines).

Further evidence for strongly differing electronic configurations is provided by the opposite deviations of the g factors from $g_{electron}$ (Table 1): whereas the radical anion complexes experience only a small lowering of the g factor, on account of low-lying unoccupied metal orbitals,[3] the manganese(II) complexes exhibit significantly higher g values, which—in agreement with theoretical investigations on $Cp(CO)_2M$ complexes[14]—indicate doubly occupied levels close to the singly occupied orbital.[3,15] The relatively strong absorptions of some of these Mn^{II} compounds in the visible[2,4,8] can accordingly be interpreted as LMCT (ligand-to-metal charge-transfer) transitions, in analogy to corresponding Cu^{II} and Ru^{III} systems.[16] It is only in this charge-transfer excited state ($d^6/5\pi \leftarrow d^5/6\pi$) that the unpaired electron is localized on the ligand (radical complex) and, as expected, the LMCT excitation energies, the g factors, and the ^{55}Mn coupling constants decrease as the electrons on the ligands become more available, such as in the series **7**, **6**, **5**, **4**. In the compound $[Cp^{1}(CO)_2(\mathbf{4})Mn]$, the separation between the ground state and the LMCT excited state has already decreased to $\approx 11\,500$ cm^{-1}, so that the first evidence of a super-hyperfine interaction with the ligand **4** is recognizable (Table 1). This, species, which is stabilized by the extreme donor effect of a deprotonated *p*-phenylenediamine ligand, must nonetheless be viewed as a Mn^{II} system.

The $Cp(CO)_2Mn$ fragments thus form two different classes of stable paramagnetic complexes: as neutral and diamagnetic Mn^{I} fragments with d^6 metal configuration, they can stabilize radical anion ligands by π back-bonding.

In contrast, the less common oxidized form of the organometal fragment with the metal center present as low-spin Mn^{II} is stabilized[17, 18] if very nucleophilic diamagnetic ligands are employed.

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4-H^+, 99-98-9; **5**-H^+, 106-49-0; **6**-H^+, 504-24-5; **7**-H^+, 288-32-4; $[Cp^1(CO)_2(\mathbf{1})Mn]$, 98104-71-3; $[(\mathbf{2})\{Cp^1(CO)_2Mn\}_2]$, 91798-54-8; $[(\mathbf{3})\{Cp^1(CO)_2Mn\}_2]$, 98104-72-4; $[Cp^1(CO)_2(\mathbf{4})Mn]$, 98104-73-5; $[Cp^5(CO)_2(\mathbf{5})Mn]$, 98104-74-6; $[Cp^1(CO)_2(\mathbf{6})Mn]$, 98104-75-7; $[Cp^1(CO)_2(\mathbf{7})Mn]$, 98126-12-6; $[Cp^1(CO)_2(\mathbf{3})Mn]$, 98104-76-8; $[Cp^1(CO)_2(thf)Mn]$, 51922-84-0; $[Cp^1(CO)_2(\mathbf{4}\text{-}H^+)Mn]$, 98104-77-9; $[Cp^1(CO)_2(\mathbf{5}\text{-}H^+)Mn]$, 98104-78-0; $[Cp^1(CO)_2(\mathbf{6}\text{-}H^+)Mn]$, 98104-79-1; $[Cp^1(CO)_2(\mathbf{7}\text{-}H^+)Mn]$, 98104-80-4; $[Cp^5(CO)_2(thf)Mn]$, 86155-78-4; $Cp(CO)_2Mn$, 38548-46-8.

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[6] Cf. K. Wieghardt, H. Cohen, D. Meyerstein, *Angew. Chem. 90* (1978) 632; *Angew. Chem. Int. Ed. Engl. 17* (1978) 608.

[7] Cf. F. Gerson: *Hochauflösende ESR-Spektroskopie*, Verlag Chemie, Weinheim 1967, and references cited therein.

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[13] CH_3CN, electrolyte 0.1 M nBu_4ClO_4: glassy carbon working electrode vs. saturated calomel reference electrode; $T = 25°C$, $v = 100$ mV/s.

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[16] K. Krogh-Jespersen, H. J. Schugar, *Inorg. Chem. 23* (1984) 4390.

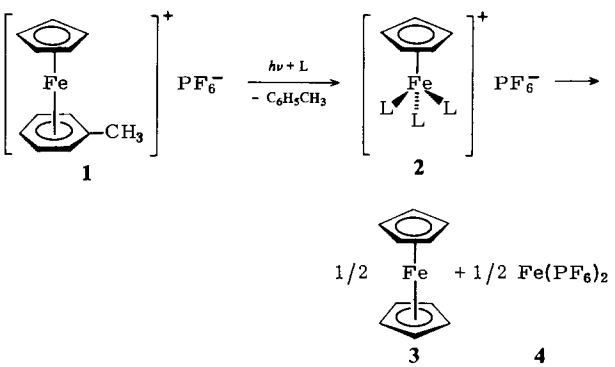
[17] For stabilization of organometal fragments in high oxidation states, see W. A. Herrmann, R. Serrano, H. Bock, *Angew. Chem. 96* (1984) 365; *Angew. Chem. Int. Ed. Engl. 23* (1984) 383.

[18] A binuclear Mn^{II}/Mn^{I} compound with thiolate ligands was recently characterized at −40°C; J. W. McDonald, *Inorg. Chem. 24* (1985) 1734; the first Mn^{II}/Mn^{I} complexes that are stable at room temperature can be detected in the oxidative reaction of $[Cp^1(CO)_2(thf)Mn]$ with alkoxides: R. Gross, W. Kaim, unpublished results.

Reactions in the Ligand Sphere of Iron(II): Synthesis of Crown Ethers

By *Kurt Meier** and *Grety Rihs*

Cationic arene-iron complexes are thermally and chemically very stable, but, upon excitation with light, can undergo ligand exchange reactions with high quantum yields.[1–3] Thus, irradiation of the toluene complex **1** in aprotic solvents in the presence of the ligands L = CO, RNC results in the formation of the isolable complexes **2**; in the absence of suitable ligands, one-half molar equivalent of both ferrocene **3** and iron(II) hexafluorophosphate **4** are formed.



The Lewis acids generated by irradiation are active for the polymerization of bi- and multifunctional epoxides to give insoluble polyethers.[4, 5] These photoinitiator properties of arene-iron complexes have found technical applications in resist and surface-protection technology.

When complex **1** is irradiated in dichloromethane in the presence of a tenfold excess of ethylene oxide, one-half molar equivalent of ferrocene **3** is again formed along with

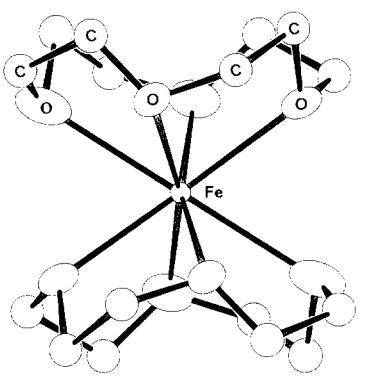
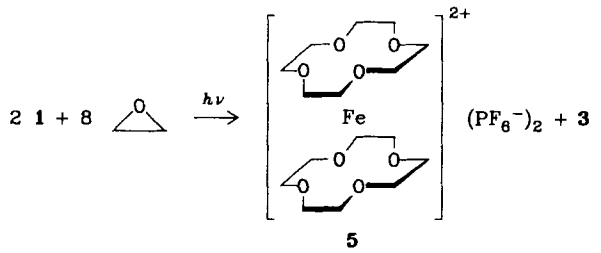


Fig. 1. ORTEP plot of the structure of the cation of **5**. Aba 2, $a = 17.819$, $b = 20.663$, $c = 8.882$ Å, $Z = 4$; $R = 0.112$ for 1910 observed reflections ($I > 2\sigma(I)$). The cation has C_2 symmetry. The mean Fe–O bond length is 2.40 Å. The relatively poor R factor is due to disorder of the $-CH_2-CH_2-$ bridges. Further details on the crystal structure investigation are available from the director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW (England) by giving the full journal citation.

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a white crystalline product, which, after a single recrystallization, affords fine needles of the [12]crown-4 complex **5**.[6] Addition of 2,2'-bipyridine (bpy) to the solution of the recrystallized complex **5** gives $[Fe(bpy)_3]$ $(PF_6)_2$ and two molar equivalents of [12]crown-4. The single-crystal X-ray structure determination of **5** (Fig. 1) shows a sandwich-like arrangement of the crown ether ligands around the central iron atom. The coordination geometry at iron corresponds to that of a cube twisted by 19°, in which the eight ligating oxygen atoms occupy the corner positions. For the $[Ag([12]crown\text{-}4)_2]AsF_6$ complex formed from ethylene oxide and $AgAsF_6$ in SO_2,[7] the faces of the cube are twisted by 30°, while the analogous manganese[8] and sodium complexes[9] exhibit the coordination geometry of a regular square antiprism.



When 2,2'-bipyridine is added to a solution of non-recrystallized **5**, 85% [12]crown-4 and 15% [15]crown-5 are obtained. When (η^5-cyclopentadienyl-η^6-toluene)iron(II) tetrafluoroborate is used as starting material, the 12- and 15-membered crown ethers are formed in a ratio of 10:1; for the analogous hexafluoroantimonate complex, the ratio is 3:2. The irradiated solution contains, in addition to ferrocene and unreacted ethylene oxide, traces of 1,4-dioxane.

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1·2 PF_6, 98194-82-2; **1**·2 BF_4, 98194-85-5; **1**·2 SbF_6, 98194-86-6; **3**, 102-54-5; **5**, 98194-84-4; [12]crown-4, 294-93-9; [15]crown-5, 33100-27-5; $[Fe(bpy)_3](PF_6)_2$, 70811-29-9; ethylene oxide, 75-21-8.

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[6] Experimental procedure: (η^5-cyclopentadienyl-η^6-toluene)iron(II) hexafluorophosphate **1** (7.16 g, 20 mmol) and ethylene oxide (8.8 g, 200 mmol) were irradiated for 1 h in 300 mL of dichloromethane under argon in a photochemical reactor using an immersion tube made of Pyrex and a 125-W high-pressure mercury lamp. The mixture was stirred for a further 16 h and then treated with 400 mL of hexane. The crystalline material formed was separated and dried at room temperature in vacuum (6.8 g). Recrystallization from CH_3CN/Et_2O afforded 3.05 g (4.4 mmol) **5**, m.p. > 250°C (decomp.).
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Lithium-Coordinated α-Sulfonyl Carbanions: Synthesis and X-Ray Structure Determination of $[\{CH_2(SO_2C_6H_5)\}Li(tmeda)]_2$**

By *Hans-Joachim Gais,* Hans Jörg Lindner,** and *Jürgen Vollhardt*

α-Sulfonyl carbanions $[R^1R^2C{-}SO_2R^3]^-$ are important, asymmetrically reacting ($R^1 \neq R^2$) intermediates in organic synthesis.[1] Their structure is the topic of considerable controversy, and definitive information is still lacking. Whereas experimental[2a] and theoretical[2b] studies on cation-free α-sulfonyl carbanions postulate a chiral structure without free rotation around the CS bond, a planar configuration at the C atom, and stabilization via (n_C-d_S) or (n_C-$\sigma^*_{SR^3}$) π-overlap, corresponding investigations of the lithium-coordinated species suggest chiral four- or five-center chelate structures with intramolecular coordination of the Li, O, and C atoms and a nonplanar configuration at the C atom.[3] We present here the X-ray structure determination of the $[\{CH_2(SO_2C_6H_5)\}Li(tmeda)]$ dimer **1** (tmeda = N,N,N',N'-tetramethylethylenediamine)—the first X-ray analysis of a lithiated alkyl sulfone[4]—which provides decisive information regarding the structure of lithium-coordinated α-sulfonyl carbanions.

1 was prepared by metalation of methyl phenyl sulfone with *n*-butyllithium (*n*BuLi) in TMEDA.[5] The single-crystal X-ray structure determination of **1**[6] shows dimers with a crystallographic center of inversion (Fig. 1).

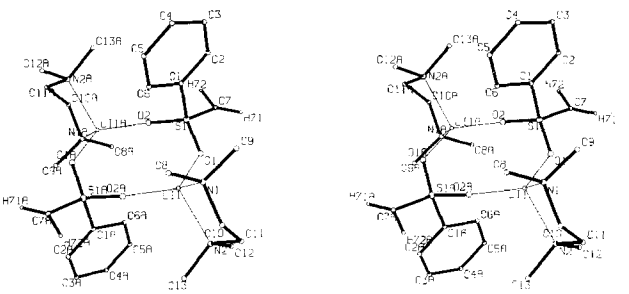


Fig. 1. Stereoscopic view of the structure of **1** in the crystal (H atoms, with the exception of those on C7 and C7A, not shown). Important distances [Å] and angles [°]: S1-C7 1.608(3), S1-C1 1.812(2), S1-O1 1.464(2), S1-O2 1.456(2), Li1-O1 1.908(4), Li1-O2A 1.864(4), Li1-N1 2.148(4), Li1-N2 2.123(4); H71-C7-H72 137(3), C7-S1-C1 114.5(1), O1-S1-C1 102.1(1), O1-S1-C7 111.4(1), O1-S1-O2 114.9(1), O1-Li1-N1 114.8(2), O1-Li1-N2 108.0(2), O2A-Li1-N1 108.1(2), O2A-Li1-N2 112.1(2), N1-Li1-N2 87.6(2), O1-Li1-O2A 121.2(2), S1-O1-Li1 134.1(2), S1-O2-Li1A 155.0(2); H71-C7-S1-C1 81(3), H72-C7-S1-C1 −81(3), C2-C1-S1-C7 −14.0(6), H71-C7-S1-O1 −34(3), H72-C7-S1-O2 34(3).

Li, S, and O atoms form a flat, chair-like, eight-membered ring with the S atoms above and below the plane formed by the Li and O atoms. On the ring, the methylene groups are in equatorial and the phenyl rings in axial positions. The two TMEDA molecules are so arranged that the Li atoms are tetrahedrally coordinated by two O and two N atoms. The methylene group bonded to the sulfur lies *outside* the coordination sphere of Li. Within the limits of

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experimental measurement, this is nearly planar. The deviation of C7 from the plane S1-H71-H72 is only 0.12 Å, and the hydrogen atoms are slightly directed toward the phenyl ring. The unusually short S1-C7 bond (1.608 Å) suggests a true CS double bond. It is nearly the same length as that in the sulfine [1.610(4) Å][8a] and in its derivatives.[8b] This result, along with the orthogonality of the C7-S1-C1 and H71-C7-H72 planes, is in agreement with the results of ab initio calculations on cation-free α-sulfonyl carbanions[2b] as well as with investigations of $[\{CH_2(SO_2C_6H_5)\}Li]$[3b] by IR spectroscopy, and confirms their stabilization by an effective π overlap. However, the theoretically[2b] and experimentally[3b] predicted lengthening of the S1-O1(2) and S1-C1 bonds is not supported. Their bond lengths in **1**, 1.464 (1.456) Å and 1.812 Å, respectively, are nearly the same as in methyl phenyl sulfone [S-O1(2) 1.465 (1.453), S-C1 1.832, S-C7 1.761 Å].[9] **1** is a compound comparable to the lithium enolates.[10]

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[5] Experimental procedure: A solution (17.8 mL) of *n*BuLi (28 mmol) in *n*-hexane was added under argon to a solution of methyl phenyl sulfone (4.68 g, 30 mmol) in 250 mL of anhydrous, deoxygenated TMEDA at −20 °C. The mixture was allowed to stand for 2 h at 0 °C. Precipitated **1** was redissolved by heating the solution to ca. 60 °C (with addition of TMEDA if necessary) and the solution was cooled within 20 h to 25 °C. The crystals that separated out were freed of mother liquor and amorphous material (cannula, Ø 2 mm, under flowing argon), washed with TMEDA, and dried (25 °C, 10^{-3} torr). **1** (2.58 g, 31%) was obtained as pale yellow crystals that were suitable for X-ray structure determination and stable for several months at 25 °C under argon.

[6] A single crystal was mounted in a glass capillary under argon. $P2_1/c$, $a = 12.531(2)$, $b = 9.613(2)$, $c = 17.140(3)$ Å, $\beta = 129.149(3)°$, $V = 1601.2$ Å^3, $Z = 4$, $\rho_{calcd.} = 1.154$ g·cm^{-1}, $\mu(Cu_{K\alpha}) = 16.8$ cm^{-1}. Intensity measurements at room temperature. STOE four-circle diffractometer, $Cu_{K\alpha}$ radiation, graphite monochromator, 2519 reflections ($1.5° < \theta < 60°$) measured, 2248 symmetry-independent reflections with $|F| > 2\sigma(F)$ [7], SHELX, direct methods, all hydrogen atoms by difference Fourier synthesis, 242 variables, $R = 0.039$. Maximal residual electron density 0.253 Å^3 in the S1-C7 bonding region on the side facing C1-S1. Further details of the crystal structure investigation are available on request from the Fachinformationszentrum Energie, Physik, Mathematik GmbH, D-7514 Eggenstein-Leopoldshafen 2, by quoting the depository number CSD 51495, the names of the authors, and the journal citation.

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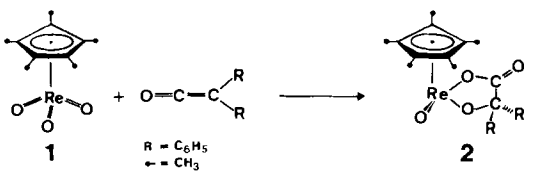
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Novel C–O Bond Formation via [3+2] Cycloaddition of Diphenylketene to a Dioxo Metal Moiety**

By *Wolfgang A. Herrmann,* Ulrich Küsthardt, Manfred L. Ziegler,* and *Thomas Zahn*

The Re^{VII} complex trioxo(η^5-pentamethylcyclopentadienyl)rhenium **1** has proved to be a valuable starting material for the preparation of high-valent organorhenium compounds.[1-3] Whereas all previously described functionalizations have proceeded with partial deoxygenation of the ReO_3 fragment, we have now discovered a novel cycloaddition reaction in which the integrity of this group is retained.

When compound **1** is reacted with excess diphenylketene in tetrahydrofuran (THF) at room temperature, the violet cycloadduct **2**[4] is formed rapidly and nearly quantitatively.



A single-crystal X-ray structure determination afforded the initially surprising result that the heterocumulene is not bonded to the ReO group via the CO moiety, as in the known complex $[(\eta^5\text{-}C_5Me_5)ReO\{\eta^2\text{-}O_2C{=}C(C_6H_5)_2\}]$,[2b] but rather via the CC double bond. This results in a nearly planar five-membered ReO_2C_2 metallacycle (sum of angles 539.4°). As a consequence of the formation of two carbon-oxygen bonds [C1-O3, 133; C2-O2, 147 pm], the two oxygen-rhenium bonds involved are lengthened to very different extents. The Re-O3 distance (202 pm) corresponds to that of a single bond; the Re-O2 distance (184 pm) is between that of a single bond and that of a double bond. The length of the exocyclic Re-O1 bond (168 pm) is typical for a double bond. As a result of the cyclization, the C1-C2 distance (151 pm) is markedly increased compared with that in free and π-coordinated ketenes (127-135 pm)[5] and therefore best looked upon as a single bond. In accord with this interpretation, compound **2** eliminates carbon dioxide upon thermolysis of the solid at 180 °C. The other MO_2C_2 metallacycles known up to now exhibit different bonding arrangements.[6]

The reaction described here is the first example of a [3+2] cycloaddition of a ketene to an organometallic dioxo metal moiety, and is one more indication of the high stability of the rhenium-oxygen bonds in complex **1** if oxy-

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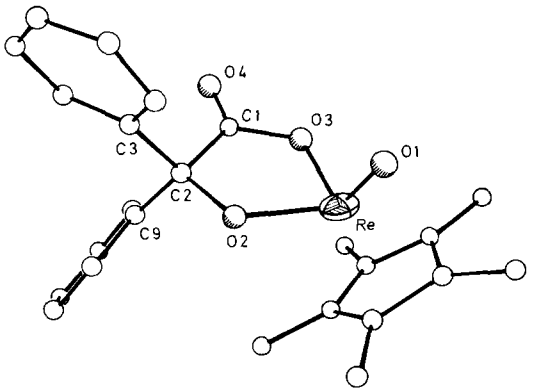
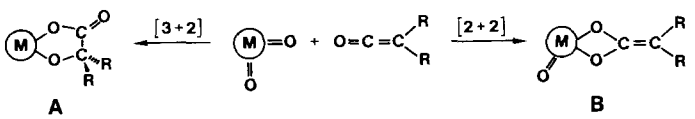


Fig. 1. Crystal structure of the metallacycle **2** (without hydrogen atoms). Selected bond distances [pm] and bond angles [°]: Re-O1 168(1), Re-O2 184(1), Re-O3 202(1), C2···Re 289.4, O2-C2 147(2), C1···Re 289.9, O3-C1 133(2), O4-C1 120(2), C2-C3 155(2), C2-C9 151(2); C1-C2 151(2); O2-Re-O3 79.7(4), O2-C2-C1 107(1), C3-C2-C9 110(1), C1-C2-C3 107(1), C2-C1-O3 113(1), C2-O2-Re 122(1), C1-O3-Re 118(1).—$P2_1/a$; $a=878.2(3)$, $b=1383.1(6)$, $c=1824.7(9)$ pm; $\beta=101.12(4)°$; $V=2175\cdot10^6$ pm^3; $Z=4$; $R_{aniso}=0.098$, $R_{iso}=0.068$, $R_w=0.059$. Further details of the crystal structure investigation are available on request from the Fachinformationszentrum Energie, Physik, Mathematik GmbH, D-7514 Eggenstein-Leopoldshafen 2, by quoting the depository number CSD 51476, the names of the authors, and the journal citation.

gen-abstracting reducing agents (e.g., phosphanes[2]) are absent.

The marked oxyphilicity of rhenium in higher oxidation states allows two types of reaction to occur. The [2+2] cycloaddition to give the four-membered ring **B** apparently occurs only when the metal center is capable of attaining an even higher coordination number. This is the case for all reactions of the Re^V compound $[(\eta^5\text{-}C_5Me_5)ReO_2]_2$,[2a] since this is always found as the mononuclear fragment $(\eta^5\text{-}C_5Me_5)ReO_2$ in the subsequent products. In contrast, **1** already contains the stable, pyramidal ReO_3 fragment, the metal center of which is not readily accessible, and therefore undergoes the type **A** reaction described here.



A **B**

Despite the very different geometries in **A** and **B**, the products always contain the ReO_3 moieties, which, taking into consideration the π-bonded cyclopentadienyl ligands, form (distorted) trigonal pyramids. The oxo ligands that are not involved in the cycloadditions remain largely unchanged with respect to their bonding relationships to the transition metal (double bonds), whereas the lengths of the Re-O bonds incorporated into the four- and five-membered structures **B** and **A**, respectively, are increased, approaching those of single bonds. The significance of the [2+3] cycloaddition reaction described here, the first of its type, lies in the oxidation of carbon-carbon multiple bond systems, like those that have been carried out with oxo derivatives of higher-valent osmium.[7]

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[4] Washed with *n*-hexane, recrystallized from THF/*n*-hexane; yield ca. 90%, analytically pure. Violet, air-stable crystals, m.p. = 138–142 °C.—IR (KBr, [cm^{-1}]): 1722 (vs, νCO)), 1495 (m), 1447 (m), ν(ReO) vibrations in the region 900–1000 cm^{-1} could not be assigned.—^{1}H-NMR (CD_2Cl_2, 270 MHz, 29 °C): $\delta=1.92$ (s, 15H, CH_3), 7.2–7.5 (m, 10H, C_6H_5).—EI-MS (Varian MAT CH7, $T_q=150$, $T_e=200$ °C; ^{187}Re): *m/z* 564 (M^+, 18%), 520 ($[M-CO_2]^+$, 54), 354 ($[C_5Me_5ReO_2]^+$, 51), 338 ($[C_5Me_5ReO]^+$, 100).

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Skeletal Isomerization of the $[Pt_3(\mu\text{-}PPh_2)_3Ph(PPh_3)_2]$ Cluster by Recrystallization in Various Solvents

By *Robert Bender, Pierre Braunstein,* Antonio Tiripicchio,* and *Marisa Tiripicchio Camellini*

The long-standing interest in polymetallic chemistry involving bridging μ-PR_2 groups arises from both the electronic properties of this three-electron donor ligand and its unique geometrical flexibility. The M-P-M angle can vary from ca. 70 to 110° depending on whether metal-metal bonds are present or not.[1] A rich chemistry is being developed using this and other related ligands[2] and it can be anticipated that the class of phosphane-/phosphido-rich clusters, as yet little studied, will display new features and properties, not encountered in their analogues containing better π-accepting ligands (e.g., CO).

We report here a unique example of a cluster having two structural isomers, whose formation is dependent on the solvent used for crystallization. Heating a solution of $[Pt(C_2H_4)(PPh_3)_2]$ in acetone affords a red solution from which the Pt_3 cluster **1a** is isolated as bright red needles.[3]

$$3\,[Pt(C_2H_4)(PPh_3)_2] \xrightarrow[\text{acetone}]{\Delta} [Pt_3(\mu\text{-}PPh_2)_3Ph(PPh_3)_2] + 3\,C_2H_4 + PhH + \cdots$$

1a

1a has imposed m symmetry[4] (Fig. 1). The same complex was obtained as a C_6H_6 solvate (C_2 symmetry) by *Carty* et al.[5] During the numerous attempts to grow crystals of **1a** suitable for X-ray analysis, we surprisingly found that dark red crystals of an isomer of **1a** (**1b**·$2CH_2Cl_2$, Fig. 2) formed in CH_2Cl_2/pentane at −20 °C.[4] Interestingly, recrystallization of **1b**·$2CH_2Cl_2$ in toluene/pentane at room temperature affords **1a**. The solvent used for crystallization is therefore of considerable

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importance for the isolation of a given isomer, although the same molecular species might always be present in solution.

$$\mathbf{1a} \underset{\text{recrystallization from toluene/pentane}}{\overset{\text{recrystallization from } CH_2Cl_2\text{/pentane}}{\rightleftharpoons}} \mathbf{1b}\cdot 2CH_2Cl_2$$

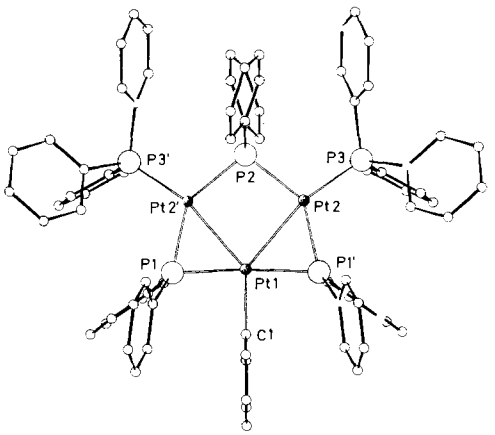


Fig. 1. Molecular structure of **1a**. The mirror plane of the molecule includes Pt1, P2 and the phenyl ring bonded to Pt1. The phenyl groups on P2 are disordered and distributed in two positions in such a way as to give an overall m symmetry to the complex. Only one position of the phenyl groups is represented for clarity. Selected bond lengths [Å] and angles [°]: Pt1-Pt2 2.758(3), Pt1-P1 2.28(2), Pt2-P1′ 2.23(2), Pt2-P2 2.29(1), Pt2-P3 2.24(2), Pt1-C1 2.00(1); Pt2-Pt1-Pt2′ 81.1(1), Pt1-P1-Pt2′ 75.4(6), Pt2-P2-Pt2′ 103.1(1).

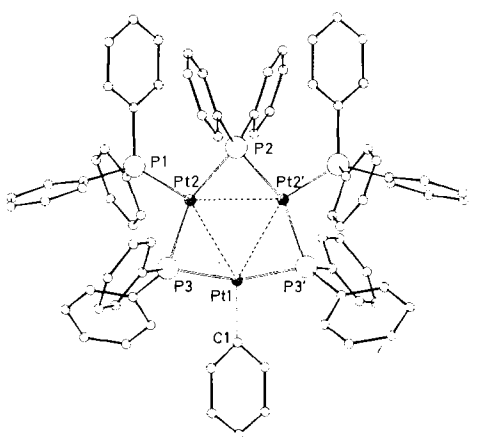


Fig. 2. Molecular structure of $\mathbf{1b}\cdot 2CH_2Cl_2$. Selected bond lengths [Å] and angles [°]: Pt1···Pt2 2.956(3), Pt2···Pt2′ 3.074(4), Pt2-P1 2.244(4), Pt2-P2 2.252(3), Pt1-P3 2.250(4), Pt2-P3 2.297(3), Pt1-C1 2.011(17); P3-Pt1-P3′ 159.8(1), P2-Pt2-P3 148.5(2), Pt1-P3-Pt2 81.1(1), Pt2-P2-Pt2′ 86.1(1), Pt2-Pt1-Pt2′ 62.6(1), Pt1-Pt2′-Pt2 58.7(1).

The two isomers differ in their Pt-Pt distances and Pt-P-Pt angles. **1a** contains a bent Pt_3 chain with two short Pt-Pt distances (2.758(3) Å) and a long Pt2-Pt2′ separation (3.586(2) Å). The Pt atoms are connected by three μ-PPh_2 ligands, their P atoms being roughly coplanar with the Pt atoms (deviations 0.17(5) Å for P1 and P1′, 0.08(7) Å for P2). In $\mathbf{1b}\cdot 2CH_2Cl_2$, the C_2 axis passes through Pt1 and P2: the three Pt atoms form an isosceles triangle with edges of 2.956(3) and 3.074(4) Å. These values are greater than conventional Pt-Pt distances,[6] but do not rule out the existence of Pt-Pt interactions.[7] Whereas P2 is coplanar with the Pt atoms, P3 and P3′ are displaced ±0.627(4) Å from this plane. The value of 86.1(1)° for the Pt2-P2-Pt2′ angle in $\mathbf{1b}\cdot 2CH_2Cl_2$ contrasts with that of 103.1(1)° in **1a**. Whereas the phenyl ring bonded to Pt1 is orthogonal to the Pt3 plane in **1a**, it makes an angle of 59.2(3)° with it in $\mathbf{1b}\cdot 2CH_2Cl_2$. No interaction involving the solvent was found in the structure of $\mathbf{1b}\cdot 2CH_2Cl_2$.

These 44e-clusters formally contain two Pt^{I} centers and one Pt^{II} center. The 4-electron-3-center bonding results in either two short and one long or in three medium Pt-Pt distances. **1** is the only example of a Pt cluster to display easy skeletal isomerism, a feature of great interest but rarely encountered in cluster chemistry.[1] Preliminary MO calculations indicate that this can be related to the presence of strong σ-donor ligands and that the energy difference between the two isomers is very small.[8] The flexibility of the μ-PR_2 ligand allows very large variations in metal-metal separations; even packing forces or solvent interactions are sufficient to induce major structural changes. Great care must be exercised when correlating ^{31}P-NMR chemical shift values of phosphido ligands (in solution) with values of the M-PPh_2-M angle (in the solid state).

1a and $\mathbf{1b}\cdot 2CH_2Cl_2$ are valuable precursors for the synthesis of phosphido-bridged mixed-metal clusters, as shown by their reaction with $Co_2(CO)_8$ in toluene, which affords Pt-Co clusters.[9]

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1a, 56938-875; **1b**, 98330-74-6; $\mathbf{1b}\cdot 2CH_2Cl_2$, 98330-75-7; $[Pt(C_2H_4)(PPh_3)_2]$, 12120-15-9; CH_2Cl_2, 75-09-2; toluene, 108-88-3; acetone, 67-64-1.

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[4] Siemens AED diffractometer ($Mo_{K\alpha}$). **1a**: Cmc 2_1, $Z=4$, $a=22.192(10)$, $b=17.650(9)$, $c=18.182(8)$ Å, $V=7122(6)$ Å^3, $3°<\theta<22°$, 2346 unique reflections, 1293 observed reflections with $I\geq\sigma(I)$, $R=0.080$, $R_w=0.098$. $\mathbf{1b}\cdot 2CH_2Cl_2$: C2/c, $Z=4$, $a=21.390(10)$, $b=18.471(9)$, $c=19.021(11)$ Å, $\beta=105.27(5)°$, $V=7250(7)$ Å^3, $3°<\theta<27°$, 7691 unique reflections, 4348 observed reflections with $I\geq 2\sigma(I)$, $R=0.045$, $R_w=0.055$. Further details of the crystal structure investigations are available on request from the Fachinformationszentrum Energie, Physik, Mathematik GmbH, D-7514 Eggenstein-Leopoldshafen 2, on quoting the depository number CSD 51522, the names of the authors, and full citation of the journal.

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Polymorphism of an Organolithium Compound: Dilithium 1,2-diphenylbenzocyclobutadienediide · 2 Tetramethylethylenediamine**

By *Gernot Boche,* Heinz Etzrodt, Werner Massa,* and *Gerhard Baum*

Dedicated to Professor Karl Dimroth on the occasion of his 75th birthday

Numerous cyclobutadiene transition metal complexes have been prepared and characterized;[1] the first derivatives of dilithium cyclobutadienediide, however, were prepared only recently.[2] We report here on X-ray structure investigations of dilithium 1,2-diphenylbenzocyclobutadienediide · 2 tmeda **1** (tmeda = *N,N,N′,N′*-tetramethylethylenediamine). Polymorphism has been observed for the first time in organolithium compounds, whereby the Li atoms in particular, and the TMEDA molecules in the two modifications I and II of **1** take on different positions (lithiotropism). The two phenyl substituents at C1 and C1′ in both modifications are bent outwards (Fig. 1). This has not been observed in comparable organolithium compounds.

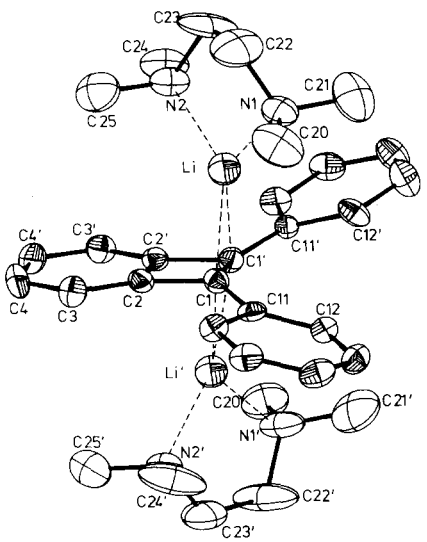


Fig. 1. ORTEP diagram of the crystal structure of **1-I** (thermal ellipsoids are depicted at the 30% probability level). Atomic numbering accounts for the pseudo-C_2 symmetry. $P2_1/n$, $a = 17.05(1)$, $b = 19.73(1)$, $c = 20.20(1)$ Å, $\beta = 113.5°$, $V = 6232$ Å^3, $Z = 8$, $\rho_{calc} = 1.071$ g/cm^3 at 213 K. $Mo_{K\alpha}$ radiation, graphite monochromator, $\lambda = 0.71069$ Å. 6003 independent reflections, 3165 observed, with $F_0 > 3\sigma(F_0)$, four-circle diffractometer (Enraf-Nonius CAD4). Direct methods (MULTAN 80 [3]), anisotropic temperature factors for all atoms except Li (isotropic) and H (at calculated positions), SHELX 76. [4] $w = 1.9/\sigma^2(F_0)$, $R_w(F) = 0.058$, $R_g = (F^2) = 0.058$. The asymmetric unit contains two independent molecules, the symmetry of which approaches C_2. Further details of the crystal structure investigation are available on request from the Fachinformationszentrum Energie, Physik, Mathematik GmbH, D-7514 Eggenstein-Leopoldshafen 2, on quoting the depository number CSD-51563, the names of the authors, and the full citation of the journal.

Surprisingly, the Li atoms in **1-I** (Fig. 1; see also Fig. 2, left) are arranged unsymmetrically above and below the four-membered ring. The distances to C1 and C1′ are slightly different, but both are noticeably shorter than those to C2 and C2′. The Li atoms lie almost directly above and below the C1C1′ bond.[5,6b] The phenyl rings deviate strongly from the almost ideal plane (maximum deviation 0.02(2) Å) of the "benzocyclobutadienediide" C atoms: C11 lies 0.27(2) Å below and C11′ 0.32(2) Å above this plane. This means that the phenyl rings are bent away from the Li atom adjacent to the C1 or C1′ atoms, respectively. Calculations on 1,2-dilithioethane, which compares with the situation here, revealed that its C_{2h} structure is the stablest.[7]

For such a bonding the two Li atoms should be of special importance, since in neutral compounds of the "*cis*-stilbene" type the two phenyl rings always evade mutual steric hindrance by twisting of the rings (40–70°)[8,9], and MNDO calculations for 1,2-diphenylbenzocyclobutadienediide gave a twisting of about 22° for the phenyl rings.[2a] In the TMEDA molecules the N–N bonds run almost parallel to the two four-membered ring diagonals.

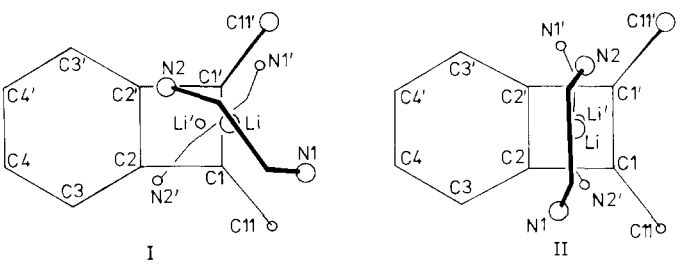


Fig. 2. Projection of a part of the structure of **1-I** (left) and **1-II** (right) onto the plane of the benzocyclobutadienediide C atoms. Important bond lengths [Å], bond angles, and dihedral angles [°] of **1-I** (average) and **1-II** (in square brackets): LiC1 2.14(1) [2.23(4)], LiC1′ 2.20(1) [2.35(4)], LiC2 2.66(1) [2.37(4)], LiC2′ 2.69(1) [2.36(4)], Li′C1 2.22(1) [2.35(4)], Li′C1′ 2.15(1) [2.23(4)], Li′C2 2.45(1) [2.36(4)], Li′C2′ 2.41(1) [2.37(4)], LiN (mean value) 2.044 [1.94], C1C1′ 1.53(1) [1.45(3)], C1C2 1.46(1) [1.48(1)], C1′C2′ 1.45(1) [1.48(1)], C2C2′ 1.44(1) [1.44(3)], C1C11 1.42(1) [1.48(2)], C1′C11′ 1.42(1) [1.48(2)]; C1C1′C11′ 138(1) [138(2)], C1′C1C11 138(1) [138(2)]; C3C2C1C11 15(4) [16(5)], C3′C2′C1′C11′ 20(3) [16(5)]. **1-II**: C2/c; $a = 14.11(1)$, $b = 13.33(1)$, $c = 16.58(1)$ Å; $\beta = 91.98(7)°$, $Z = 4$, $\rho_{calc} = 1.042$ g/cm^3 at 295 K. Lower density and higher—here also crystallographically realized—C_2 symmetry points to a high-temperature modification, but a phase-transition **1-II** → **1-I** could not be observed. Instead, a reversible phase transition into a third modification **1-III** occurs between 273–225 K [10], so that the measurements had to be made at 295 K. Only an incomplete set of low quality data has so far been obtained ($R_w(F) = 0.13$ and $R_g(F^2) = 0.12$ for 536 independent reflections) because of the attendant rapid decomposition of the crystals in the X-ray beam [11].

In **1-II** (Fig. 2, right[11,12]) the distances of the Li atoms to the four-membered ring C atoms differ less from each other than in **1-I**; in **1-II** they lie more over the center of the four-membered ring. An "asymmetry" of the Li atoms referred to C1 and C1′ is indicated also in the case of **1-II**. The phenyl rings at C1 and C1′ are once again bent away from the neighboring Li atom: C11′ and C11 respectively lie 0.24(1) Å above and below the plane of the four-membered ring. The N–N axes of the TMEDA molecule run parallel to C1–C1′.

Calculations suggest that the potential hypersurface for the position of lithium ions on delocalized "carbanions" is very flat.[5a,6d–f,13] Consequently, packing effects in the crystal could influence the structure of organolithium compounds considerably. The polymorphism and lithiotropism found in **1** provide the first experimental support. It emerges that—at least with delocalized charge in the "carbanion"—particular care must be taken when discussing

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the positions of the lithium atoms in crystalline organolithium compounds.[5a, 14]

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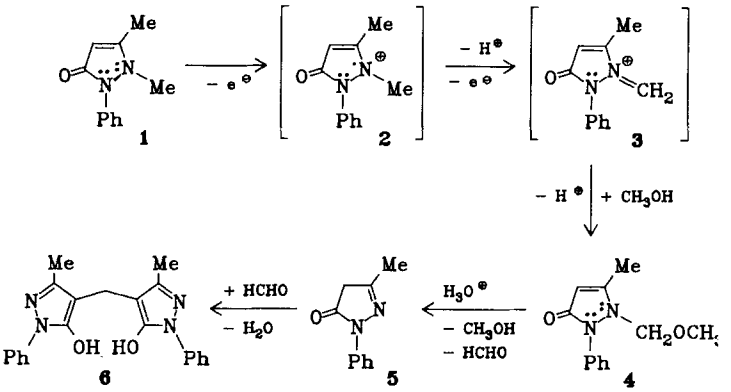
Electrochemical Methoxylation of Antipyrine**

By *Gerd Kaupp,* Fatih Köleli,* and *Eleonore Gründken*

Dedicated to Professor Hans-Jürgen Bestmann on the occasion of his 60th birthday

Anodic methoxylations of alkyl- and arylamines and of amides have been known for a long time and have been used in organic synthesis, even though the regioselectivity cannot always be predicted.[1] We report here the electrochemical methoxylation of antipyrine **1**, an *N*-methyl heterocycle with delocalized π-electrons. Antipyrine (1,2-dihydro-1,5-dimethyl-2-phenyl-3-pyrazolone) is of broad significance, for example, as a pain-killer,[2] a reagent for heavy-metal ions and nitrite,[3] and a substrate for pharmacokinetic studies.[4] Despite the high functionality of **1**, **4** is selectively obtained.

When **1** is oxidized at the platinum anode in methanolic potassium hydroxide in an undivided beaker cell, the unstable methyleneammonium ion **3** is formed apparently selectively via the radical cation **2** in which the π-electrons are delocalized. **3** undergoes solvolysis to give the derivative **4**, which is methoxylated on the *N*-methyl group. For 87% conversion of **1**, the yield of **4**, determined by NMR spectroscopy, is 85%; after complete conversion, crystalline **4** is isolated in 71% yield.[5]

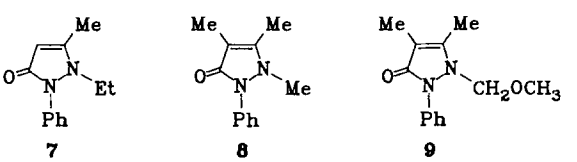


No competing reactions at the *C*-methyl group or at the unsubstituted ring C atom of **1** occur although these possibilities are largely preferred in chemical oxidations[6] and are realized, to a large extent, in human metabolic pathways (along with demethylation at the nitrogen).[7] The phenyl group, too, remains intact.

Although the anodic oxidation of **1** competes with the oxidation of the solvent (formaldehyde was detected) and thus proceeds with comparatively lower current yields (28% for 87% conversion),[8] it is especially simple and preparatively useful and affords the derivative **4**, which is functionalized at the *N*-methyl group.

Compound **4** may be viewed as a model compound for the metabolism of **1**, which results partially in demethylation (presumably via the *N*-hydroxymethyl derivative of **1**, i.e., **4** with OH instead of OCH_3).[7] Treatment of **4** with hydrochloric acid effects solvolytic cleaving off of methanol and formaldehyde. Norphenazone **5**[9] is formed, which undergoes condensation with the formaldehyde to form the methylene-bridged **6** (together 99%).[10]

The *N*-methyl methoxylation of antipyrine **1** without control of the potential leads selectively to **4**. Further oxidation of the methylene group to the dimethoxy derivative in methanolic potassium hydroxide fails because of the too high oxidation potential of **4**.[8] The first anodic peak potentials of the cyclovoltammograms (200 mV/s, CH_3CN, 0.1 M $LiClO_4$, Pt vs. SCE) of **1** and **4**, as well as of the related derivatives **7**,[11] **8**,[11] and **9** (1.22, 1.36, 1.22, 1.09, and 1.24 V, respectively) also support this interpretation. However, not only the potential determines the success of the electrochemical methoxylation. Thus, **7** (same first



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peak potential as **1**) cannot be converted into a derivative that is methoxylated on the *N*-methylene group (analogous to **4**) either under the conditions described here for **1** (mainly recovery of **7**) or by a tenfold increase in the current passage employed. It appears that one of the subsequent chemical and/or electrochemical steps (cf. scheme) is not possible.[12]

The *N*-methyl selectivity remains the most striking criterium of our synthesis to the extent that the initially formed radical cation (cf. **2**) is not particularly effectively stabilized by additional dialkylamino groups.[13] Thus, **9** is obtained nearly quantitatively from **8**[11] when the electrolysis is carried out as for **1**.

The simple preparation of compounds **4** and **9** opens up the possibility of extending the synthetic potential of *N*-(α-methoxyalkyl)amides[1] to these cyclic, vinylogous derivatives (Lewis-acid-catalyzed reaction with nucleophiles).

Experimental Procedure

1 (5.8 g, 0.031 mol), KOH (6 g) and methanol (300 mL) were subjected to electrolysis (full conversion, DC control) in a beaker at a cylindrical platinum anode (50 cm^2, wire thickness 0.125 mm, mesh size 1.00 mm) using a cylindrical V4A steel-net cathode (100 cm^2, electrode separation 9.1 mm) for 4.5 h at 2 A with magnetic stirring. The terminal voltage was 5.7 V. The solvent was rotovapped in vacuum, 50 mL of water was added, and the solution was extracted five times with 50 mL of diethyl ether. After chromatography on basic Al_2O_3 (activity III) with ethyl acetate and crystallization of the product fraction from *n*-heptane, 4.8 g (71%) **4**, m.p. = 67–68 °C, was obtained.

4 (1.00 g) was dissolved in 6 mL of methanol and treated with 4 mL of 1 N HCl. The solution was refluxed for 10 min and then cooled; 0.43 g (53%) **6**, m.p. = 149–151 °C. At pH 7, 0.37 g (46%) **5** was isolated from the mother liquor.

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1, 60-80-0; **4**, 98395-57-4; **5**, 89-25-8; **6**, 98395-58-5; 7, 3614-49-1; **8**, 5677-84-9; **9**, 98395-59-6.

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[5] Compound **4** afforded satisfactory elemental analysis. **4**: ^{1}H-NMR (80 MHz, $CDCl_3$): δ = 7.6–7.15 (m, 5H), 5.48 (q, 1H, J = 1 Hz), 4.81 (s, 2H), 3.23 (s, 3H), 2.31 (d, 3H, J = 1 Hz; for **1**, the same allylic coupling is observed); ^{13}C-NMR (20.1 MHz, $CDCl_3$): δ = 166.6, 155.6, 135.1, 129.0 (2C), 126.7, 124.3 (2C), 100.7, 76.6, 57.7, 12.3; UV (CH_3OH): $\lambda_{max}(\varepsilon)$ = 240 (10150), 262 (9600) nm; IR (KBr): ν = 1660 cm^{-1} (C=O); MS (70 eV): *m/z* 218 (14%, $M^{\oplus\oplus}$), 187 (6), 186 (6), 45 (100).

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[8] Under the preparative conditions (2% KOH in CH_3OH, Pt), current-voltage curves versus the Ag/AgCl/sat. KCl electrode gave potentials of 1.43 V for the basic solvent (equally in the presence of 0.10 M **4**) and 1.30 for a 0.10 M solution of **1** for currents of 2 A (ca. 40 mA/cm^2).

[9] Tautomerism of **5**: A. R. Katritzky, F. W. Maine, *Tetrahedron 20* (1964) 299.

[10] **6**: ^{1}H-NMR (250 MHz, $CDCl_3$, 22 °C): δ = 7.8–7.65 (*m*, 4H), 7.4–7.15 (m, 6H), 3.90 (≥2H, very br. s, $\Delta\nu_{1/2}$ ca. 180 Hz), 3.27 (2H, br. s, $\Delta\nu_{1/2}$ ≈ 5 Hz), 2.32 (6H, br. s, $\Delta\nu_{1/2}$ = 5.5 Hz); UV (CH_3OH): λ_{max} = 242, 260 nm (sh); IR (KBr): ν = 3340 (OH), 1620 (sh), 1610 (sh), 1600, 1560, 1550, 1505 cm^{-1} (C=N, C=C); MS (70 eV): *m/z* 360 (1%, $M^{\oplus\oplus}$), 358 (3), 187 (13), 186 (67), 185 (44), 174 (64), 157 (12), 105 (32), 91 (53), 77 (100); for compound **6**, the diketo form (4,4′-methylenebis(5-methyl-2-phenyl-2*H*,4*H*-pyrazol-3-one)) has been postulated up to now: U. Wrzeciono, *Justus Liebigs Ann. Chem. 1975*, 2293, and references cited therein.

[11] L. Knorr, *Justus Liebigs Ann. Chem. 238* (1887) 137; *293* (1896) 1; ^{1}H-NMR ($CDCl_3$): **7**: δ = 7.5–7.2 (m, 5H), 5.36 (q, 1H, J = 1 Hz), 3.52 (q, 2H, J = 7 Hz), 2.20 (d, 3H, J = 1 Hz), 0.85 (t, 3H, J = 7 Hz); **8**: δ = 7.5–7.2 (m, 5H), 2.93 (s, 3H), 2.14 (q, 3H, J = 1 Hz), 1.84 (q, 3H, J = 1 Hz); **9**: δ = 7.5–7.2 (m, 5H), 4.78 (s, 2H), 3.23 (s, 3H), 2.25 (q, 3H, J = 1 Hz), 1.87 (q, 3H, J = 1 Hz); yield of **9** determined by ^{1}H-NMR spectroscopy for 53% conversion of **8**: 96%.

[12] A striking parallel is found in the electrochemical methoxylation of amides. Thus, in the review [1], no methoxylations of *N*-ethylamides are described; the numerous examples are for *N*-methylamides, cyclic acylated amines, and lactams.

[13] H. Sayo, M. Masui, *Chem. Pharm. Bull. 24* (1976) 2137; *J. Chem. Soc. Perkin Trans. 2 1973*, 1640: By cyclovoltammetry (6 V/s, CH_3CN, 0.1 M $NaClO_4$ vs. SCE) anodic potentials of 1.22 and 1.65 V for **1** were measured; in contrast, the anodic potentials of 4-dimethylamino- and 4-diethylaminoantipyrine are, as expected, lower (0.34, 0.85, 1.32 and 0.39, 0.88, 1.18, 1.38 V, respectively) and it was possible to detect spectroscopically the blue-violet radical cations, from which (with the involvement, this time, of the *C*-methyl group and not the *N*-methyl group), the decomposition products acetaldehyde and diethylamine were formed in low yield.

[(η^5-C_5Me_5)(CO)$_2$M–P=P(2,4,6-*t*$Bu_3C_6H_2$)] (M = Fe, Ru), the First Diphosphenyl Complexes**

By *Lothar Weber** and *Klaus Reizig*

Dedicated to Professor Karl Dimroth on the occasion of his 75th birthday

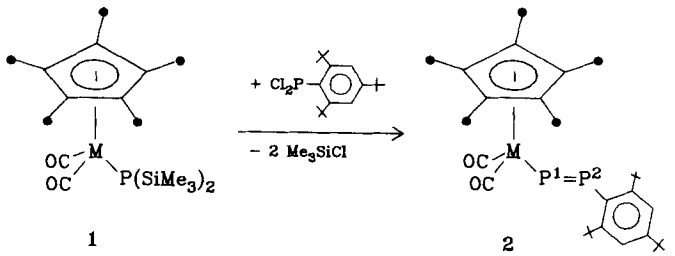
Since the preparation of bis(2,4,6-tri-*tert*-butylphenyl)diphosphene, the first stable phosphorus analogue of the long known azo compounds,[1] there has been a rapid development in the chemistry of diphosphenes and their higher homologues.[2] Diphosphenes can act not only as terminal σ-bonded ligands and as π-bonded ligands,[2] but also as bridging groups[2,3] and as building blocks for clusters.[2,4] In all of these cases, the diphosphene complexes contain an intact $R^1P{=}PR^2$ fragment. Conceivably, the groups R^1 and R^2 of a diphosphene could be replaced by transition-metal complex fragments, leading to the types of complex **A** and **B**. Here, we report the first type **A** diphosphenyl complexes of iron and ruthenium.



We have extended the syntheses of diphosphenes[5] from disilylphosphanes and dichlorophosphanes to disilylphosphido complexes of iron **1a**[6] and ruthenium **1b**[7] as starting materials. **1a**, **b** smoothly react with 2,4,6-tri-*tert*-butylphenyldichlorophosphane[1] (mole ratio 1 : 1) in tetrahydrofuran (THF) at 20 °C to give the orange-yellow title compounds **2a**, **b**.[8]

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1 2

• — = CH_3; a, M = Fe; b, M = Ru

The constitutions and configurations of the isolated complexes were confirmed by elemental analysis, molecular weight determinations, and spectroscopy. The $M(CO)_2$ groups are indicated by the two intense ν(CO) bands in the IR spectrum. The presence of unsymmetrically substituted diphosphenes is confirmed unequivocally by the ^{31}P-NMR spectra of **2a**, **b**. Two doublets at very low field with very large coupling constants[8] are diagnostic for unsymmetrical diphosphenes.[2] The largest low-field shift to date for uncomplexed diphosphenes was recorded for $(Me_3Si)_3C-P=P-C(SiMe_3)_3$ ($\delta = 599.7$).[9] The largest coupling constant up to now for an unsymmetrical diphosphene was reported by *Niecke* et al. for $(Me_3Si)_2N-P=P-N(t\text{Bu})(SiMe_3)$ ($^1J_{PP} = 670$ Hz).[10] The X-ray structure determination of **2a** shows that the complex exists in the *E* configuration like most diphosphenes [P-P 2.019(15) Å; Fe-P1-P2 109.9(4)°, P1-P2-C(aryl) 103.5(8)°].[11] The title compounds can be viewed as transition-metal-substituted diphosphenes or as the first diphosphenyl complexes. They are accordingly the phosphorus homologues of those diazenyl complexes in which the ligand functions as a 1e donor and in which, therefore, a doubly bent M–N=N–R geometry is present.[12] Attempts to synthesize diphosphenyl complexes from **1** and the less bulky mesityldichlorophosphane failed.[13]

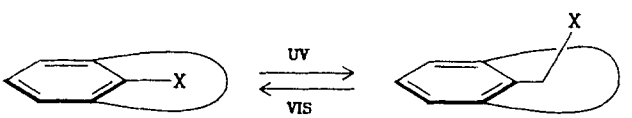
Received: June 13, 1985;
supplemented: July 12, 1985 [Z 1349 IE]
German version: *Angew. Chem. 97* (1985) 868

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[8] Experimental procedure for **2a**: Solid 2,4,6-tri-*tert*-butylphenyldichlorophosphane (1.67 g, 4.83 mmol) was added to a solution of **1a** (2.05 g, 4.83 mmol) in 40 mL of THF at 0°C. The red-brown solution was stirred at 20°C for 30 min and the solvent was then removed under vacuum. The residue was dissolved in 25 mL of hexane and filtered. The ocher-yellow residue left on the filter was washed with hexane (2 × 3 mL) and dried in vacuum. Re-precipitation from THF/pentane afforded 1.43 g (59%) **2a**, m.p. = 165–167°C. — ^{1}H-NMR (200 MHz, C_6D_6, 22°C): $\delta = 1.33$ (s, 9H, *p*-*t*Bu), 1.34 (s, 15H, $C_5(CH_3)_5$), 1.73 (s, 18H, *o*-*t*Bu), 7.65 (s, 2H, *m*-phenyl-H). — ^{13}C{^{1}H}-NMR (C_6D_6, 22°C): $\delta = 9.32$ (d, $^3J(PC) = 5.6$ Hz, $C_5(CH_3)_5$), 31.60 (s, *p*-$C(CH_3)_3$, 34.84 (s, *o*-$C(CH_3)_3$), 34.94 (s, *p*-$C(CH_3)_3$), 38.87 (s, *o*-$C(CH_3)_3$), 97.34 (s, $C_5(CH_3)_5$), 122.13 (s, *m*-phenyl-C), 148.55 and 152.32 (s and d, respectively, $J(PC) = 6.1$ Hz, phenyl-C), 216.27 (d, $^2J(PC) = 11.9$ Hz, Fe–C≡O). — ^{31}P{^{1}H}-NMR (C_6D_6, 22°C): $\delta = 715.2$ (d, $^1J(PP) = 594.2$ Hz, P–Fe), 553.5 (d, $^1J(PP) = 594.2$ Hz, P–C). — IR (cyclopentane): 2005 s, 1956 s cm^{-1} (ν(CO)). — CI-MS (Varian MAT 312): $m/z = 555$ ($M^+ + H$). — Experimental procedure for **2b**: Analogously, orange-yellow **2b** (1.21 g, 67.5%) was synthesized from 2,4,6-tri-*tert*-butylphenyldichlorophosphane (1.035 g, 2.99 mmol) and **1b** (1.40 g, 2.99 mmol) in 40 mL of THF. M.p. = 169–170°C. — ^{1}H-NMR (200 MHz, C_6D_6, 22°C): $\delta = 1.33$ (s, 9H, *p*-*t*Bu), 1.45 (s, 15H, $C_5(CH_3)_5$), 1.75 (s, 18H, *o*-*t*Bu), 7.65 (s, 2H, *m*-phenyl-H). — ^{13}C{^{1}H}-NMR (C_6D_6, 22°C): $\delta = 9.59$ (d, $^3J(PC) = 4.7$ Hz, $C_5(CH_3)_5$), 31.61 (s, *p*-$C(CH_3)_3$), 34.90 (s, *o*-$C(CH_3)_3$), 34.94 (s, *p*-$C(CH_3)_3$), 38.92 (s, *o*-$C(CH_3)_3$), 101.05 (s, $C_5(CH_3)_5$), 122.17 (s, *m*-phenyl-C), 148.56 and 152.32 (s and d, respectively, $J(PC) = 7.8$ Hz, C-phenyl), 202.06 (d, $^2J(PC) = 13.9$ Hz, Ru–C≡O). — ^{31}P{^{1}H}-NMR (C_6D_6, 22°C): $\delta = 676.5$ (d, $^1J(PP) = 597.1$ Hz, P–Ru), 551.6 (d, $^1J(PP) = 597.1$ Hz, P–C). — IR (cyclopentane): 2021 s, 1968 s cm^{-1} (ν(CO)). — CI-MS (Varian MAT 312): $m/z = 600$ ($M^+ + H$).
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A Photochemically "Switched-on" Crown Ether Containing an Intraannular 4-Methoxyphenylazo Substituent

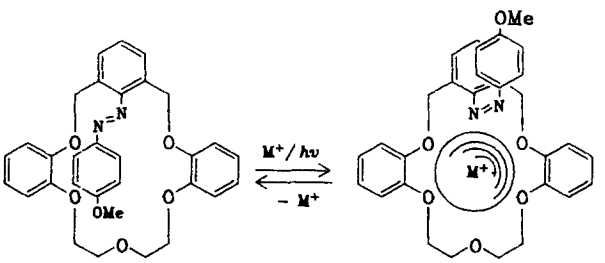
By *Seiji Shinkai*,* *Kiminori Miyazaki*, and *Osamu Manabe*

Crown ethers of type **1**, bearing an intraannular substituent X, bind metal ions to different extents, depending on the nature of X.[1–3] When X has no metal-coordination ability (X = methyl, phenyl, halides, etc.), the association



1 **2**

constant decreases.[1–4] In contrast, when it has a metal-coordination ability (X = OH, COOH, NH_2, etc.), it not only increases the association constant but may act as a pH-responsive "switch" governing the metal-binding phenomena.[1–7] Crown ethers whose intraannular substituent can change position (**1** ⇄ **2**), e.g., upon photolysis, are of particular interest since this allows specific modification of the binding properties of the crown ether.

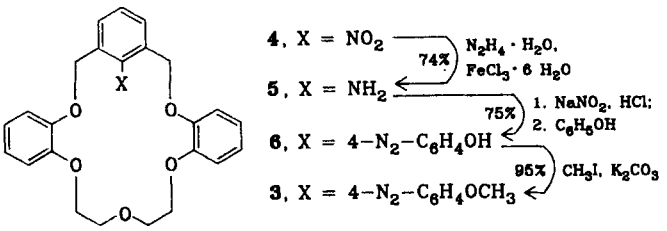


(E)-**3** *(Z)*-**3**·M^+

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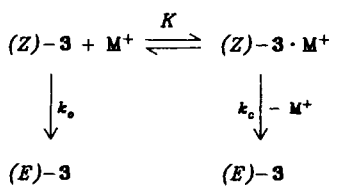
We report here the synthesis and properties of the crown ether **3**, which contains a photochemically "switched-on," intraannular 4-methoxyphenylazo substituent. By photochemically induced *E/Z* isomerization of the azo group of (*E*)-**3**, the substituent is taken out of the ring. Furthermore, one of the two azo nitrogens in (*Z*)-**3** may contribute to the binding of metal ions.

3 was synthesized from the nitro compound **4** via **5** and **6** (Scheme 1)[1-3] and identified by IR and ^{1}H-NMR spectroscopy[8] and by elemental analysis. Photoisomerization of (*E*)-**3** (λ_{max} = 352 nm, *o*-dichlorobenzene) to (*Z*)-**3** (λ_{max} = 440 nm, *o*-dichlorobenzene) was effected by irradiation (100-W high-pressure Hg lamp, color-glass filter $330 < \lambda < 380$ nm (Toshiba UV-D35)). The fraction of (*Z*)-**3** in the photostationary state is 59%.



Scheme 1.

The rate of the thermal *Z/E* isomerization was estimated spectrophotometrically at 30 °C in *o*-dichlorobenzene/methanol (5:1, v/v). The first-order rate constant ($k_0 = 9.05 \times 10^{-3}$ min^{-1}) is efficiently suppressed in the presence of Na^+ or K^+ ions (added as perchlorate salts: $[MClO_4] = 1 \times 10^{-5}$ to 5×10^{-4} M). The rate is not affected by Li^+ and only weakly by Cs^+. These findings suggest that (*Z*)-**3** shows selectivity for Na^+ and K^+ (Scheme 2).



Scheme 2.

From plots of the rate constant k vs. $[M^+]$ we determined the association constant K and the rate constant k_c:[9] $K = 64600$ M^{-1} and $k_c = 1.26 \times 10^{-3}$ min^{-1} for Na^+; $K = 46000$ M^{-1} and $k_c = 2.18 \times 10^{-3}$ min^{-1} for K^+. The rate constants for *Z/E* isomerization of the Na^+ and the K^+ complex are 7.2 and 4.2 times smaller, respectively, than those for pure **3**. The K values for complexation of Na^+ and K^+ by (*Z*)-**3** ($\lg K = 4.81$ and 4.65, respectively) are comparable to those for [18]crown-6 and dibenzo[18]crown-6.[10] This suggests that one of the azo nitrogens in (*Z*)-**3** contributes to metal coordination. In fact, the absorption spectrum of (*Z*)-**3** changes significantly on the binding of Na^+ ion (λ_{max} shifted to shorter wavelength by 5 nm).

The ion-binding ability was evaluated by solvent extraction of alkali picrates from water ([MCl] = 0.10 M, [MOH] = 1.00×10^{-4} M, [picric acid] = 1.00×10^{-4} M) into organic solvent (*o*-dichlorobenzene/1-butanol (80:20 v/v), [**3**] = 3.01×10^{-3} M), the decrease in the picrate concentration in the aqueous phase being determined. Neither (*E*)-**3** nor (*Z*)-**3** could extract Li^+. The dramatic photoirradiation effect was observed only for Na^+: (*E*)-**3** extracts no Na^+, whereas (*Z*)-**3** (52% mixed with (*E*)-**3**) extracts Na^+ (14.1%). This all-or-nothing behavior is explained as follows; the 4-methoxyphenylazo substituent in (*E*)-**3** acts as a steric spacer nesting in the crown ether ring and interferes with the interaction between Na^+ ion and the crown ether ring; it is removed by the photoinduced *E/Z* isomerization. We have found, however, that K^+ ion is bound not only to (*Z*)-**3** (21.1% extractability) but also to (*E*)-**3** (17.9%). Since the 4-methoxyphenylazo substituent in (*E*)-**3** acts as a "shallow floor"[11] of the crown ring, it is probably difficult for metal ions to bind deeply within the crown ring. Conceivably, the interaction between (*E*)-**3** and K^+ may be accommodated by the "perch-on-type" complexation. On the other hand, Na^+, which is smaller than K^+, cannot interact with (*E*)-**3** by the "perch-on-type" complexation. Therefore, the all-or-nothing change in ion-binding ability would be effected only when the cavity size of the crown ring fits the metal ion.

The 4-methoxyphenylazo substituent in (*E*)-**3** thus acts as an obstruction for metal ions, but when it is taken out by a light trigger, a metal ion is complexed deeply within the cavity. This concept should be useful in the designing of other novel "switched-on" host molecules. We are now applying the photoinduced interconversion of **3** to light-driven active transport across membranes.

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CAS Registry numbers:
(*E*)-**3**, 98303-80-1; (*Z*)-**3**, 98303-81-2; (*Z*)-**3** · Na, 98303-83-4; (*Z*)-**3** · K, 98303-84-5; **4**, 59945-42-5; **5**, 98330-16-6; **6**, 98303-82-3.

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[8] IR (KBr): ν(CO) = 1130, 1250, ν(N=N) = 1580 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ = 3.64 (t), 3.82 (t), 4.97 (d) and 5.49 (d, OCH_2), 3.74 (s, OCH_3), 6.78-7.52 (m, aromatic protons). Correct elemental analysis.
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The First Chemical Partial Synthesis of the Nickel Complex of a Cobyrinic Acid Derivative**

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Dedicated to Professor Albert Eschenmoser on the occasion of his 60th birthday

With exception of the cobalt-containing derivatives prepared by transformation of the naturally occurring vitamin

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[**] We thank Professor Dr. *A. Gossauer* for support of this work.

B_{12} chromophore, metal chelates of corrinoids have hitherto only been accessible either by total synthesis[1] or by complexation of metal-free corrinoids that are isolated from the culture media of phototrophic bacteria.[2] The demetalation and/or transmetalation of cobalt-containing corrinoids is therefore of interest from both a theoretical and practical point of view.

All attempts to replace directly the complex-bound cobalt ion by other metal ions have so far failed[3] because of the extremely high stability of corrin-cobalt complexes.

An alternative route, developed by *Inhoffen* et al., consists in the *regioselective* cleavage of the corrin ring, subsequent demetalation of the resulting *seco*-corrinoid, remetalation, and, finally, recyclization to the new metal complex. In the heptamethyl dicyanocobyrinate series, ring closure was possible in the case of the cobalt complex,[4] but not in the case of the rhodium and palladium analogues.[5]

In earlier studies on the reactivity of the corrin chromophore we found that thermolysis of **1** afforded the "pyrocobyrinate" **2a**[6] in 60% yield,[7] and that *regioselective* oxidation of **2a** with photochemically generated singlet oxygen led to formation of the dioxomono-*seco*-compound **3a** in 95% yield.[8] In the present communication we report on the first transformation of **2a** into the nickel complex **2b**.

Initially, all attempts to demetalate **3a** failed. Neither reaction with H_2S in pyridine/methanol[4] nor reaction with dithiols in presence of acids[9] yielded any satisfactory results. Success was first achieved upon reaction of **3a** with P_4S_{10} in acetonitrile, which furnished unstable **3c** in good yields (ca. 80% of crude product). The *seco*-corrinoid **3c** was converted by reaction with nickel perchlorate into the corresponding complex **3b** (overall yield **3a**→**3b**: 80%), which could be cyclized under the conditions of the

Table 1. Physical properties of compound **2b**.

UV/VIS (CH_3OH): λ_{max} [nm] ($\log\varepsilon$): 529 (4.05), 458 (sh), 392 (3.43), 337 (4.41), 262 (4.14)

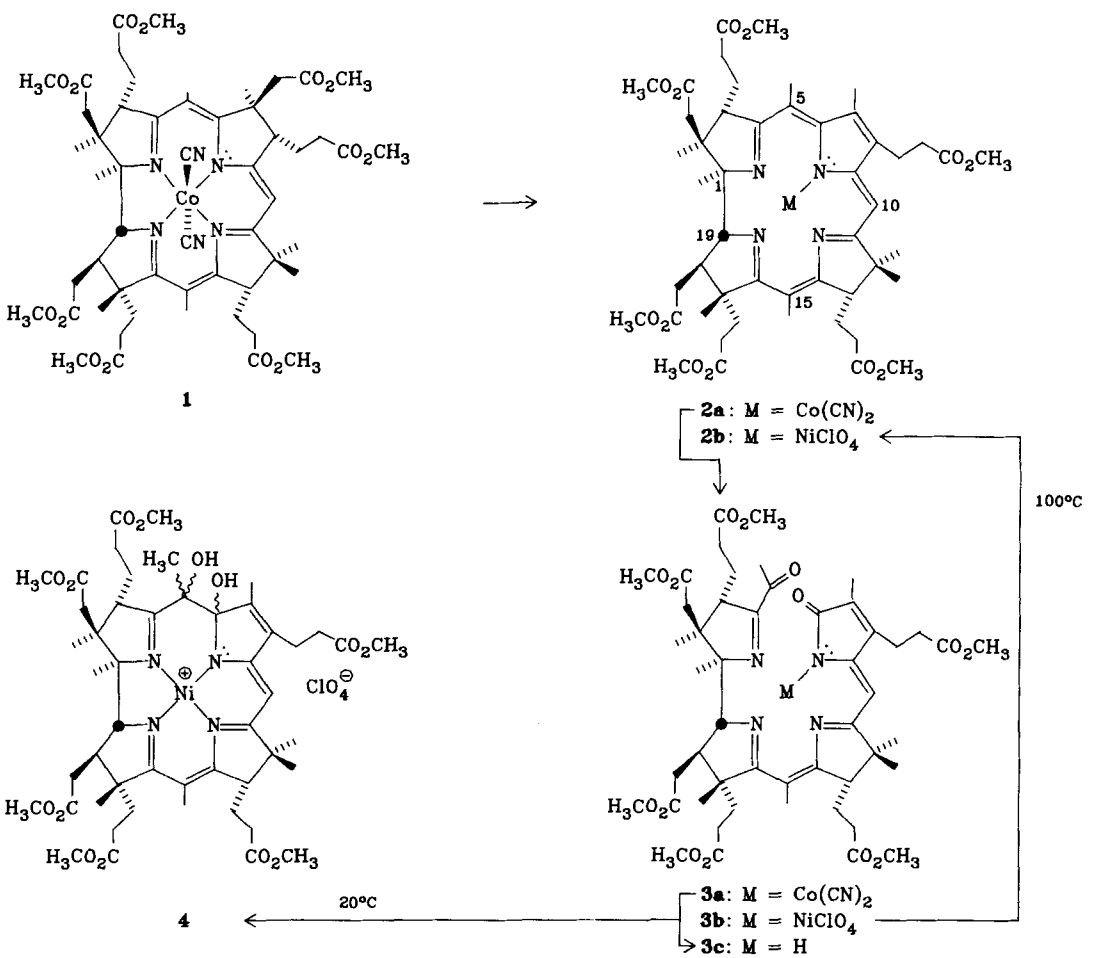
IR ($CHCl_3$): ν [cm^{-1}] (among others): 3020 (CH), 2945 (CH), 1730 (ester C=O), 1610, 1570, 1480

CD (CH_3OH): λ_{max} [nm] ($\theta°$): 264 (−89803), 295 (0), 336 (110284), 359 (0), 397 (−12603), 436 (0), 530 (−15755), 597 (0)

FAB-MS (glycerol): m/z (%) (among others): 962 (100, $(M+1)^+$), 945 (21), 934 (15), 918 (10), 903 (12), 887 (17), 872 (14), 859 (10), 844 (10)

^{1}H-NMR (360.13 MHz, $CDCl_3$, TMS int.): δ values, J [Hz]): 6.62 (s, 1H, H-10); 4.54 (d, 1H, J=10, H-19); 4.08 (d, 1H, J=8.4); 3.77, 3.72, 3.71, 3.67 (6H), 3.60 (all s, 18H, 6×OCH_3); 3.36, 3.12 (2H), 2.90 (all m, 4H, H-3, -13, -18, and H_D-8[2]); 2.73 (s, 3H, CH_3-C7); 2.52 (s, 3H, CH_3-C5); 2.43 (s, 3H, CH_3-C15); 1.59, 1.54, 1.43, 1.38, 1.28 (all s, 15H, CH_3-C1, -C2, -C17, α-C12, β-C12); 2.9–1.6 (side chain CH_2 groups)

^{13}C-NMR (90.56 MHz, $CDCl_3$, TMS int.): δ values, J [Hz]: 174.44, 172.84, 172.79, 172.52 (2C), 172.22, 171.95, 171.87, 171.36 (all s, C4, C11, C16 and 6× ester C=O); 163.96 (s, C9); 156.83 (s, C6); 152.27 (s, C14); 143.67 (s, C7); 142.84 (s, C8); 113.82 (s, C5): 106.12 (s, C15); 92.39 (d, C10); 85.32 (s, C1); 75.88 (d, C19); 58.15 (s, C17); 55.97 (d, C3); 53.41 (d, C13); 52.41, 52.01 (2C), 51.93, 51.87, 51.77 (all q, 6×OCH_3); 47.07 (s, C12); 45.35 (s, C2); 41.71 (t, $C2^1$); 39.92 (d, C18); 34.21 (t, $C8^2$); 33.54 (t, $C3^2$); 32.39 (t, $C17^1$); 31.95 (q, β-CH_3-C12); 31.41 (t, $C18^1$); 30.92 (t, $C13^2$); 29.79 (t, $C17^2$); 25.82 (t, $C13^1$); 25.19 (t, $C3^1$); 25.19 (q, CH_3-C1); 20.63 (q, α-CH_3-C12); 19.98 (t, $C8^1$); 19.47 (q, CH_3-C17); 17.53 (q, CH_3-C7); 17.23 (q, CH_3-C2); 16.48 (q, CH_3-C5); 15.59 (q, CH_3-C15)



McMurry reaction.[10] Reaction of **3b** with $TiCl_3/Zn$ in dioxane at room temperature led initially to formation of a lemon-yellow compound (41% yield) whose structure **4** could be assigned on the basis of spectroscopic data. When the reaction was carried out at 100°C, perchlorato-7-de(carboxymethyl)-7,8-didehydronickelobyrinic acid hexamethyl ester **2b** was formed in 43% yield.

The structure of **2b** was confirmed by comparison of the spectroscopic data with those of **2a** (UV/VIS; IR; FAB-MS; ^1H and ^{13}C NMR) (Table 1).

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Cl_2C-Cl-$Cl^{\odot\oplus}$, Cl_2C-Cl-$Br^{\odot\oplus}$, and Br_2C-Br-$Cl^{\odot\oplus}$ by Gas-Phase Decarbonylation of $CX_3COY^{\odot\oplus}$**

By *Thomas Drewello, Thomas Weiske,* and *Helmut Schwarz**

Dedicated to Professor Rolf Huisgen on the occasion of his 65th birthday

Whereas carbon tetrachloride and its dication $CCl_4^{2\oplus}$ (C_{2v})[1] are very well known, no stable radical cation $CCl_4^{\odot\oplus}$ has so far been generated and characterized. Electron impact ionization,[2a,b] charge-exchange mass spectrometry[2c] or radiolysis of CCl_4 do not afford any detectable molecular ion, but exclusively fragments such as $CCl_n^{\oplus}$ (n = 1–3), $Cl^{\odot}$ or doubly charged ions of the type $CCl_m^{2\oplus}$ (m = 1, 2). Although according to semi-empirical molecular orbital calculations[3] (MINDO/3) at least seven minima should exist on the energy hypersurface of $CCl_4^{\odot\oplus}$ (the global minimum corresponding to a $CCl_4^{\odot\oplus}$ with C_{2v} symmetry, followed by isomers of the following point groups: C_{3v}, D_2, T_d, D_{2d}, D_{2h} and D_{4h}), it is not surprising that vertical ionization of CCl_4 with generation of $\tilde{X}(^2T_2)CCl_4^{\odot\oplus}$ does not lead to a stable radical cation; Reaction (1) is exothermic (5–6 kcal/mol), and an activation energy of 1.4 kcal/mol (referred to $\tilde{X}(^2T_2)CCl_4^{\odot\oplus}$) is calculated for the decomposition.[3] A lifetime of $t \leqslant 2 \times 10^{-10}$ s is assigned to the radical cation generated by direct ionization of CCl_4.[2d] The lifetime for metastable $CCl_4^{\odot\oplus}$ in the gas phase is estimated to be $t \leqslant 10^{-5}$ s.[2e]

$$\tilde{X}(^2T_2)CCl_4^{\odot\oplus} \longrightarrow \tilde{X}(^1A_1')CCl_3^{\oplus} + Cl^{\odot} \quad (1)$$

We report here on a simple experiment[4] for the generation of $CCl_4^{\odot\oplus}$ with a lifetime $t \geqslant 10^{-5}$ s. Electron impact ionization (70 eV) of CCl_3COCl affords $CCl_3CO^{\oplus}$ and $CCl_3^{\oplus}$ (100%), and a further weak (intensity 0.5%) but clearly detectable signal in the range *m/z* 152–158. According to the isotope pattern (0.330 : 0.407 : 0.200 : 0.009) this signal arises from the decarbonylation product of $CCl_3COCl^{\odot\oplus}$; that is, a stable $CCl_4^{\odot\oplus}$ radical cation must have been formed. Upon collisional activation,[5] $CCl_4^{\odot\oplus}$ decomposes to $CCl_3^{\oplus}$ (95.8% total ion current), $CCl_2^{\odot\oplus}$ (3.1), $CCl^{\oplus}$ (0.5), and $Cl^{\oplus}$ (0.6). What is the constitution of $CCl_4^{\odot\oplus}$? It has been demonstrated mass spectrometrically that a chlorine radical is readily split off (generation of $CCl_3^{\oplus}$), whereas the elimination of Cl_2 (formation of $CCl_2^{\odot\oplus}$) should require more energy. These results are fully consistent with structure **1**. We have calculated the most important reaction paths on the hypersurface of $CCl_4^{\odot\oplus}$ for **1** using RHF-MNDO[6] (Fig. 1): The reaction **1** → $CCl_3^{\oplus} + Cl^{\odot}$ requires ca. 6 kcal/mol, the process **1** → $CCl_2^{\odot\oplus} + Cl_2$ ca. 15 kcal/mol. The isomerization of **1** to the radical cation **2** of carbon tetrachloride ($CCl_4^{\odot\oplus}$, C_{2v}), which corresponds to the global minimum on the MINDO/3-[3] and MNDO-hypersurfaces, requires ca. 10 kcal/mol. The *direct* decomposition path **2** → $CCl_3^{\oplus} + Cl^{\odot}$ with by-passing of **1** is, according to both MINDO/3[3] as well as MNDO, energetically more demanding than the reaction sequence **2** → **1** → $CCl_3^{\oplus} + Cl^{\odot}$.

1, which could be regarded as an ion/dipole complex of Cl_2 with $CCl_2^{\odot\oplus}$,[7] is better described as a $CCl_3^{\oplus}$ cation interacting with a chlorine atom. The resulting Cl–Cl bond is the weakest in the whole radical cation (bond order (*BO*)[8] 0.56); the bond between carbon and the hypervalent chlorine, with a *BO* = 0.76, is indeed markedly stronger, but

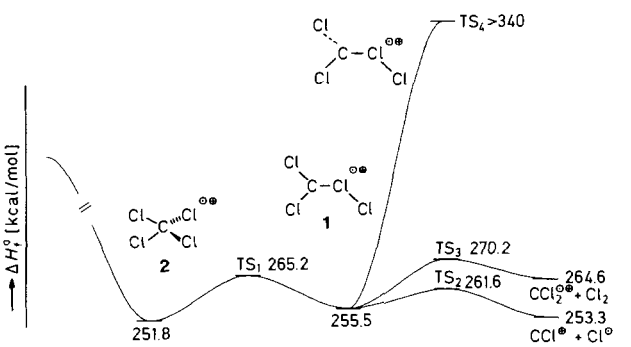
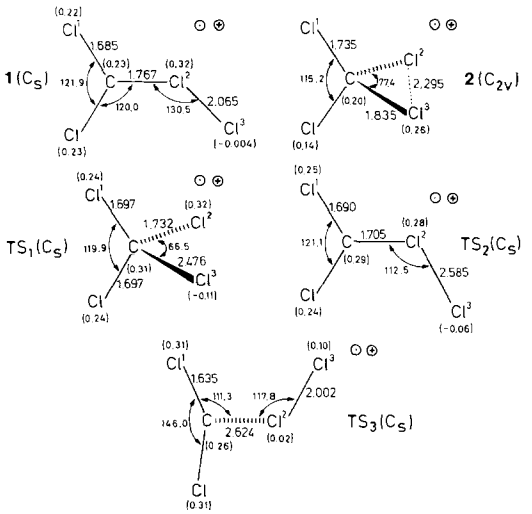


Fig. 1. MNDO reaction path for $CCl_4^{\odot\oplus}$.

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still considerably weaker than the two remaining C–Cl bonds ($BO = 1.24$ and 1.22). The positive charge is carried almost quantitatively by the CCl_3 unit (see Scheme 1); the fourth chlorine atom, which has been transferred intramolecularly from the acid chloride moiety in the course of the cleavage is practically neutral.

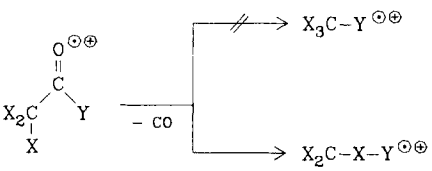


Scheme 1. Geometry (angles [°], bond lengths [Å]) and charge distribution (in brackets) of **1**, **2**, and the transition states TS_{1-3} (TS_4, which is irrevelant for the discussion, could not be characterized).

All attempts to analyze the reaction path $CCl_3COCl^{\odot\oplus} \rightarrow CCl_4^{\odot\oplus} + CO$ computationally, and thus to be able to decide whether **1** and **2** are generated independently of each other were thwarted by the fact that we could not cleanly localize the molecular ion. In the course of the geometric optimization, decomposition to $CCl_3^{\oplus}$ occurs, which also dominates in the mass spectrometer. In view of the fact that, with one (explainable) exception,[9] the dissociative ionization of carboxylic acid derivatives (cleavage of CO or CO_2) always leads to ion/dipole-like ions such as **1** and the isomeric ions with normal valence are not generated, we think that decarbonylation of $CCl_3COCl^{\odot\oplus}$ also preferably yields **1**. The following observations also lend support to such an interpretation: On using an extremely sensitive tandem mass spectrometer (Vacuum Generator type ZAB-3F) we were able for the first time to detect an, admittedly, weak (intensity $< 0.01\%$) but, nevertheless, clearly recognizable signal for $CCl_4^{\odot\oplus}$ when CCl_4 was ionized with 70 eV. The kinetic energy T_k released on cleavage of $Cl^{\odot}$ from the mass-selected $CCl_4^{\odot\oplus}$ ion is, with a value of 160 meV, significantly greater than the T_k value for the analogous reaction of those $CCl_4^{\odot\oplus}$ ions that have been generated from $CCl_3COCl^{\odot\oplus}$ ($T_k = 7.8$ meV). This finding, and the fact that the line shapes of the corresponding transition signals are characteristically different ("dished" in the first case and pure gaussian[10] in the second) unquestionably require that the two $CCl_4^{\odot\oplus}$ ions are structurally different. Furthermore, the different T_k values support the reaction profile described by MINDO/3[3] and MNDO calculations: Direct decomposition of **2** to $CCl_3^{\oplus}$ and $Cl^{\odot}$ is not possible; instead, in the energy-determining step isomerization to excited **1** takes place and, finally, **1** decomposes with liberation of a larger amount of translational energy to $CCl_3^{\oplus}$ and $Cl^{\odot}$, as is the case when **1** is generated directly by decarbonylation.[11]

Loss of CO is also observed with $CCl_3COBr^{\odot\oplus}$,[4] whereas no decarbonylation takes place in the case of $CCl_3COF^{\odot\oplus}$.

Remarkable in the case of $CCl_3Br^{\odot\oplus}$ is that the dominating mode of decomposition corresponds to the elimination of $Br^{\odot}$. This could indicate that here, analogously to $CCl_4^{\odot\oplus}$, a hypervalent radical ion (Cl_2C–Cl–$Br^{\odot\oplus}$) has once again been generated from which Br can be readily cleaved. Since, however, preferred cleavage of the C–Br bond is to be expected also in the radical cation of CCl_3Br, we have studied $CBr_3COCl^{\odot\oplus}$, the spectrum of which shows a signal for $[M-CO]^{\odot\oplus}$ with the correct isotope pattern. If this decarbonylation product corresponds to a $CBr_3Cl^{\odot\oplus}$ ion, then a preferred loss of $Br^{\odot}$ ought to be observed here also, whereas $Cl^{\odot}$ ought to be eliminated from the hypervalent Br_2C–Br–$Cl^{\odot\oplus}$ in analogy to Cl_2C–Cl–$Cl^{\odot\oplus}$ with cleavage of the Br–Cl bond. Experimentally, it is observed that the mass-selected decarbonylation product with *m/z* 288 (which corresponds to an isotope mixture of 25% $^{12}C^{79}Br_2{}^{81}Br^{37}Cl$ and 75% $^{12}C^{79}Br^{81}Br_2{}^{35}Cl$) decomposes on collisional activation *exclusively* with loss of ^{37}Cl and ^{35}Cl in the ratio 1 : 3. It therefore follows that loss of CO from $CBr_3COCl^{\odot\oplus}$ leads specifically to Br_2C–Br–$Cl^{\odot\oplus}$ and that also in the usual decarbonylation processes only the hypervalent radical cations **1**, **3**, and **4** are generated [Eq. (2)].[12]



(2)

1: X = Y = Cl; **3**: X = Cl, Y = Br; **4**: X = Br, Y = Cl

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Reactions of Per(chloro,fluoro)ethanes with Aryloxide and Alkoxide Ions—Evidence for Chlorophilic Attack on C–Cl Bonds

By *Xing-ya Li,* He-qi Pan, Xi-kui Jiang,* and *Zheng-yun Zhan*

Dedicated to Professor Rolf Huisgen on the occasion of his 65th birthday

Reactions of nucleophiles with per(fluoro,halo)alkanes (halogen = iodine or bromine) have been intensively studied,[1,2] and most likely the C–I or C–Br bonds are always attacked in the initial steps. However, only a few cases have been reported for nucleophilic reactions of per(chloro,fluoro)alkanes,[3–6] which are well-known for their inertness.[7] As to reactions involving oxygen nucleophiles, we know of only two instances.[5,6] Recently, *Sawyer* et al.[6] suggested that the degradations of substrates containing trichloromethyl groups by the hyperoxide ion ($O_2^{\ominus}$) are initiated by electron transfer. *McBee* et al.[5] used phenoxide ions in butanone; these reactions, however, are most likely initiated by carbanions (from butanone) rather than by oxygen nucleophiles. We report here evidence for direct attack on C–Cl bonds by oxygen nucleophiles, as well as a useful method for the preparation of aryl and alkyl per(chloro,fluoro)ethyl ethers of the type **2** from the per(chloro,fluoro)ethanes **1** (see Table 1).

$$\underset{\mathbf{1}}{ROK} + XCF_2{-}CCl_2Y \longrightarrow \underset{\mathbf{2}}{RO{-}CF_2{-}CCl_2Y} + \underset{\mathbf{3}}{RO{-}CF_2{-}CClHY}$$

X,Y = Cl,F

yield depend strongly on the nature of the solvent. The reactions are usually faster in polar aprotic solvents like dimethylsulfoxide (DMSO), dimethylformamide (DMF), and hexamethylphosphoric triamide (HMPA), which also give higher yields of **2** for aryloxides. For alkoxides, better yields are obtained in weakly polar solvents, such as diglyme or triglyme. If ROH/KOH is used instead of ROK, the reaction becomes dramatically slower, but, in some cases, good yields can still be obtained. The reaction is sensitive to water and other proton-donating species, but light, oxygen, and dinitrobenzene do not seem to have any effect.

In all the products, the aryloxy or alkoxy groups are attached to CF_2. Since direct S_N2 attack of $RO^{\ominus}$ on a carbon of the CF_2–X type (X = Cl, F) is improbable[9a] and the formation of the hydrogen-containing product **3** is also incompatible with this sort of attack, our results are best rationalized by an anionic chain mechanism (Scheme 1).

$$RO^{\ominus} + \mathbf{1} \longrightarrow ROCl + XCF_2{-}CClY^{\ominus} \quad (1)$$

$$XCF_2{-}CClY^{\ominus} \longrightarrow CF_2{=}CClY + X^{\ominus} \quad (2)$$

$$RO^{\ominus} + CF_2{=}CClY \longrightarrow \underset{\mathbf{4}}{RO{-}CF_2{-}CClY^{\ominus}} \quad (3)$$

$$\mathbf{4} + \mathbf{1} \longrightarrow \mathbf{2} + XCF_2{-}CClY^{\ominus} \quad (4)$$

$$\mathbf{4} + H^{\oplus}\ \text{donor} \longrightarrow \mathbf{3} \quad (5)$$

Scheme 1.

Table 1. Selected results for the reactions of **1** with ROK or ROH/KOH at room temperature.

Substrate	Nucleophile	Solvent	*t* [h] [a]	Yield [%] [b]	
				2	**3**
$ClCF_2{-}CCl_2F$	C_6H_5OK	DMSO	1	89 (79)	< 1
1a	$C_6H_5CH_2OK$	diglyme [c]	3	61 (53)	< 1
	$C_2H_5C(CH_3)_2OK$	triglyme	1	79 (75)	< 1
$CF_3{-}CCl_3$	C_6H_5OK	DMSO	1	90 (78)	< 1
1b	*p*-$CH_3OC_6H_4OH$/KOH	DMF	30	89 (76)	1
	$C_6H_5CH_2OK$	diglyme [c]	3	76	2
	$C_2H_5C(CH_3)_2OK$	triglyme	1	41	< 1
$ClCF_2{-}CCl_3$	C_6H_5OK	DMSO	1	(88)	2
1c	*p*-$CH_3C_6H_4OH$/KOH	DMF	40	(91)	4
	p-$NH_2C_6H_4OH$/KOH	DMF	40	(74)	2.4
	p-ClC_6H_4OH/KOH	DMF	30	(70)	3.7
	$C_6H_5CH_2OK$	triglyme	3	61	2.4
	$C_2H_5C(CH_3)_2OK$	triglyme	1	41	< 1

[a] Not optimized. [b] Based on ROK, determinded by GC; the numbers in parentheses are isolated yields. [c] Contains 2×10^{-3} M dibenzol[18]crown-6.

Compounds **1** react spontaneously with potassium alkoxides at room temperature or below to afford the ethers **2** in fair to good yields. The carefully purified and dried reactants are usually used in molar ratios of 2:1 to 3:1. Distillation after work-up furnishes the products **2**, usually in high purity. Small amounts of hydrogen-containing products **3** were found in all cases.[8] The reaction can take place in a wide variety of aprotic solvents, but its rate and

This mechanism is similar to two previously reported reactions involving chlorophilic attack by $PhS^{\ominus}$ ions[3] and bromophilic attack by $PhO^{\ominus}$ ions;[2] it is the first confirmed chlorophilic attack on C–Cl bonds by oxygen nucleophiles. The proposed propagation steps (2) and (3) are supported by GC detection of small amounts of olefins $CF_2{=}CClY$ and, especially, by the exclusive linkage of the entering RO groups to the CF_2, because it is well established that all nucleophiles add regiospecifically to that end of polyhalogenated double bonds.[9b] The fact that the same product $RO{-}CF_2{-}CCl_3$ is obtained from either **1b** or **1c** is also good evidence for the intermediacy of $CF_2{=}CCl_2$. The chain process is supported by the ability

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of added CF_2=CClY to greatly accelerate the reaction. For example, in diglyme, **1a** reacts with C_6H_5OK so slowly that only trace amounts of **2a** can be detected after 24 h, but when 5 mol-% CF_2=CClF (relative to C_5H_5OK) is added, **2a** (15%) and **3a** (3%) are formed in 20 min.

The reactions described here afford a facile route to ethers, one of whose alkyl groups is fully halogenated; such ethers are not readily available via other preparative methods. More interestingly, these observations are the first good evidence for a chlorophilic attack on C–Cl bonds by oxygen nucleophiles.

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[4] A. E. Platt, B. Tittle, *J. Chem. Soc. C 1967*, 1150; A. W. Frank, C. F. Baranauckas, *J. Org. Chem. 30* (1965) 3970; M. Schlosser, *Helv. Chim. Acta 58* (1975) 2575; P. Johncock, *Synthesis 1977*, 551.

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Increased Production of Specific Antibodies by Presentation of the Antigen Determinants with Covalently Coupled Lipopeptide Mitogens

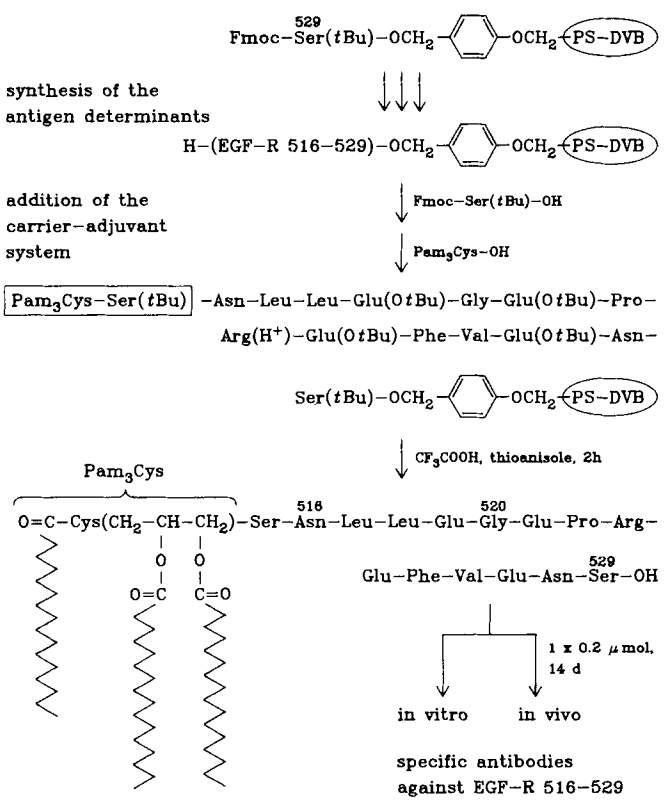
By *Günther Jung,* Karl-Heinz Wiesmüller, Gerhard Becker, Hans-Jörg Bühring,* and *Wolfgang G. Bessler*

In the conventional methodology for the production of antisera against antigenic determinants (epitopes) of a protein, synthetic partial sequences are coupled with high-molecular carriers such as serum albumin; subsequently, immunization is carried out with addition of *Freund*'s adjuvant. The reproducibility, both of the preparation of the conjugate as well as of the immunization, is frequently unsatisfactory. With the concept described herein, long immunization times, multiple administrations, high titers of undesired antibodies, and serious inflammations of the immunized animals can be avoided.

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The initiating process in antibody formation is the endocytosis and processing of antigens by leukocytes and their subsequent "presentation" on cell surfaces, the molecular details of which are largely unknown. Our concept is based on the idea of employing for the immunization a chemically unequivocally defined *low molecular* conjugate such as **2** in which the carrier-antigen-adjuvant principles are coupled with one another. Such a conjugate was designed as a potential synthetic vaccine in connection with the "Pam_3Cys-antigen-helix" system.[1] Our conjugate differs in essential points from the high molecular polylysine conjugates with antigens and muramyl dipeptide[2] as well as from other adjuvants[3] that were merely admixed but cannot perform any special carrier function. Most of the systems developed so far require multiple antigen administrations in vivo.

We have, for the first time, covalently coupled a B-cell mitogen, which is an excellent carrier and concomitantly a strongly active adjuvant, with a synthetic antigenic determinant. To do this we used the synthetic lipopeptide *N*-palmitoyl-*S*-[(2*RS*)-2,3-bis(palmitoyloxy)propyl]-cysteinyl-serine (Pam_3Cys-Ser),[4] which constitutes the *N*-terminal of the lipoprotein from the outer membrane of *Escherichia coli*.[5] The covalently bonded conjugate of Pam_3Cys-Ser and antigen exhibits pronounced amphiphilic properties. They guarantee, on the one hand, a stable anchoring of the three fatty acid residues in the lipid layer of the cell membrane (Scheme 1) and, on the other, that the usually stronger polar antigen (hapten) is 'presented' in the outer hydrophilic layer of the membrane. A decision on the pos-



Scheme 1. Production of antibodies using the covalently bound carrier and adjuvant Pam_3Cys-Ser. Fmoc = fluorenylmethoxycarbonyl; *t*Bu = *tert*-butyl; PS-DVB = styrene-divinylbenzene (1%) copolymer with 4-(hydroxymethyl)phenoxymethyl anchor groups; EGF-R = receptor of the epidermal growth factor (cf. synthetic example).

sible micellar/monomeric distribution of the conjugate in the cell culture medium can probably be made by spin- and fluorescence-labeling.

Since the activating effect of the lipoprotein is brought about by its *N*-terminal moiety,[6] in all conjugates which contain the Pam_3Cys-Ser or analogues its immunostimulating action remains preserved. Pam_3Cys-Ser-antigen-conjugates can be routinely prepared in the last step in Merrifield syntheses of partial sequences (Scheme 1). Preferably an alkoxybenzyl alcohol-resin as well as N^{α}-fluorenylmethoxycarbonyl-, *tert*-butyl-, and *tert*-butoxycarbonyl protective groups are used in the peptide segment.[7] Since Pam_3Cys is stable towards trifluoroacetic acid,[4] the conjugate can be cleaved from the carrier without problem free of protective groups. The conjugate, which is usually readily soluble in aqueous organic systems or liposomes, can be chromatographed and can be characterized unequivocally by all analytical methods including NMR spectroscopy.

As example we cite the use of our concept for the generation of specific antibodies against the receptor of the epidermal growth factor (EGF-R).[8] The extracytoplasmic region 516–529 was selected by computer-supported epitope search, built up by Merrifield synthesis, and finally coupled with Fmoc-Ser(*t*Bu)-OH.[4] After cleavage from the resin, the analytically pure conjugate **2** was administered, *without further additives,* intraperitoneally to mice in a *single* dose. High titers of specific antibodies (IgM and IgG) against the tetradecapeptide EGF-R 516–529 could be established by ELISA assays[9] after two weeks (Fig. 1). The vital point is that no significant antibody titers were obtained by the tetradecapeptide alone in control experiments. A conventional immunization by a tetradecapeptide-serum-albumin conjugate required multiple antigen administration with addition of *Freund*'s adjuvant, in order to achieve comparable antibody production. With the Pam_3-Cys-Ser-antigen conjugate **2** we were already able to prepare monoclonal antibodies that were detectable in cell culture supernatants and as ascites.

Pam_3Cys conjugates are also strongly immunogenic in cell cultures[9] (Fig. 1). Hence, conventional and monoclonal antibodies against weakly immunogenic compounds can also be obtained in a rapid and elegant way by in-vitro immunization. The antibody titers shown in Figure 1 reflect the well-known finding that only a minor immune response can be elicited by primary in-vitro immunization.

The advantages of our concept are: simple preparation of chemically unambiguously defined antigen-adjuvant-conjugates in any desired amount; in contrast to other conjugates single administration without multiple boosting; high efficiency in vivo and in vitro. A considerable saving of experimental animals, often a complete elimination of in-vivo immunizations, and a drastic saving of time, especially for gene-technological studies are evident. Experiments with other antigens are presently being carried out in mouse cell and human cell cultures to demonstrate the general applicability of our system.

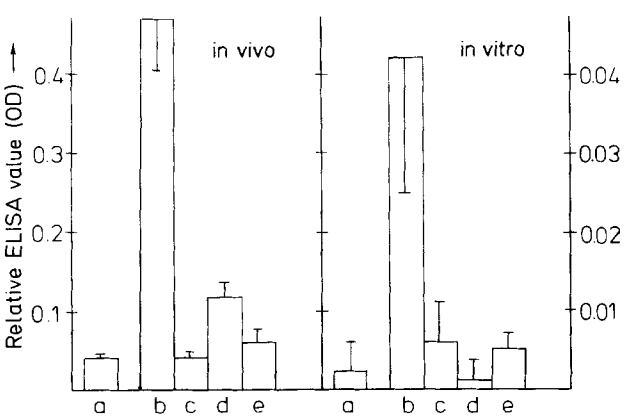


Fig. 1. Formation of specific antibodies against the tetradecapeptide EGF-R 516–529. In-vivo experiment: Control (a), immunization (single i.p. 0.2 μmol, groups of 3–5 mice (Balb/c)) [9] with the conjugate Pam_3Cys-Ser-(EGF-R 516–529) **2** (b), with the tetradecapeptide EGF-R 516–529 (c), with the adjuvant Pam_3Cys-Ser alone (d), and with a mixture of EGF-R 516–529 and Pam_3Cys-Ser (e). 14 days after the immunization the serum antibody titer was determined by ELISA (enzyme-linked immunosorbent assay) [9]. As a measure of the antibody production (specific antibody titer against EGF-R 516–529 coupled to bovine serum albumin), in each case the mean values ± standard deviation of three measurements (OD at 405 nm) are quoted; the values of the serum albumin-specific antibody (OD 0.000–0.034) are subtracted from these values.—In-vitro experiments: The experiments were carried out in microtiter plates (Falcon Plastics, Los Angeles) at a cell density of 2.5×10^6 cells/mL (37 °C, 5% CO_2, 5 days) [6c]. Concentration of the reagents used: 5×10^{-7} mM.

Synthetic example

Following the usual stepwise synthesis (Merrifield synthesis with N^{α}-Fmoc/(*t*Bu)-protection with dicyclohexylcarbodiimide/hydroxybenzotriazole (DCC/HOBt) and symmetrical anhydrides) of the EGF-R segment 516–529 [10], Fmoc-Ser(*t*Bu)-OH was incorporated as the last amino acid. After cleavage of the Fmoc group with piperidine/dimethylformamide (DMF) (1 : 1, 15 min) the resin-bound pentadecapeptide protected in the side chain by *t*Bu (1 g, loading 0.5 mmol/g) was coupled with Pam_3Cys-OH **4a** (2 mmol, in DMF/CH_2Cl_2 (1 : 1)) and DCC/HOBt (2 mmol, preactivated for 20 min at 0 °C) (16 h, then 2nd coupling, 4 h). The protected lipohexadecapeptide **1** was removed from the polymeric carrier with trifluoroacetic acid (5 mL) in the presence of thioanisole (0.25 mL) within 2 h and thereby freed also from protective groups. Yield: 960 mg (76%) **2** x CF_3COOH (correct amino acid analysis, no racemization).

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2, 98125-76-9; Pam_3Cys, 87420-41-5; FmocSer(*t*-Bu)OH, 71989-33-8; Asn-Leu_2GluGlyGluProArgGluPheValGluAsn, 98104-60-0; SerAsnLeu_2GluGly-GluProArgGluPheValGlu, 98104-61-1; EGF, 62229-50-9.

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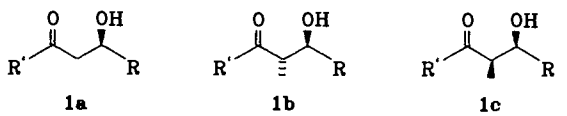
[9] W. G. Bessler, B. Suhr, H.-J. Bühring, C. P. Muller, K.-H. Wiesmüller, G. Becker, G. Jung, *Immunobiology,* in press.

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Enantio- and *anti*-Diastereoselective Aldol Additions of Acetates and Propionates via *O*-Silyl Ketene Acetals**

By *Günter Helmchen,** *Ulrich Leikauf,* and *Irmtraud Taufer-Knöpfel*

The structural units **1a–c** are present in numerous natural products. For their direct construction by enantio- and diastereoselective aldol addition, usually via carboxylic acid derivatives, excellent solutions have been found for the case of **1c**.[1] Methods for the direct synthesis of **1a**[2] and **1b**[3] have only recently been reported; as a rule, circuitous routes are chosen that can be tedious.[4] In the course of our investigations of asymmetric syntheses with enolates of esters of the alcohols **2a** and **2b**[5] we have now found that the structural units of **1a** and, albeit judged on the basis of one example only, of **1b** can be obtained highly selectively by $TiCl_4$-catalyzed addition of aldehydes to *O*-silyl ketene acetals (Mukaiyama reaction).[6]

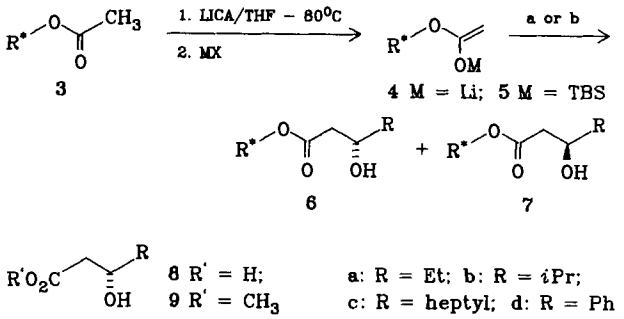


1a **1b** **1c**



2a **2b**

Reaction of the acetates **3**, R*-OH = **2a** or **2b**, with lithium cyclohexylisopropylamide (LICA) in tetrahydrofuran (THF) affords the lithium enolates **4**, which on subsequent reaction with *t*-butyldimethylsilyl chloride (TBSCl) furnish the *O*-silyl ketene acetals **5** in good yields.[7] The latter react with $TiCl_4$-complexes of achiral aldehydes to give the crystalline β-hydroxycarboxylates **6** and **7** with a diastereoselectivity of >93:7 (yield: 50–70%),[8] whereas the lithium enolates **4** react unselectively with aldehydes (Table 1). The diastereomers **6** and **7** can be separated by liquid chromatography, thus enabling determination of the diastereomeric ratio by high performance liquid chromatography (HPLC) and purification by medium pressure liquid chromatography. In the case of the Mukaiyama reaction the main product **6** can also be obtained in essentially pure form by recrystallization. Hydrolysis of the esters **6** (1.5 N methanolic KOH, room temperature) affords the carboxylic acids **8a–d** with known absolute configuration in quantitative yield. As was to be expected,[5] the esters of the alcohols **2a** and **2b** yielded enantiomeric carboxylic acids.



Scheme 1. Aldol addition of the acetate of **2a** or **2b** (R*–OH) to give β-hydroxycarboxylic acid derivatives; a: RCHO, THF, –60°C (M = Li); b: RCHO/$TiCl_4$ (1:1.1), CH_2Cl_2, –80°C (M = TBS).

Table 1. Conversion of the acetates **3** of the reagents **2a** or **2b** via lithium enolates **4** or *O*-silyl ketene acetals **5** [a] into β-hydroxycarboxylates **6** and **7** (Scheme 1) [b].

Reagent	M	R	Diastereoselectivity **6** : **7** [c]	Yield [%] **6** + **7** [d]	Abs. Config. **8** or **9** [e]
2a	Li	Et	73 : 27	89 (91)	*S*
2a	Si*t*BuMe$_2$	Et	93 : 7	67 (83)	*S*
2a	Li	*n*-Heptyl	72 : 28	96	*S*
2a	Si*t*BuMe$_2$	*n*-Heptyl	93 : 7	59 (68)	*S*
2a	Li	*i*Pr	74 : 26	90	*R*
2a	Si*t*BuMe$_2$	*i*Pr	97 : 3	51 (89)	*R*
2b	Li	*i*Pr	30 : 70	85	*S*
2b	Si*t*BuMe$_2$	*i*Pr	5 : 95	62 (80)	*S*
2b	Li	Ph	38 : 62	99	*S*
2b	Si*t*BuMe$_2$	Ph	6 : 94	69 (83)	*S*

[a] Preparation: reaction of the lithium enolates **4** with 2.2 equivalents *t*BuMe$_2$SiCl/2 equivalents hexamethylphosphoric triamide (HMPT) (THF, –63°C→0°C) followed by extractive work-up (pentane/water). [b] Mukaiyama reaction: dropwise addition of a solution of *O*-silyl ketene acetal **5** in CH_2Cl_2 at –80°C to a mixture of aldehyde and $TiCl_4$ (molar ratio 1:1.1). [c] HPLC peak area ratios (silica gel, petroleum ether/ethyl acetate 9:1). [d] In brackets: corrected with respect to recovered reactant **3**. [e] **9a**: $[\alpha]_D^{20}$ +20.4 (undiluted); T. Tannabe, Y. Izumi, *Bull. Chem. Soc. Jpn. 46* (1973) 1550, (*S*)-**9a**: $[\alpha]_D^{20}$ +18.6 (undiluted). **8b**: $[\alpha]_D^{25}$ +40.2 (c = 1.2, $CHCl_3$); D. A. Evans, T. R. Taber, *Tetrahedron Lett. 21* (1980) 4675, (*R*)-**8b**: $[\alpha]_D$ +40.5 (c = 0.6, $CHCl_3$). **8c**: $[\alpha]_D^{20}$ +21.3 (c = 1, $CHCl_3$); M. Nakahata, M. Imaida, H. Ozaki, T. Harada, A. Tai, *Bull. Chem. Soc. Jpn. 55* (1982) 2186; (*S*)-**8c**: $[\alpha]_D^{20}$ –20.8 (c = 1, $CHCl_3$). **8d**: $[\alpha]_D^{25}$ –17.9 (c = 2.2, 95% EtOH) [2c]; (*R*)-**8d**: $[\alpha]_D^{25}$ +17.9 (c = 2.3, 95% EtOH).

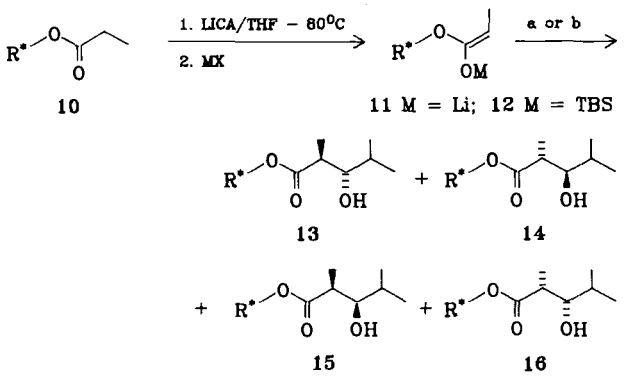
According to *Chan* et al.[9] the Mukaiyama reaction with (*E*)-*O*-silyl ketene acetals leads preferably to *anti*-3-hydroxy-2-methylcarboxylates. Since, under the conditions employed for acetates, the propionates **10** of the alcohols **2a** and **2b** furnish (*E*)-*O*-*t*-butyldimethylsilyl ketene acetals with a selectivity of 98:2, the *O*-silyl ketene acetal **12** was reacted with isobutyraldehyde-$TiCl_4$ complex in order to test the diastereoselectivity. The four diastereomeric adducts **13–16** can be readily separated by chromatography. In this case also, the Mukaiyama reaction is remarkably diastereoselective, whereas the reaction of the corresponding lithium enolate **11** once again proceeded unselectively (Table 2).

Surprisingly, the reactions of the *O*-silyl ketene acetals **5** and **12** proceed with configuratively inverse enantioface-differentiation of the aldehyde, i.e. with Re attack in the case of **5** and Si attack in the case of **12**. The diastereoface-differentiation at C-2 of **12** corresponds configura-

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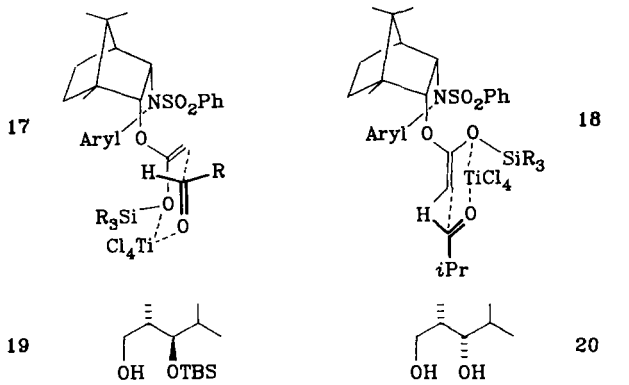
Scheme 2. Aldol reaction of the propionate **10**, R*-OH = **2a** with isobutyraldehyde; a, b: as *in Scheme 1*.

Table 2. Conversion of the propionate **10** of the alcohol **2a** via the lithium enolate **11** or *O*-silyl ketene acetal **12** with isobutyraldehyde into the β-hydroxy esters **13**–**16** (Scheme 2) [a].

Reagent	M	Diastereoselectivity *13* : *14* : *15* : *16* [b]	Yield [%] **13**–**16** [c]
2a	Li	27 : 13 : 0 : 60	94
2a	SiᵗBuMe₂	1.5 : 92 : 1.5 : 5	66 (89)

[a] For reaction conditions see Table 1. [b] [c] as in Table 1.

tively to that of the alkylation of the corresponding lithium enolate **11**. If one assumes a transition state of the Zimmermann-Traxler type and addition of the electrophile from the sterically more favorable half space of C-2, the configurational relationships can be rationalized on the basis of the transition states **17** and **18**.



The assignment of configuration with regard to C-2 and C-3 of the adducts **13**–**16**[10] was combined with an application in natural product synthesis, in that the TBS derivative of the ester **14** was reduced to the alcohol **19**, which, as building block for a synthesis of avermectin, was recently prepared via a different route.

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2a (α-*t*-butyldimethylsilyl acetate), 98269-18-2; **2b** (α-*t*-butyldimethylsilyl acetate), 98391-90-3; **3** (R* = **2a**), 98269-08-0; **3** (R* = **2b**), 98391-79-8; **4** (R* = **2a**), 98269-09-1; **4** (R* = **2b**), 98391-80-1; **5** (R* = **2a**), 98269-10-4; **5** (R* = **2b**), 98391-81-2; **6a** (R* = **2a**), 98269-11-5; **6b** (R* = **2a**), 98269-13-7; **6b** (R* = **2b**), 98391-82-3; **6c** (R* = **2a**), 98269-12-6; **6d** (R* = **2b**), 98269-14-8; **7a** (R* = **2a**), 98391-83-4; **7b** (R* = **2a**), 98391-85-6; **7b** (R* = **2b**), 98391-86-7; **7c** (R* = **2a**), 98391-84-5; **7d** (R* = **2b**), 98391-87-8; (*R*)-**8b**, 77981-87-4; (*R*)-**8c**, 19525-80-5; (*S*)-**8c**, 19526-23-9; (*R*)-**8d**, 2768-42-5; (*S*)-**8d**, 36567-72-3; (*S*)-**9a**, 42558-50-9; **10** (R* = **2a**), 76529-59-4; **11** (R* = **2a**), 98269-15-9; **12** (R* = **2a**), 98269-16-0; **13** (R* = **2a**), 98269-17-1; **14** (R* = **2a**), 98391-88-9; **15** (R* = **2a**), 98391-89-0; **16** (R* = **2a**), 98392-66-6; **19**, 97848-37-8; **20**, 98391-91-4; Et-CHO, 123-38-6; *i*-PrCHO, 78-84-2; $CH_3(CH_2)_6CHO$, 124-13-0; PhCHO, 100-52-7; *t*-butyldimethylsilyl chloride, 18162-48-6.

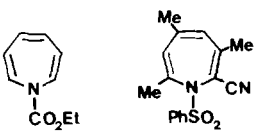
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[6] T. Mukaiyama, *Org. React. 28* (1982) 203.
[7] With chlorotrimethylsilane under the same conditions the *C*-silylated product is obtained.
[8] The acetates **3** and α-*tert*-butyldimethylsilyl acetates of the alcohols **2a** and **2b** are formed as by-products.
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[10] The relative configuration at C-2/C-3 of the acyl groups of **13**–**16** was assigned on the basis of the ^{1}H-NMR coupling constants. For determination of the absolute configuration, **14** was converted into **19** and **16** into **20**. **19** from **14**: $[\alpha]_D^{25}$ −9.4 (c = 0.6, $CHCl_3$); **19** (cf. [4c]): $[\alpha]_D$ −7.5 (c = 1.8, CH_2Cl_2); **20** from **16**: $[\alpha]_D^{25}$ +11.3 (c = 0.6, $CHCl_3$); *ent*-**20** (vgl. [11]): $[\alpha]_D^{25}$ −10.3 (c = 0.2, $CHCl_3$).
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A Previously Unrecognized 1*H*-Azepine Synthesis**

By *Hartwig Perst,* Werner Massa, Michael Lumm,* and *Gerhard Baum*

Dedicated to Professor Karl Dimroth on the occasion of his 75th birthday

In 1963 the *N*-ethoxycarbonyl derivative **1** was described as the first monocyclic, 1-substituted 1*H*-azepine.[1]



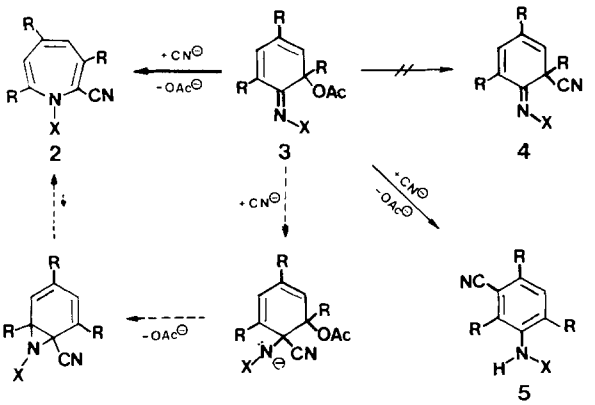
An entry to the monocyclic 1*H*-azepine **2a** first reported as long ago as 1956 by *Adams* and *Brower* seems to have been overlooked, because the authors could not, at the time, elucidate the structure of **2a**. Upon reaction of triethylammonium cyanide with the linearly conjugated 6-benzenesulfonyliminocyclohexadienyl acetate **3a** they obtained—apart from the expected 3-cyanoanilide derivative **5a** (18.5% yield)—a pale yellow compound (55% yield).[2] The structure 6-cyanocyclohexadienylideneamide **4a** proposed for this substance[3] should, according to our recent findings, be replaced by the 1*H*-azepine structure **2a**.

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On further investigation we were able to confirm the ready formation of **2a** (58% yield); furthermore, we were also able to extend this convenient entry to 2-cyano-1*H*-azepines **2** to the imines **3b**–**3d**,[4] which can be smoothly generated by oxidation of the corresponding anilides with lead tetraacetate.[5]

Attack by cyanide at the imine carbon atom of **3** followed by nitrogen neighboring-group participation with loss of the acetate residue results in formation of the 1*H*-azepines **2a**–**d** (via azanorcaradiene intermediates).[6] The competing Michael addition of the cyanide ion leads to 3-cyanoanilides **5** and, starting from **3a**–**c**, proceeds only up to a maximum of 20%, whereas in the case of **3d** it is the preferred reaction (ca. 75%).[7] In no case could a 6-cyanocyclohexadienylideneamide **4** be detected.



2–5	R	X	Yield **2** [%]
a	Me	Ph-SO_2	58
b	Me	*p*-$MeC_6H_4SO_2$	61
c	Me	Me-SO_2	59
d	Ph	*p*-$MeC_6H_4SO_2$	22

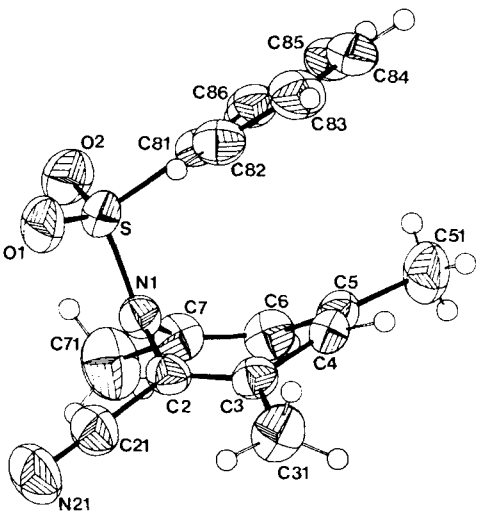


Fig. 1. Crystal structure of **2a**. ORTEP diagram, thermal ellipsoids depicted at the 50% probability level. Selected bond lengths [pm] and angles [v]: N1-C2 143.1(3), C2-C3 134.2(3), C3-C4 144.8(3), C4-C5 134.8(3), C5-C6 145.5(3), C6-C7 133.1(3), C7-N1 144.1(3), N1-S 165.1(2), S-O1 142.6(2), S-O2 142.5(2), S-C81 176.0(2), C2-C21 144.0(3), C21-N21 113.9(3); C2-N1-C7 115.9(2), N1-S-C81 106.9(1), O1-S-O2 121.1(1), C2-C21-N21 177.8(3).

The 1*H*-azepine constitutions of the compounds **2a**–**c** (pale yellow) and **2d** (deep yellow) have been confirmed by an X-ray structure analysis of **2a** (see Fig. 1).[8] ^{1}H- and ^{13}C-NMR data ruled out a cyclohexadienylideneamide formulation **4**, yet at the same time did not provide unequivocal evidence in favor of **2**.[9]

The seven-membered ring in **2a** has a boat-shaped configuration typical for 1*H*-azepines;[1c,6] the angles between the C2, C3, C6, C7 plane and the N1, C2, C7 and C3, C4, C5, C6 planes are 128.7 and 154.4°, respectively. The slightly pyramidal nitrogen center N1 lies 18 pm outside of the C2, C7, S plane; the N1–S bond is bent at an angle of 20° (towards the axial position). The phenyl ring in the *endo* position to the seven-membered ring is oriented almost parallel to the C3, C4, C5, C6[11] plane (deviation 6.8°).

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[1] a) Prior to 1965, only benzoannelated 1*H*-azepines were known; for the synthesis of monobenzo derivatives cf. K. Dimroth, H. Freyschlag, *Chem. Ber. 89* (1956) 2602; *90* (1957) 1628; b) for the synthesis of **1**: K. Hafner, *Angew. Chem. 75* (1963) 1041, and references cited therein; see also W. Lwowski, T. J. Maricich, T. W. Mattingly, Jr., *J. Am. Chem. Soc. 85* (1963) 1200; c) recent review: R. K. Smalley in A. R. Katritzky, C. W. Rees (Eds.): *Comprehensive Heterocyclic Chemistry, Vol. 7*, Pergamon Press, Oxford 1984, chap. 5.16.

[2] R. Adams, K. R. Brower, *J. Am. Chem. Soc. 78* (1956) 4770.

[3] *R. Adams*' reservation "... a new quinonoid substance probably having structure **X**", cf. [2] is taken into account in the entry of **4a** (≡**X**) in Beilsteins Handbuch, 4th suppl., Vol. 11, Springer, Berlin 1984, p. 80, by the additional comment "(?) ... presumably ..."

[4] The synthetic procedure follows that given in [2]; instead of hydrocyanic acid, however, trimethylsilyl cyanide is used. Quantities: 2.0 mmoles of **3a**–**d**, 10 mmoles of $SiMe_3CN$, 4.0 mmoles of NEt_3 in 95% (25 mL) EtOH. We thank *B. Ziegler* (Marburg) for the synthesis of **2d**.

[5] a) R. Adams, L. Werbel, *J. Am. Chem. Soc. 80* (1958) 5799, and references cited therein [2]; b) H. H. Eckhardt, H. Perst, *Tetrahedron Lett. 1979*, 2125.

[6] Cf. the analogously realizable 1*H*-azepine synthesis by reaction of 4-methoxy-2,5-cyclohexadienylideneamides with nucleophiles: H. H. Eckhardt, D. Hege, W. Massa, H. Perst, R. Schmidt, *Angew. Chem. 93* (1981) 713; *Angew. Chem. Int. Ed. Engl. 20* (1981) 599, and references cited therein.

[7] In the case of 2,4-cyclohexadienylideneamines, nucleophilic attack at the imine C-atom is the exception, while Michael addition is the rule, cf. [2]. This similarly holds for 2,4-cyclohexadienones. Review: J. Bracht, E.-L. Dreher, A. Rieker, P. Schneider in *Houben-Weyl-Müller: Methoden der Organischen Chemie*, 4th edit., *Vol. VII/3b*, Thieme, Stuttgart 1979, p. 749, and references cited therein.

[8] **2a**: Inversion twin (ca. 1:1) in space group $P3_1(P3_2)$; $a = 1105.4(2)$, $c = 1101.3(3)$ pm, $Z = 3$, $\rho_{calc} = 1.284$ g cm^{-3}; 1443 independent reflections, 1423 of which were used, with $F_o > 3\sigma$. $R_g(F^2) = 0.024$, $R_w(F) = 0.020$, $R(F) = 0.023$. Further details of the crystal structure investigation are available on request from the Fachinformationszentrum Energie, Physik, Mathematik GmbH, D-7514 Eggenstein-Leopoldshafen 2, on quoting the depository number CSD-51503, the names of the authors, and the full citation of the journal.

[9] Selected NMR data for **2a** (m.p. 161°C; 156–157°C [2]: ^{1}H NMR (100 MHz, $CDCl_3$, δ, TMS int.): 5.90 (br., 1H, H-6), 5.48 (br., 1H, H-4), 2.27 (d, 3H, $J = 1.0$ Hz, Me-71), 2.08 (s, 3H, Me-31), 1.54 (d, 3H, $J = 1.2$ Hz, Me-51); ^{13}C NMR (100.6 MHz, $CDCl_3$, δ ($CDCl_3$) = 77.0): 151.6 (C3), 144.1 (C5), 138.8 (C7), 128 (C6), 127.8 (C4), 116.3 (C21), 102.1 (C2), 24.1 (C51), 23.3 (C71), 19.7 (C31) [10]. ^{1}H and ^{13}C NMR data for **2b** (m.p. 141°C), **2c** (m.p. 134°C), and **2d** (m.p. 200°C) are essentially similar.—IR (KBr): for **2a**–**d**, ν_{CN} between 2210 [2] and 2200 cm^{-1}. **2a**–**d** were additionally characterized by elemental analyses and mass spectra.

[10] We thank Priv.-Doz. Dr. *S. Berger* (Marburg) for determining the ^{13}C-connectivities by the INADEQUATE technique. Cf. also H.-O. Kalinowski, S. Berger, S. Barun, *^{13}C-NMR-Spektroskopie*, Thieme, Stuttgart 1984; p. 66, and references cited therein.

[11] Two other *N*-arylsulfonyl-1*H*-azepine derivatives, unlike **2a**, exhibit *exo*-aryl orientation; cf. J. C. Paul, S. M. Johnson, L. A. Paquette, J. M. Barrett, R. J. Haluska, *J. Am. Chem. Soc. 90* (1968) 5023; R. Allmann, A. Frankowski, J. Streith, *Tetrahedron 28* (1972) 581.

Photochemical Synthesis of an L-Erythrose Building Block and Its use in the Preparation of Methyl 2,3,*O*-Isopropylidene-β-L-apio-L-furanoside**

By *Alfred Nehrings, Hans-Dieter Scharf,** and *Jan Runsink*

The addition of electronically excited chiral phenylglyoxylates **1**[1] to electron-rich olefins (e.g. **2**) in the sense of a Paterno-Büchi reaction[2,3] leads to oxetanes in high diastereomeric excesses.[4,5]

Thus, the oxetane **4a** is formed exo- and diastereoselectively (*de* ≥ 96%, *exo* ≥ 99%) by photochemical addition of (1*R*,3*R*,4*S*)-(−)-8-phenylmenthyl phenylglyoxylate **1a** to 2,2-dimethyl-1,3-dioxole **2**.[6] When the menthyl esters **1b** or **1c** are used, the *de* values are 57 and 56%, respectively (see Table 1). The exoselectivity is not a result of the chiral ester grouping, for it is also observed with the achiral methyl ester (**1**, R* = Me),[7] which leads to the racemate of the oxetanes **3** and **4** (R* = Me).

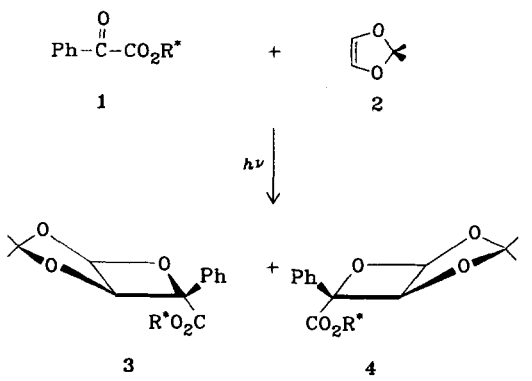


Table 1. Chemical yields and diastereomeric excesses (*de*) in the Paterno Büchi reaction of the phenyl glyoxylates **1a**–**1c**.

Alcohol R*OH	R*	Chem. yield of oxetane	*de* [a]	Excess oxetane
a	(−)-8-Ph-Menthyl [9]	99%	≥ 96%	**4a**
b	(−)-Menthyl	99%	57%	**4b**
c	(+)-Menthyl	99%	56%	**3c**

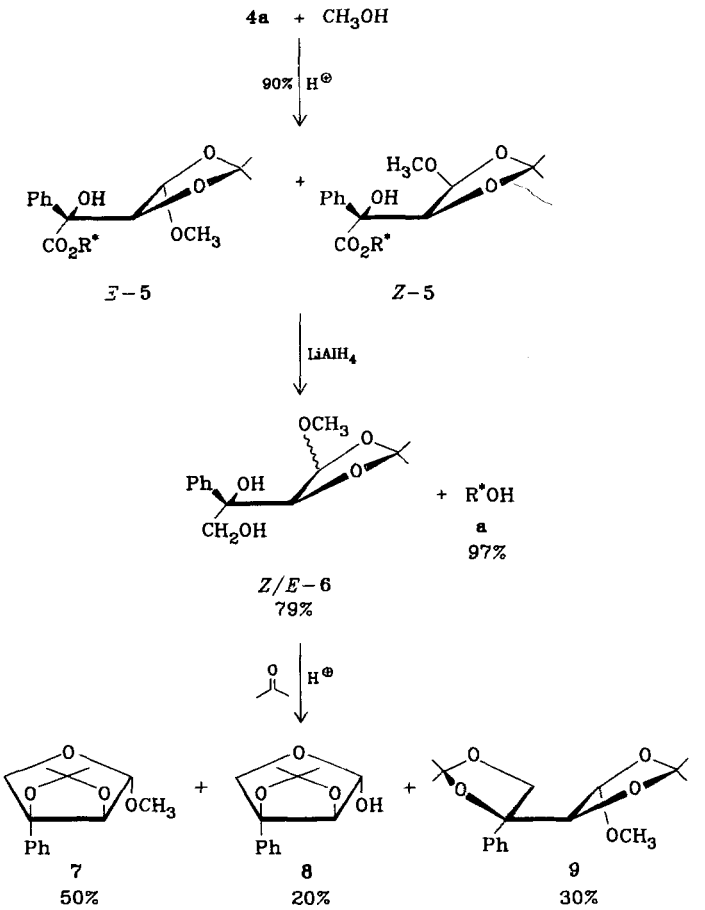
[a] Determined by ^{13}C-NMR spectroscopy.

Three chiral centers are established in a single face-differentiating reaction step. Of these three centers, two remain when the oxetane **3/4** is considered as a masked aldol[8] (photo-aldol reaction).

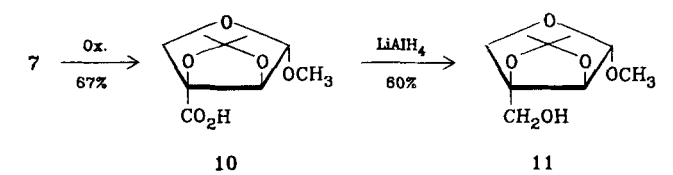
The oxetane **4a** can, for example, be used for the preparation of the apiose derivative **11**. The oxetane ring of **4a** is opened in an intermolecular transacetalization with methanol.[8] An ion-exchanger is employed as catalyst, thus facilitating easy work-up: The liquid is decanted off, filtered over silica gel, and the *Z*/*E* mixture (1:12) of the 1-*O*-methyl-1,2-*O*-isopropylidene-3-*C*-phenyl-L-*erythro*-tetruronic acid (1*R*,3*R*,4*S*)-(−)-8-phenylmenthyl ester **5** is obtained in 90% yield.[10] The reduction of this mixture *Z*/*E*-**5** with $LiAlH_4$[11] leads to recovery of the chiral alcohol in 97% yield (87% overall yield based on all reaction steps).

The *Z*/*E* mixture of 1-*O*-methyl-1,2-*O*-isopropylidene-3-*C*-phenyl-L-erythrose **6** is formed in 79% yield.

Z/*E*-**6** is cyclized by intramolecular transacetalization to the furanoside **7**, the vic. diol being protected at the same time. The furanose **8**[12] and the diacetonide **9** are obtained as by-products. The furanoses **7** and **8**, which are suitable for further syntheses are formed together in 70% overall yield.



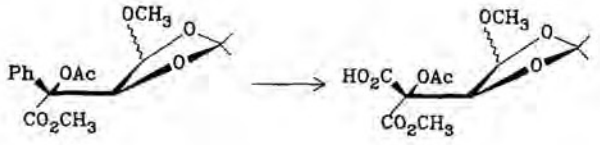
Methyl-2,3-*O*-isopropylidene-3-*C*-phenyl-β-L-*erythro*-furanoside **7**[13a] should, by way of example, serve for the synthesis of methyl-2,3-*O*-isopropylidene-β-L-apio-L-furanoside **11**.[13b] The phenyl group **7** is oxidized according to the method described by *Sharpless* et al.[14] to the carboxy group (67%) and reduced with $LiAlH_4$ in ether to give the apiose derivative **11** (60%). The structure of the apioside **11** was determined by ^{1}H- and ^{13}C-NMR spectroscopy.



In addition, a comparison with data in the literature is possible, since *Ball et al.*[15] have recorded the ^{1}H-NMR spectrum as well as measured an optical rotation ($[\alpha]_D^{25} = -108$ ($c = 3.9$, $CHCl_3$)) for the enantiomer, a derivative of D-apio-D-furanose—the naturally occurring form. The ^{1}H-NMR spectra were identical, while the synthetic product was found to have an optical rotation of $[\alpha]_D^{25} = +105$ ($c = 1.5$, $CHCl_3$).

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[**] Chiral Induction in Photochemical Reactions, Part 3. The firms Bayer AG and Haarmann & Reimer GmbH supported this work by gifts of basic chemicals.—Part 2: [5].



12 13

Degradation (or oxidation) of the phenyl group in the acetal **12**, chemoselective reduction of the carboxylic acid **13** to the alcohol, and subsequent cyclization affords access also to the *threo*-configurated derivative of the apiose, an L-apio-D-furanose derivative. It is thus shown, by way of example, that this chiralic controlled photo-aldol reaction is suitable for the general synthesis of branched carbohydrates starting from "non-sugar building blocks".[16]

Experimental

1a: A solution of pyridine (13.5 g) and (−)-8-phenylmenthol (alcohol **a**) in toluene (100 mL) was added dropwise at 0–5 °C to a solution of PhCO-COCl (20.2 g) in toluene (100 mL). After ca. 12 hours' stirring the reaction mixture was washed with 10% HCl, 5% $NaHCO_3$, and water, then dried with $MgSO_4$, and finally evaporated to dryness. Subsequent recrystallization (three times, hexane-ether 6:1) of the residue furnished 22 g of the ester **1a** (51%), m.p. 90–91.5 °C. It should be noted that, unless the alcohol **a** has been purified via its chloroacetic acid ester, a separation of diastereomers is carried out during the recrystallization, since the (−)-8-phenylmenthol synthesized according to the method given in the literature[9] contains up to 15% of an isomer.

4a: A solution of **1a** (16.4 g) and **2** (4.5 g) in anhydrous benzene (500 mL) was irradiated for 6 h with a T718Z2 (Hanau Heraeus) lamp in a falling-film apparatus. The solution was then evaporated, filtered over silica gel (CH_2Cl_2), and the residue remaining after the removal of solvent was dried. Yield 20.7 g (99%) of oxetane **4a**, m.p. 73 °C; $[\alpha]_D^{25} = -9.1$ ($c = 0.98$, EtOH). Since the volume of the irradiation vessel was ca. 1000 mL, up to 40 g of oxetane could be synthesized in one batch.

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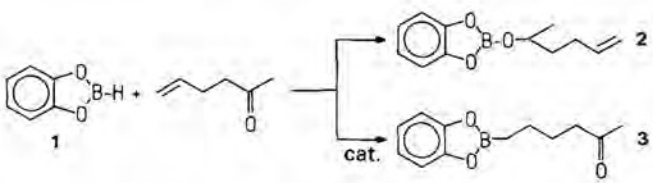
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[10] Yield referred to isolated substance.
[11] The reduction was carried out as usual, with $LiAlH_4$ in ether; the separation of *Z*/*E*-**6** and alcohol was achieved by column chromatography (silica gel, petroleum ether/acetone (6:1).
[12] The reaction was not optimized; in the presence of a drying agent the formation of **8** should be suppressed in favor of **7**.
[13] a) **7**: ^1H NMR (90 MHz, $CDCl_3$, int. TMS): $\delta = 1.21$ and 1.56 (each s, 3H, CH_3), 3.42 (s, 3H, OCH_3), 3.82 (d, $J = 10$ Hz, 1H, H-4), 4.11 (d, $J = 10$ Hz, 1H, H-4'), 4.55 (s, 1H, H-2), 5.04 (s, 1H, H-1), 7.2–7.45 (m, 3H, *m,p*-H), 7.45–7.6 (m, 2H, *o*-H); ^{13}C NMR ($CDCl_3$, int. TMS): $\delta = 26.53$ and 27.03 (each CH_3), 54.42 (OCH_3), 80.09 (C-4), 91.77 (C-2), 92.72 (C-3), 108.71 (C-1), 112.69 [$C(CH_3)_2$], 125.43 (Ph-C-2), 127.36 (Ph-C-4), 128.19 (Ph-C-3), 141.39 (Ph-C-1); b) **11**: ^1H NMR (90 MHz, $CDCl_3$, int. TMS): $\delta = 1.39$ and 1.47 (each s, 3H, CH_3), 2.85 (br. s, CH_2OH), 3.32 (s, 3H, OCH_3), 3.75 (s, 2H, CH_2OH), 3.80 (d, $J = 10$ Hz, 1H, H-4), 3.97 (d, $J = 10$ Hz, 1H, H-4'), 4.29 (s, 1H, H-2), 4.95 (s, 1H, H-1); ^{13}C NMR ($CDCl_3$, int. TMS): $\delta = 27.63$ [$C(CH_3)_2$], 54.21 (OCH_3), 64.46 (CH_2OH), 74.09 (C-4), 86.13 (C-2), 92.35 (C-3), 107.87 (C-1), 113.43 [$C(CH_3)_2$].
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Catalytic Hydroboration with Rhodium Complexes

By *Detlef Männig* and *Heinrich Nöth**

The catalytic hydrosilylation,[1] hydrocyanation,[2] and metal-catalyzed additions of element-hydrogen compounds to unsaturated functional groups of organic substrates, in particular to CC double and triple bonds, have long been known and are of industrial importance. The hydroboration of unsaturated CC systems with hydroboration agents such as H_3B/tetrahydrofuran (THF), $H_3B \cdot S(CH_3)_2$, disiamylborane, thexylborane, or $H_2BCl \cdot O(C_2H_5)_2$ proceeds even in the absence of catalysts with a high rate. Probably for this reason, no catalytic hydroborations using simple borane derivatives[4] have been described up to now despite the broad scope of hydroboration in organic synthesis.[3] There are, however, a number of hydroboration agents, such as 1,3,2-benzodioxaborole **1**, whose low activity could be considerably increased catalytically.

We have now found that hydroboration with 1,3,2-benzodioxaborole (catecholborane) **1** is catalyzed by rhodium complexes—i.e., the hydroboration of alkynes and alkenes with **1**, which requires temperatures of 70 and 100 °C (2–4 h), respectively, without a catalyst,[5] occurs without difficulty at room temperature in the presence of a catalyst. It has thereby been possible to activate the CC double bonds of olefins so strongly that they are preferentially hydroborated even in the presence of the much more reactive keto group (Table 1). For example, without a catalyst, 5-hexen-2-one reacts rapidly and quantitatively to give 2-(1-methyl-4-pentenyloxy)-1,3,2-benzodioxaborole **2**, whereas, in the presence of Wilkinson's complex, $[ClRh\{P(C_6H_5)_3\}_3]$, the ketone **3** is preferentially formed.



1 2 3

This rhodium complex is characterized by particularly high activity. The complexes $[RhCl(CO)\{P(C_6H_5)_3\}_2]$, $[RhCl(CO)\{As(C_6H_5)_3\}_2]$, and $[RhCl(cod)]_2$ (cod = 1,5-cyclooctadiene) are also suitable as catalysts for the hydroboration with **1**. Significantly lower activity is observed for $[HRuCl(CO)\{P(C_6H_5)_3\}_3]$; complexes of platinum, palladium, iridium, and cobalt exhibit no or only minor catalytic effects.

The order of reactivity of the olefins studied (Table 1) is the same as that found for $BH_3 \cdot THF$. In the case of ketones containing CC double bonds, only the keto group is reduced by **1** in the absence of $[ClRh\{P(C_6H_5)_3\}_3]$. In the presence of the catalyst, however, the CC double bond is preferentially hydroborated. The two hydroboration products formed can be separated by distillation. In contrast to the keto group, the aldehyde group is so reactive[6] that, even in the presence of the catalyst, it is not possible to activate the CC double bond sufficiently for it to compete with the CHO group.

We were also able to enhance the reactivity of 2,2,4-trimethyldioxaborinane catalytically, although less effec-

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Table 1. Catalytic hydroboration with catecholborane **1**.

Hydroboration of olefins and 1-hexyne [a]

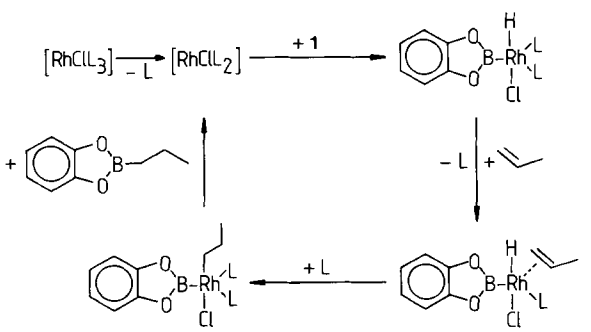
Substrate	2-Organo-1,3,2-benzodioxaborole (Yield [%])	B.p. [°C]/[torr]	$\delta(^{11}B)$
1-octene	77.7	96–97/0.12	35.8
cyclopentene	83.3	62/0.01	36.9
cyclohexene	21.5	71/0.01	35.4
3-vinylcyclohexene [b]	50.0	83/0.01	35.4
1-hexyne [c]	52.5	79/0.01	31.3

Hydroboration of ketones and nitriles containing CC double bonds [d]

Substrate	Mole ratio: Product analogous to **3** (yield[%])	: Product analogous to **2** (yield[%])	Catalyst	Main product: B.p. [°C]/[torr]	$\delta(^{11}B)$
5-hexen-2-one	0	: 100 (75.8)	no	74/0.08	23.2
5-hexen-2-one	83 (53.8)	: 17	yes	102/0.09	35.7
5-norbornen-2-one	0	: 100 (92.0)	no	96–97/0.1	23.3
5-norbornen-2-one	83 (76.7) [e]	: 17	yes	124/0.02	35.5
5-norbornene-2-carbaldehyde [f]	0	: 100 [f] (75)	no	101/0.1	23.5
5-norbornene-2-carbaldehyde	0	: 100 (74)	yes	101/0.1	23.5
2-propenyl cyanide	≈80 (48) [g]	: ≈20	yes	102/0.07	34.9

[a] Reaction conditions: 45 mmoles of substrate and of **1**, 7.5 mL of benzene, 0.05 mol-% $[ClRh nP(C_6H_5)_3]_3]$, 20°C; distillative workup after 25 min. Hydroboration does not occur under these conditions without a catalyst. [b] Only hydroboration of vinyl groups. [c] Reaction to give the alkenyl compound. [d] Reaction conditions: 22.5 mmoles of substrate and of **1**, 70 mL of benzene, 0.5 mol-% $[ClRhnP(C_6H_5)_3]_3]$ or no catalyst, 0°C. Distillative workup after 2 h. Product distribution determined by ^{11}B-NMR spectroscopy before distillation. [e] Mixture of *exo-endo* isomers, 72:28. [f] Mixture of *exo-endo* isomers, 80:20. [g] Mixture of 3- and 1-cyanopropyl compound (60:40).

tively than **1**; however, 1,3-dimethyl-1,3,2-diazaborolidine or dialkylboranes could not be activated. We suggest as an explanation that only sufficiently acidic borane components can be catalytically activated. **1** adds oxidatively to Wilkinson's complex, and the adduct formed, $[\{(C_6H_5)_3P\}_2Rh(H)Cl(BO_2C_6H_4)]$,[7] which had not previously been characterized in detail, reacts stoichiometrically with olefins, resulting in hydroboration and formation of $[\{(C_6H_5)_3P\}_2RhCl]_2$.[8]



The catalytic hydroboration of olefins by **1** is at least as good as the standard hydroboration with hydroboration agents that are more reactive than **1** and superior in the case of thermally labile olefins. Moreover, the method has the advantage that the CC double bond is preferentially hydroborated even in the presence of reactive functional groups and thus is an additional method of selective reduction.[8]

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[5] H. C. Brown, S. K. Gupta, *J. Am. Chem. Soc. 93* (1971) 1816.
[6] For the relative reactivity of unsaturated functional groups toward boranes, see [3]. The aldehyde group is much more reactive than the keto group.
[7] H. Kono, K. Ito, *Chem. Lett. 1975*, 1095. We have synthesized $[\{(C_6H_5)_3P\}_2Rh(H)Cl(BO_2C_6H_4)]$ from **1** and $[ClRh\{P(C_6H_5)_3\}_3]$ in benzene in 57% yield: IR: $\nu(RhH) = 2130\ cm^{-1}$; ^{11}B-NMR (CD_2Cl_2): $\delta = 37.7$; ^{1}H-NMR (CD_2Cl_2): $\delta = 7.8$–6.6 (m, 34H), -14.65 (dt, 1H, $J(RhH) = 27$, $^2J(PH) = 14$ Hz); m.p. = 78°C (decomp.).
[8] We will report elsewhere further evidence for the proposed mechanism and on the reduction of the olefinic double bond in the presence of other functional groups (e.g., epoxides).

Polymeric Tris[trimethyltin(IV)]hexacyanocobaltate(III), a Compound Non-Analogous to "Super Prussian Blue," and Its Tris[tricyclopentadienyluranium(IV)] Homologue**

By *Kenan Yünlü, Nils Höck,* and *R. Dieter Fischer**

Dedicated to Professor Helmut Behrens on the occasion of his 70th birthday

Organouranium(IV) and organotin(IV) compounds of the type R_3MX and $[R_3MXY]^q$ having pseudotetrahedral

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[**] Chemistry of the Tricyclopentadienyluranium(IV) Cation in Aqueous Solution, Part 4. We thank *J. P. Jacobsen* for his assistance. This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.—Part 3: [1a].

(ψ-T_d) and trigonal-bipyramidal (tbp) configuration, respectively (M = U, R = η^5-C_5H_5 = Cp; M = Sn, R = alkyl or aryl; X and Y = halide, pseudohalide; q = 0, +1, −1), exhibit similar chemical behavior.[1] Various observations[2–6] suggest that such tbp fragments of either metal (e.g., with X = Y = CN^-) might be able to incorporate d-transition-metal ions M'^{n+} (M') into one-, two-, and three-dimensionally linked coordination polymers, $\{M'[(CN)_2MR_3]_n\}_\infty \triangleq \{(R_3M)_nM'(CN)_{2n}\}_\infty$ (n = 1–3). Compounds with n = 3 deserve particular interest since large cavities "padded" by organic groups could be generated in their lattices.

The air-stable compound **1** forms spontaneously and quantitatively in aqueous solution.[7]

$$3\,Me_3SnCl + K_3[Co(CN)_6] \xrightarrow[-3\,KCl]{H_2O} [(Me_3Sn)_3Co(CN)_6]_\infty \quad \mathbf{1}$$

The fine, white precipitate can be easily purified; **1** is nonvolatile and insoluble in commonly used solvents.[8] The relatively simple vibrational spectra of **1** are devoid of H_2O bands; the spectral behavior in the ν(CN) range suggests weakly distorted O_h symmetry for the $Co(CN)_6$ units, while the Sn atoms appear to be uniformly tbp-coordinated (ψ-D_{3h} symmetry).[9,10] The ^{59}Co-NMR spectrum of the solid[11] shows one broad singlet, the high-field shift of which, along with the higher ν(CN) values of **1** (as compared with those of $K_3[Co(CN)_6]$) indicate the formation of Co−C≡N→Sn bridges.[12] In the ^{119m}Sn Mössbauer spectrum,[13] a doublet is observed which is, also in view of ΔE,[14] in accord with tbp coordination. The X-ray powder diffraction pattern[15] shows noticeably sharp reflections, the positions of which rule out a cubic lattice.

The single-crystal X-ray structure determination[16] confirms the presence of distorted octahedral $Co(CNSn)_6$ fragments (C_i microsymmetry) and tbp-configurated N_2SnMe_3 units within a strictly three-dimensional network (Fig. 1). Surprisingly, only one-third of all $(Co-C\equiv N-Sn-N\equiv C)_\infty$ chains are linear (angle between nonparallel, linear $(CoCNSnNC)_\infty$ chains, 80°); the remaining Co−C≡N−Sn sections are bent at the N atom (157.7 or 146.2°[17]). The two non-identical *trans*-$(CN)_2SnMe_3$ units (i.e., the components of linear and zigzag $(CoCNSnNC)_\infty$ chains, respectively) cannot be differentiated by vibrational spectroscopy.[18]

Apparently, compound **1** does not form an equally plausible, quasi-cubic isomer with exclusively linear $(CoCNSnNC)_\infty$ chains ("super Prussian blue" analogue; for Co_8 cubes with an edge length of 10.62 Å, $\rho_{calcd} = 0.978$ g·cm^{-1}[16]). The relatively short C···C distances between methyl groups bonded to different Sn atoms (e.g., C4···C8, C4···C7, C5···C8; 3.65–3.70 Å) along with the markedly distorted C_3 symmetry of the Sn2-C4-C5-C6 fragment (Fig. 1) do not rule out the possibility that increasing steric bulk of the group R (R ≠ Me) might force all CNSn angles to become 180°, resulting in a marked expansion and simplification of the lattice.

The extremely air-sensitive uranium complex $[(Cp_3U)_3Co(CN)_6]_\infty$ **2**, which is formally analogous to **1**, separates out as a light green, colloidal precipitate after mixing concentrated aqueous solutions of Cp_3UCl and $K_3[Co(CN)_6]$.[19] A likewise polymeric structure for **2** is suggested by its nonvolatility in high vacuum,[20] considerable thermal stability,[21] and low solubility in a variety of solvents.[22] The NIR/VIS absorption spectrum[23] shows the f-f ligand-field transitions that are very characteristic for tbp-configurated $[Cp_3UX_2]^q$ systems. The occurrence of only one ν(CN) absorption in the IR spectrum[23] is fundamentally in accord with a conceivable structure of a "super Prussian blue" analogue. Inspection of space-filling models of **1** and **2** clearly indicates that the rather expanded Cp ligands are likely to fill, and even to stabilize, the inner surfaces of the individual Co_8 cubes (with, on the average, nine Cp units per Co_8 cube) better than methyl ligands, and that UNC angles smaller than 180° should hardly be possible.[24] From an equimolar solution of Me_3SnCl and Cp_3UCl, a light green, surprisingly Sn-deficient (Sn : U ≈ 1 : 3) precipitate **3** forms (m.p. = 250 °C (decomp.)) upon addition of $K_3[Co(CN)_6]$; **3** is stable to air for several minutes but hardly differs **2** IR spectroscopically.

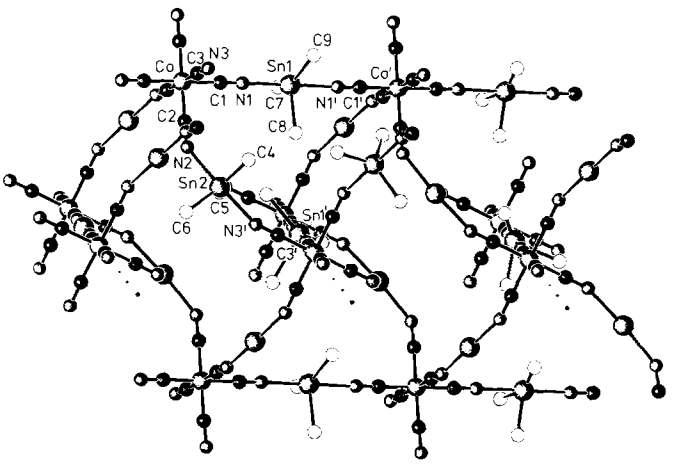


Fig. 1. SCHAKAL plot of a section of the lattice of **1**. Selected distances [Å] and angles [°]: Co-C1 1.87(2), Sn1-N1 2.35(1), C1-N1 1.10(2), Sn2-C4 2.15(3), Sn2-C5, Sn2-C6 2.083; C1-Co-C3 90.2(8), N2-Sn2-N3 173.5(7), C1-N1-Sn1 178.3(2), C2-N2-Sn2 146.5(2), C3-N3-Sn2 157.6(2), C4-Sn2-C5 120.9(1), C5-Sn2-C6 125.7(1), C4-Sn2-C6 113.3(1).

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CAS Registry numbers:
1, 98104-58-6; **2**, 98088-33-6; $R_3[Co(CN)_6]$, 13963-58-1; $(CH_3)_3SnCl$, 1066-45-1; CP_3UCl, 1284-81-7; Prussian blue, 12240-15-2.

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[6] K. Yünlü, *Dissertation*, Universität Hamburg 1983.

[7] **1**: A solution of $K_3[Co(CN)_6]$ (0.72 g, 2.1 mmol) in 20 mL of H_2O was added slowly to a stirred aqueous solution (20 mL) of $(CH_3)_3SnCl$ (1.3 g, 6.5 mmol). The white precipitate was filtered off (G4 sintered glass filter), washed in portions with 100 mL of H_2O, and dried in a drying cabinet at 100 °C for 1 h. M.p. = 335 °C (decomp.). IR (KBr): ν = 3000 (m, br.), 2915 (m), 1198 (w), 790 (vs, br.), 438 (vs, br.); Raman: ν = 2995 (s, br.), 2920 (vs), 1210 (m, br.).—Correct elemental analyses. Corresponding reactions were carried out successfully with R = C_2H_5, *n*-C_3H_7, *n*-C_4H_9, and C_6H_5, as well as with $[Fe(CN)_6]^{3-}$, instead of $[Co(CN)_6]^{3-}$ (R = CH_3)[6].

[8] E.g., H_2O, tetrahydrofuran (THF), C_6H_6, and CCl_4, but not dimethylsulfoxide or mineral acids.

[9] IR: Perkin Elmer Model 325, Nujol mull, ν = 2172 (s, CN), 2155 (vs, br., CN), 554 (s, $(SnC)_{as}$) cm^{-1}. KBr: ν = 2175 (unclear, sh), 2157 (s).

[10] Raman spectrometer Cary (Varian) Model 82; ca. −200 °C (very poor scattering power at room temperature). ν = 2195 (vs, CN), 2180 (s, CN), 2170 (sh, br., CN), 556 (m, br., $(SnC)_{as}$), 524 (s, $(SnC)_{sym}$) cm^{-1}. We thank Prof. *H. Schomborg*, Kiel, for the measurements.

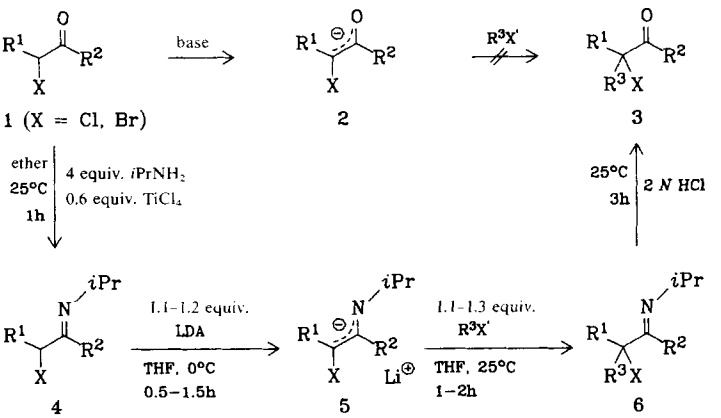
[11] JEOL Model JNM-C-60 HL ($K_3[Co(CN)_6]/H_2O$ ext.) $\delta = -225$. We thank *Dr. W.-D. Basler*, Hamburg, for the measurement.
[12] See also: a) D. R. Eaton, C. V. Rogerson, A. C. Sandercock, *J. Phys. Chem. 86* (1982) 1365; b) H. Siebert, M. Weise, *Z. Naturforsch. B30* (1975) 669.
[13] Mössbauer spectrometer FHT 400 (Frieseke and Höpfner); γ-source: $CaSnO_3$; standard: SnO_2; $-150°C$; $\delta = 1.72$; $\Delta E = 3.84$ mm s^{-1}. We thank Prof. *K. Nagorny*, Hamburg, for the measurement.
[14] See also: K. C. Molloy, M. B. Hossain, D. van der Helm, D. Cunningham, J. J. Zuckerman, *Inorg. Chem. 20* (1981) 2402, and references cited therein.
[15] Debye-Scherrer procedure; Philips PW 1050 powder diffractometer ($Cu_{K\alpha}$, Ni filter); we thank Dr. *W. Metz*, Hamburg, for the measurement.
[16] a) Colorless, transparent crystals of **1** were grown from an initially clear THF/H_2O solution (ca. 80 mL THF, 10–15 mL H_2O) containing $(CH_3)_3SnCl$ (1.75 g, 9 mmol) and $K_3[Co(CN)_6]$ (0.96 g, 3 mmol) after approximately 7 d at 4°C; b) structure determination: Hilger and Watts (Y290) four-circle diffractometer, $Mo_{K\alpha}$ ($\lambda = 0.71069$ Å), 18°C, $\rho_{exp} = 1.50$ g·cm^{-1}, $\rho_{calcd} = 1.58$ g·cm^{-1}; space group P2; due to unsatisfactory standard deviations, alternative refinement also for C2/c (75 reflections with $4\sigma \le I \le 15\sigma$ were not accounted for). The results of the two calculations differ only in the positions of the methyl groups on the linear $[-CoCNSnNC-]_\infty$ chains; $a = 16.857(6)$, $b = 12.941(7)$, $c = 14.664(5)$ Å, $\beta = 106.99(3)°$, $V = 3083(4)$ Å^3, $Z = 4$, $\theta/2\theta$-scan ($4° < 2\theta < 50°$); from 5940 mostly symmetry-related reflections, 1123 independent reflections with $|I| > 3\sigma$ were obtained (in C2/c); $R = 0.0780$.—We thank Dr. *J. Kopf*, Hamburg, for valuable discussions.—Further details of the crystal structure investigation are available on request from the Fachinformationszentrum Energie, Physik, Mathematik GmbH, D-7514 Eggenstein-Leopoldshafen 2, by quoting the depository number CSD 51436, the names of the authors, and the journal citation.
[17] Nonlinear MNC linkages have also been identified in, e.g., coordination polymers of the $[Fe(CN)_6]^{4-}$ ion. a) $K_2Zn_3[Fe(CN)_6]_2 \cdot x\,H_2O$; Zn-N-C 155–158°; P. Gravereau, E. Garnier, A. Hardy, *Acta Crystallogr. B35* (1979) 2843; b) $KCe(H_2O)_3Fe(CN)_6 \cdot H_2O$, Ce-N-C 155.9°; D. F. Mullica, W. O. Milligan, J. D. Oliver, *Inorg. Nucl. Chem. Lett. 15* (1979) 1; c) the tbp cation $[(CH_3CN)_2Sn(c\text{-}C_6H_{11})_3]^+$ is nearly linear (C_2NSnNC_2) but lacks a mirror plane (ψ-D_{3h}): Sn-N-C 168–173°, Sn-N 2.37–2.47 Å; W. A. Nugent, R. J. McKenney, R. L. Harlow, *Organometallics 3* (1984) 1315.
[18] Two likewise nonequivalent Me_3SnO_2 (tbp) units are present in one-dimensionally polymeric trimethyltin(IV) α-phenylphosphonate [14].
[19] **2**: Cp_3UCl (1.92 g, 4.1 mmol) was dissolved in ca. 150 mL of O_2-free H_2O on a G-4 Schlenk fritted glass filter and filtered. A solution of $K_3[Co(CN)_6]$ (0.46 g, 1.4 mmol) in 30 mL of H_2O was rapidly added to the green filtrate. The finely dispersed, light-green precipitate was collected, washed with a small amount of H_2O, and dried for ca. 2 h in high vacuum (ca. 30°C). Yield: 1.1 g (61.8%). Correct elemental analysis. Paramagnetism: $\mu_{eff}(293\,K) = 2.30$ B.M. [25]. An X-ray powder diffraction pattern could not be obtained [15].
[20] In contrast to the tbp systems $[Cp_3U(NCS)(NCCH_3)]$ and $[Cp_3UCN]_\infty$ [1], **2** did not afford a recognizable mass spectrum below 200°C.
[21] M.p. ≥ 310°C (decomp.). For comparison, $[Cp_3UNCS]$: m.p. = 180°C (decomp.), $[Cp_3UCN]_\infty$: m.p. = 200°C (decomp.); see [1b].
[22] For example, H_2O, C_2H_5OH, CH_3CN, $(CH_3)_2CO$, THF, C_6H_6.
[23] NIR/VIS: Cary 17 spectrometer; Teflon pellet in transmission; $\nu = 16470$ (s), 9700 (w), 7735 (s), 6486 (vs) cm^{-1} [1, 4, 6]. IR (KBr; Nujol) $\nu = 2145$ cm^{-1}; $\Delta\nu$ relative to $K_3[Co(CN)_6]$: +20 cm^{-1}.
[24] Compare also the space-filling model (a) of the anionic tbp system $[Cp_3U(NbW_5O_{19})_2]^{5-}$: V. W. Day, W. G. Klemperer, D. J. Maltbie, *Organometallics 4* (1985) 104.
[25] We thank Prof. *B. Kanellakopulos*, Karlsruhe, for susceptibility measurements in the range 4.2–320 K.

Regiospecific α-Alkylation of α-Haloalkylidenamines ("α-Haloketimines")

By *Norbert De Kimpe,* Paul Sulmon,* and *Niceas Schamp*

α-Heterosubstituted carbanions are powerful reagents for the synthesis of a large variety of compounds.[1] They may be generated from a variety of precursors, including nitriles, sulfides, sulfoxides, phosphonates, and silanes, which contain halogens, S, O, P, N, Ge, or Si in the α position. Only rarely are they prepared from α-halocarbonyl compounds, with the exception of α-haloesters (cf. Darzens reaction) and α-halocarboxylic acids. α-Haloketones are usually not susceptible to the generation of stabilized α-anions because of their high reactivity (e.g., Favorskii rearrangement, tar formation). Some α-haloenolate anions of type **2** have been described,[2–4] but most of them lack hydrogen atoms in the α′ position. Very recently, α-fluoroenolates were used in directed aldol condensations with high diastereoselectivity.[5] The remarkable progress in α-lithioimine chemistry in recent years[6] prompted us to investigate the chemical behavior of α-lithio-α-haloalkylidenamines ("α-haloketimines") **5**.[7]

The α-chloroalkylidenamines **4a,b** are readily deprotonated with lithium diisopropylamide (LDA) in tetrahydrofuran (THF) at 0°C (1–2 h) to give 3-chloro-1-azaallylic carbanions **5a,b**, which are stable for at least one day at



a: $R^1 = R^2 = Me$, X = Cl; **b**: $R^1 = Ph$, $R^2 = Me$, X = Cl;
c: $R^1 = Me$, $R^2 = Ph$, X = Br; **d**: $R^1 = Me$, $R^2 = Ph$, X = F

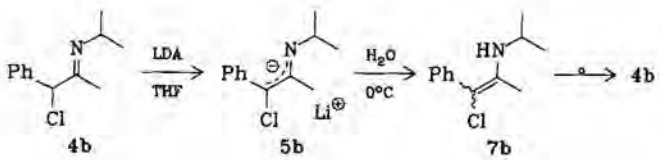
Table 1. α-Alkylation of **4** via **5** to give **6** [a].

4	R^3X'	Yield [%]
a	MeI	86 [b]
a	*i*PrI	68 [c]
a	$CH_2{=}CH(CH_2)_3Br$	65
b	MeI	88 [d]
b	BuI	72
c	MeI	72 [e]
c	$CH_2{=}CHCH_2Br$	86
c	$CH_2{=}CH(CH_2)_3Br$	88
d	MeI	92 [f]
d	$Cl(CH_2)_3Br$	88 [g]

[a] Azaallylic anions **5** are generated from **4** and LDA (1.1–1.2 equiv.) in THF (N_2, 0°C). After 0.5–1.5 h the carbanions are treated with the electrophiles (1.1–1.3 equiv., room temperature, 1–2 h), followed by quenching with water and extraction with ether or dichloromethane. The compounds **6** were obtained free of side products and were characterized by ^{1}H-NMR, ^{13}C-NMR, IR, and MS.—Selected spectroscopic data for **6** and **3**: *N*-(2-chloro-1,2,3-trimethylbutylidene)isopropylamine **6a**, $R^3 = i$Pr: IR (NaCl): 1656 cm^{-1} (ν(C=N)). ^{1}H-NMR (CCl_4) $\delta = 0.78$ and 1.05 (2d, 6H, $J = 7$ Hz, C-CH*Me*$_2$), 1.09 (d, 6H, $J = 6.5$ Hz, N-CH*Me*$_2$), 1.50 (s, 3H, *Me*CCl), 1.95 (s, 3H, *Me*C=N), 2.35 (sept., 1H, $J = 7$ Hz, CC*H*), 3.67 (sept., 1H, $J = 6.5$ Hz, NC*H*). ^{13}C-NMR ($CDCl_3$) $\delta = 13.16$ (q, *Me*C=N), 17.82, 22.37, 23.05 and 23.27 (4q, 4 Me), 36.52 (d, *C*HCCl), 50.7 (d, NCH), 81.77 (s, *C*Cl), 165.31 (s, *C*=N). 3-chloro-3,4-dimethyl-2-pentanone **3a**, $R^3 = i$Pr: IR (NaCl): 1720 cm^{-1} (ν(C=O)). ^{1}H-NMR (CCl_4) $\delta = 0.90$ and 1.02 (2d, 6H, $J = 7$ Hz, CH*Me*$_2$), 1.43 (s, 3H, *Me*CCl), 2.27 (s, 3H, *Me*C=O), 2.2 (sept., 1H, $J = 7$ Hz, covered, C*H*Me$_2$). Spectroscopic data, cf. [10] and N. De Kimpe, P. Sulmon, R. Verhé, L. De Buyck, N. Schamp, *J. Org. Chem. 48* (1983) 4320. [b] **6a**, R^3 = Me: b.p. = 42–45°C/11 torr. [c] Hydrolysis of **6a**, $R^3 = i$Pr, in acidic medium affords exclusively **3a**, $R^3 = i$Pr. [d] **6b**, R^3 = Me: b.p. = 52–54°C/0.04 torr. [e] **6c**, R^3 = Me: b.p. = 50–51°C/0.01 torr. [f] **6d**, R^3 = Me: m.p. = 47°C. [g] **6d**, $R^3 = (CH_2)_3Cl$.

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0 °C under N_2 and react with alkyl halides at room temperature to afford *C*-alkylated products **6** exclusively. Primary and secondary as well as functionalized alkyl halides can be used (Table 1) without giving side products. In most cases the use of hexamethylphosphoric triamide is not necessary. When the phenyl-substituted azaallylic anion **5b** is treated cautiously at 0 °C with water, protonation occurs exclusively on nitrogen to generate the fairly stable β-chloroenamine **7b** (one stereoisomer), which slowly rearranges to the α-chloroalkylidenamine **4b**. An analogous reaction sequence has been observed recently for aldimines.[7] The alkylation **4** → **6** also takes place for α-bromo- and α-fluoroalkylidenamines, **4c** and **4d**, respectively (Table 1).



The new strategy developed here allows the α-alkylation of α-haloketones **1**, even when there are hydrogen atoms in the α′ position (direct treatment of such α-haloketones with strong bases often results in tar formation). By masking the α-haloketones as α-haloalkylidenamines,[10] this transformation (**1** → **3**) becomes possible. For example, 3-chloro-2-butanone **1a** was converted via **4a** and **5a** into 3-chloro-3,4-dimethyl-2-pentanone **3a**, $R^3 = i$Pr, in 65% yield. This masking strategy demonstrates the usefulness of α-haloimines in synthetic organic chemistry.[11]

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4a, 78827-36-8; **4b**, 78827-43-7; **4c**, 98394-18-4; **4d**, 98394-19-5; **6a** (R^3 = Me), 78827-38-0; **6a** (R^3 = Pr-i), 98394-20-8; **6a** ($R^3 = (CH_2)_3-CH=CH_2$), 98394-21-9; **6b** (R^3 = Me), 87207-66-7; **6b** (R^3 = Bu), 98394-22-0; **6c** (R^3 = Me), 98394-23-1; **6c** ($R^3 = CH_2-CH=CH_2$), 98394-24-2; **6c** ($R^3 = (CH_2)_3-CH=CH_2$), 98394-25-3; **6d** (R^3 = Me), 98394-26-4; **6d** ($R^3 = (CH_2)_3-Cl$), 98394-27-5; **7b**, 98394-28-6; MeI, 74-88-4; *i*-PrI, 75-30-9; $CH_2=CH-(CH_2)_3-Br$, 1119-51-3; BuI, 542-69-8; $CH_2=CHCH_2Br$, 106-95-6; $Cl(CH_2)_3Br$, 109-70-6.

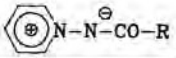
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[7] α-Lithio-α-bromoaldimine anions were synthesized by metalation with *t*BuLi of α,α-dibromoaldimines at −70 °C or deprotonation of α-bromoaldimines with LDA at −110 °C: L. Duhamel, J.-Y. Valnot, *Tetrahedron Lett. 1979*, 3319. Other examples of α-lithio-α-haloimino compounds include anions generated from cyclic α-haloimidates [8, 9].
[8] G. R. Malone, A. I. Meyers, *J. Org. Chem. 39* (1974) 618.
[9] R. Liddell, C. Whiteley, *J. Chem. Soc. Chem. Commun. 1983*, 1535.
[10] For a general synthesis of α-haloimines from α-haloketones, see N. De Kimpe, R. Verhé, L. De Buyck, L. Moëns, N. Schamp, *Synthesis 1982*, 43.
[11] For review articles on α-haloimines, see: N. De Kimpe, R. Verhé, L. De Buyck, N. Schamp, *Org. Prep. Proced. Int. 12* (1980) 49; N. De Kimpe, R. Verhé in S. Patai, Z. Rappoport (Eds.): *The Chemistry of Functional Groups, Supplement D*, Wiley, New York 1983, p. 549.

Photoreactions of *N*-(1-Pyridinio)amidates in Monolayers and Liposomes

By *Michael Haubs* and *Helmut Ringsdorf**

The variation of membrane properties via excitable assemblies is one of the essential features of cell membranes and is often triggered by photoreactions.[1] In connection with the investigation of membrane models,[2] we have studied the photochemical modification of liposomal surfaces and of monolayers using the synthetic amphiphiles **1**–**8** with the mesoionic chromophore $C_5H_5\overset{\oplus}{N}-\overset{\ominus}{N}-CO-$ as hydrophilic head group (Table 1). The photoreaction of *N*-(1-pyridinio)amidates, $C_5H_5\overset{\oplus}{N}-\overset{\ominus}{N}-CO-R$, leads to 1,2-diazepines,[3] which are markedly less polar. This opens up interesting possibilities to drastically vary the surface character of organized assemblies, such as micelles,[4] mono- and multilayers,[5] and liposomes.[6]

Table 1. Single- and double-chain amphiphiles **1**–**8** [a] with the photoreactive pyridinioamidate group $C_5H_5\overset{\oplus}{N}-\overset{\ominus}{N}-CO-$ as head group.



Compound	R	M.p. [°C]
1	C_9H_{19}	67
2	$OCH_2CH_2OCOC_{11}H_{23}$	50
3	$C_{17}H_{35}$	90
4	$C_{25}H_{51}$	100.5
5	$OC_{18}H_{37}$	92
6	$CH_2CH_2CON(C_{18}H_{37})_2$	60
7	$N(C_{18}H_{37})_2$	56
8	$N(CH_2CH_2OCOC_{15}H_{31})_2$	75

[a] The pyridinioamidates **1**–**8** were synthesized by adding the corresponding activated carbonyl component in tetrahydrofuran to a solution of 1-aminopyridinium chloride in ethanol or acetonitrile in the presence of excess K_2CO_3 [7]. The products were purified by recrystallization from acetone and hexane or by column chromatography on silica gel using chloroform/methanol (10:1) as eluent (yields: 50–90%). The 1,2-diazepines were prepared by photolyses (λ = 366 nm) of the corresponding pyridinioamidates (1% solutions in chloroform) and purified by column chromatography on silica gel using chloroform/ethanol (100:1) as eluent (yields: 40–95%). All compounds were characterized by elemental analysis and by ^{1}H-NMR, UV, and mass spectra.

Ultrasonication of the single-chain amphiphile **4** and of the double-chain amphiphiles **6**–**8** in water yields liposomes as shown by electron microscopy and dye inclusion experiments (Azure A, Rhodamine B). Formation of liposomes was also confirmed by fluorescence microscopy on large (1–10 μ) vesicles containing 1 mM Rhodamine B. Liposomal suspensions are stable at room temperature for months when kept in the dark. Liposomes are only formed in slightly acidic solution (pH 3), whereas sonication in pure water leads to a suspension of microcrystals. This may be rationalized by partial protonation of the head group, rendering it more hydrophilic. The extent of protonation is approximately 15% (at pH 3) as calculated from pH measurements and from the UV spectra, which for the protonated form do not show the long-wavelength absorption band of pyridinioamidates (Fig. 1).

The photoreactions of pyridinioamidates in organized assemblies show marked differences compared with those in solution: the quantum yield of the rearrangement is considerably lower, and the photoreaction strongly depends on the structure of the lipids and on the wavelength of ir-

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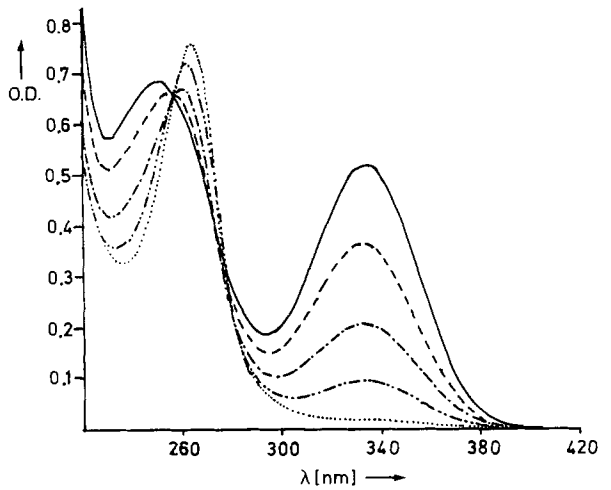
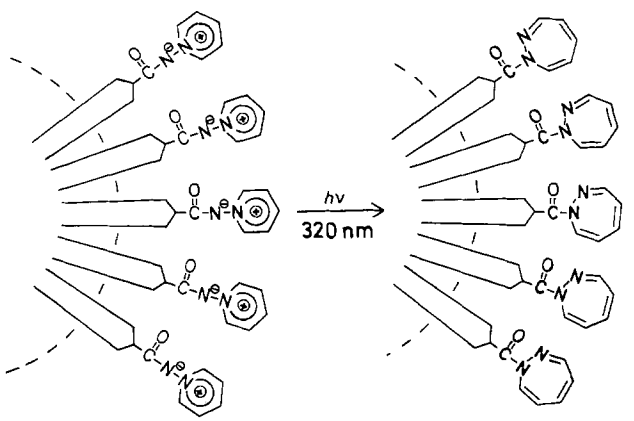


Fig. 1. UV spectra of liposomes from **8** at pH 4.1 (—), pH 2.7 (---), pH 2.2 (-·-·-), pH 1.8 (-··-··-), and pH 1.4 (····); $c = 1.8 \times 10^{-4}$ mol/L.

radiation. The lipid **8**, which contains a flexible spacer between the hydrophilic head group and each of the hydrophobic alkyl chains, is photoisomerized in the liposome to a lipid with 1,2-diazepine head groups in high yield upon irradiation with long-wavelength UV light ($\lambda = 366$ nm) (Scheme 1).



Scheme 1. Photochemical transformation of liposomes prepared from **8**.

This transformation of the polar into a nonpolar head group strongly influences the stability of the liposomal membrane. The photolyzed vesicles are metastable and collapse on mechanical stress (shearing, ultrasonication, filtration). In contrast, the photoreaction of liposomes prepared from **4**, **6**, or **7** yields a complex reaction mixture with only minor amounts of the corresponding diazepine.

Compounds **1** and **2** dissolve in water to form micelles. The foaming solutions solubilize hydrophobic dyes and chloroform, which precipitate or are released on photolysis. Compounds **3**–**8** are water-insoluble and give stable monolayers at the air-water interface. Single-chain derivatives exhibit typical collapse areas of 0.34 nm^2/molecule (packing of the head groups), whereas the monolayers of double-chain derivatives collapse at 0.45 nm^2/molecule (chain-packing).

Upon irradiation with 254-nm UV light the films prepared from **3**–**7** form stable, solid-analogue monolayers. The collapse areas of single-chain compounds decrease by approximately 40% (transition from head-packing to chain-packing). Kinetic studies with intermittent irradiation show that the decrease in area at constant surface

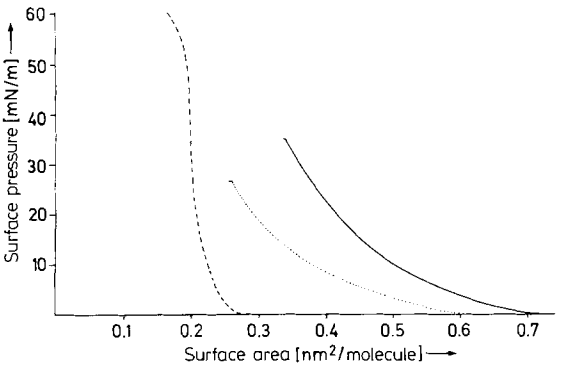


Fig. 2. Surface pressure-area isotherms of monolayers at the air-water interface at 22°C; single-chain derivative **3** (—), 254-nm photoproduct (---), and pure 1,2-diazepine (····). The compounds were spread from a 0.1% solution in $CHCl_3$ on a Langmuir film balance.

pressure solely takes place during exposure to UV light. This indicates a change in monolayer structure rather than a partial solubilization. As expected, the double-chain derivatives exhibit only slight differences in collapse areas upon irradiation because the monolayer packing is determined by the hydrophobic alkyl chains, which are not involved in the photoreaction. Figure 2 shows the spreading behavior of the single-chain compound **3**, its 254-nm photoproduct, and the corresponding pure diazepine.

TLC analyses of the photoproducts of **3**–**7** ($\lambda = 254$ nm) reveal a complex mixture in which the diazepine is just one of many components. By exposing the monolayer of **5** to 302-nm UV light, however, the corresponding diazepine is formed as the main product.

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1, 98105-01-2; **2**, 98105-02-3; **3**, 98105-03-4; **4**, 98105-04-5; **5**, 56677-45-3; **5** (1,2-diazepine), 98105-08-9; **6**, 98105-05-6; **7**, 98105-06-7; **8**, 98105-07-8; **8** (1,2-diazepine), 98105-09-0; 1-aminopyridinium chloride, 28460-19-7.

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Construction of Disaccharide *N*-Glycopeptides—Synthesis of the Linkage Region of the Transmembrane-Neuraminidase of an Influenza Virus**

By *Horst Kunz** and *Herbert Waldmann*

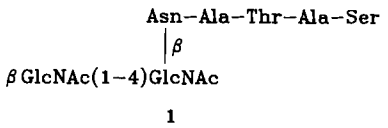
Dedicated to Professor Günter Viktor Schulz on the occasion of his 80th birthday

Glycoproteins play an important role in biological recognition processes on cell membranes, as occur in im-

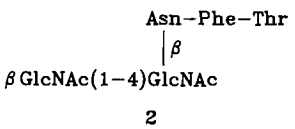
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[**] This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.

mune reactions and infection processes.[1] Important for an exact study of and the directed influence on these processes are well-defined model compounds which correspond to characteristic structural elements of glycoproteins that participate in these recognition processes. We now describe the synthesis of two such partial structures of *N*-glycoproteins, a glycopentapeptide of the linkage region **1** of the transmembrane-neuraminidase of the influenza virus strain A/Tokyo/3/67[2] and a glycopeptide of the linkage region **2** of the factor B of the human complement system.[3] Both structures contain the disaccharidic core of the di-*N*-acetylchitobiose which is characteristic for *N*-glycoproteins and which is bound *N*-glycosidically to the amide function of the asparagine of the peptide chain.

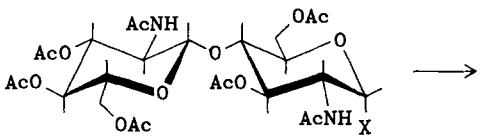


1

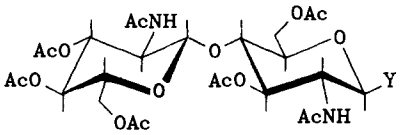


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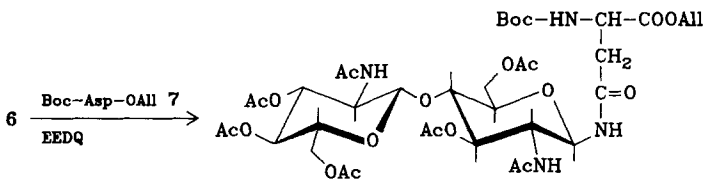
For construction of the target structures **1** and **2** the octaacetate of the chitobiose **3** is first obtained from chitin by acetylating acid hydrolysis and is converted by reaction with HCl in acetyl chloride into the peracetylated chitobiosyl chloride **4**.[4] The conversion of **4** into the β-azide **5** carried out hitherto with the aid of the sensitive silver azide was accomplished smoothly as a phase-transfer catalyzed S_N2 reaction with sodium azide in the presence of tri-*n*-caprylmethylammonium chloride in chloroform/water. Hydrogenolysis of the azide furnished the chitobiosylamine **6**, which was coupled in the presence of ethyl 2-ethoxy-1,2-dihydroquinoline-1-carboxylate (EEDQ)[5] with allyl *N*-*tert*-butyloxycarbonyl aspartate **7** in high yields to give the fully protected chitobiosylasparagine unit **8**.



3: X = OAc **4**: X = Cl, 88%

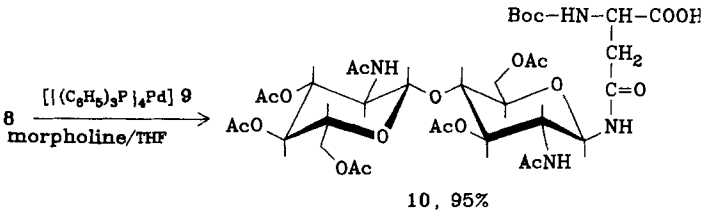


5: Y = N_3, 75% **6**: Y = NH_2, 60%

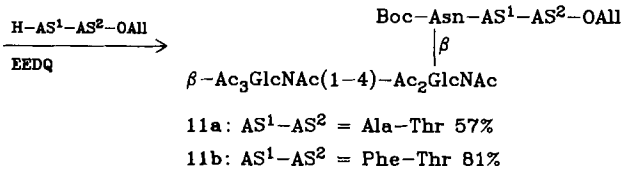


All = Allyl 8, 91%

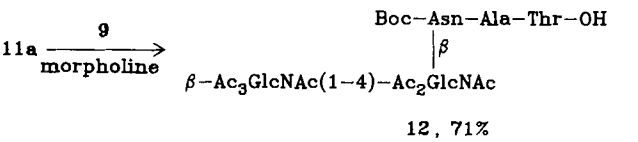
Decisive for further success of the synthesis is that the complex compound **8** containing *N*- and *O*-glycosidic bonds can be almost specifically and quantitatively *C*-terminally deblocked by palladium(0)-catalyzed allyl ester cleavage.[5] Chain lengthening at the *C*-terminal with dipeptide allyl esters[6] is then possible.



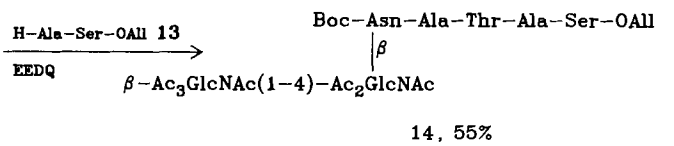
10, 95%



11a: AS^1–AS^2 = Ala–Thr 57%
11b: AS^1–AS^2 = Phe–Thr 81%



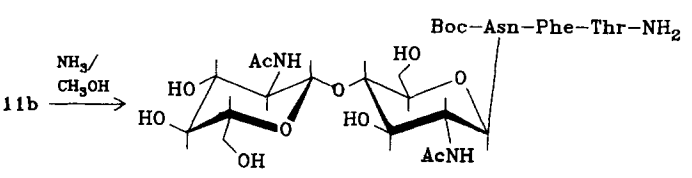
12, 71%



14, 55%

With EEDQ as condensation agent in dichloromethane the protected chitobiosylasparagine tripeptides **11** are formed, whereby the yield of **11a** is reduced due to cyclization of the less hindered dipeptide ester to the diketopiperazine during the course of the reaction. This disaccharide glycopeptide **11a** can also be selectively deblocked at the carboxyl group by Pd(0)-catalyzed allyl transfer to morpholine in dioxane at room temperature. Chromatographic separation affords the analytically pure compound **12**.[7] With the dipeptide allyl ester **13**,[6] which once again tends to undergo cyclization, the chitobiosylasparagine pentapeptide **14** is formed, which corresponds to the protected partial structure **1** of the influenza virus neuraminidase. Chromatographic separation (chloroform/ethanol 9 : 1) afforded pure **14**, which was then characterized spectroscopically.[8]

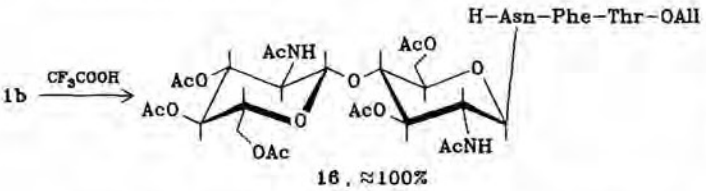
The carbohydrate hydroxyl groups of the synthetic glycopeptide can be removed under very gentle conditions with ammonia in methanol at room temperature, as was demonstrated with the compound **11b**, the protected partial structure **2** of the human complement factor B.[9] The allyl ester is concomitantly aminolyzed. The compound **15** can be isolated directly as pure crystals from methanol/chloroform and can be used for model biochemical and immunological reactions.



15, 86%

If removal of the *tert*-butyloxycarbonyl group from the glycopeptide is also desired, this does not succeed in the mainly deblocked molecule **15**. The *O*-glycoside bond of

the chitobiose is partially cleaved, both with anhydrous trifluoroacetic acid as well as with aqueous hydrochloric acid. In contrast, *N*-terminal deblocking in the fully protected glycopeptide **11b** to give **16** proceeds readily and selectively with anhydrous trifluoroacetic acid.



The hydro salt of the *N*-deblocked compound **16** opens up the possibility of both directed *N*-terminal chain lengthening as well as further deblocking in the sense outlined above.

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CAS Registry numbers:
3, 7284-18-6; **4**, 7531-49-9; **5**, 29625-70-5; **6**, 29673-51-6; **7**, 88224-27-5; **8**, 98304-16-6; **10**, 98304-17-7; **11a**, 98304-18-8; **11b**, 98304-21-3; **12**, 98330-20-2; **13**, 98304-19-9; **14**, 98330-21-3; **15**, 98304-20-2; **16**, 98330-22-4; H-Ala-Thr-OAll, 98304-22-4; H-Phe-Thr-OAll, 98304-23-5; neuraminidase, 9001-67-6.

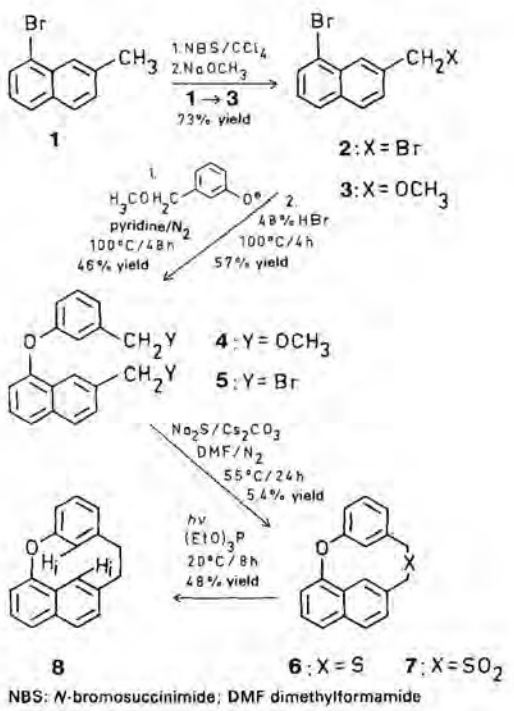
[1] Summary: E. F. Neufeld, G. Ashwell in W. J. Lennarz (Ed.): *The Biochemistry of Glycoproteins and Proteoglycans*, Plenum Press, New York 1980.
[2] C. W. Ward, T. C. Ellman, A. A. Azad, *Biochem. J. 207* (1982) 91.
[3] D. L. Christie, J. Gagnon, *Biochemistry 201* (1982) 555.
[4] M. Spinola, R. W. Jeanloz, *J. Biol. Chem. 245* (1970) 4158.
[5] H. Kunz, H. Waldmann, *Angew. Chem. 96* (1984) 49; *Angew. Chem. Int. Ed. Engl. 23* (1984) 71; here the reaction takes place within 4 h at room temperature in tetrahydrofuran (THF)/dimethyl sulfoxide (DMSO) (4:1).
[6] Preparation according to: H. Waldmann, H. Kunz, *Liebigs Ann. Chem. 1983*, 1712.
[7] Procedure: A solution of **11a** (0.28 g, 0.26 mmol) in anhydrous dioxane (10 mL) was treated under argon and in the absence of light with 30 mg (0.026 mmol) of tetrakis(triphenylphosphane)palladium(0) and then dropwise with 0.26 g (3 mmol) of morpholine. The mixture was stirred for 12 h at room temperature, evaporated to dryness, and the resulting *C*-terminally deblocked di-*N*-acetylchitobiosaminyl tripeptide **12** purified chromatographically on silica gel, the impurities being first removed with chloroform/ethanol (9:1) and **12** then being eluted with methanol. Yield 0.19 g (71%); m.p. 218–220°C; $[\alpha]_D^{22} = 6.2$ ($c = 0.2$, DMSO).—270-MHz ^{1}H NMR ([D$_6$]DMSO): $\delta = 8.51$ (d, $J = 10$ Hz, 1H, γ-NH Asn), 8.05 (d, $J = 10$ Hz, 1H, NH), 7.94 (d, $J = 8.5$ Hz, 1H, NH), 7.87 (d, $J = 9$ Hz, 1H, NH), 7.53 (d, $J = 7.5$ Hz, 1H, NH), 6.86 (d, $J = 9.2$ Hz, 1H, NH urethane), 5.11 (dd, J(H1/NH) = 10, J(H1/H2) = 9.5 Hz, 1H, H1), 4.68 (d, J(H1'/H2') = 8.3 Hz, 1H, H1'), 2.49 (dd, $J_{gem} = 11.9$, $J_{vic} = 7.5$ Hz, 1H, β-CH$_a$ Asn), 2.03, 2.0, 1.94, 1.93 and 1.91 (5s, 15H, 5CH$_3$-COO), 1.74 (s, 6H, 2CH$_3$-CONH), 1.38 (s, 9H, (CH$_3$)$_3$C), 1.20 (d, $J = 6$ Hz, 3H, CH(OH)-CH$_3$), 0.95 (d, $J = 6.2$ Hz, 3H, CH-CH$_3$).
[8] M.p. 202°C; $[\alpha]_D^{22} = -3.3$ ($c = 0.1$, DMSO).—FAB mass spectrum: m/z_{calc} 1219, m/z_{obs} 1258 ($(M+K)^+$).—270-MHz ^{1}H NMR ([D$_6$]-DMSO): $\delta = 8.5$–8.4 (m, 2H, NH), 8.22 (d, $J = 7.6$ Hz, 1H, NH), 8.02 (d, $J = 9.1$ Hz, 1H, NH), 7.83 (d, $J = 7.5$ Hz, 1H, NH), 7.24 (d, $J = 7.8$ Hz, 1H, NH), 5.9 (ddt, 1H, CH=CH$_2$), 5.31 (dd, $J_{trans} = 17.3$, $J_{gem} = 1.7$ Hz, 1H, CH=CH$_{2\,trans}$), 5.19 (dd, $J_{cis} = 9.6$, $J_{gem} = 1.7$ Hz, 1H, CH=CH$_{2\,cis}$), 4.68 (d, J(H1'/H2') = 8.2 Hz, 1H, H1'), 4.57 (d, $J = 4.8$ Hz, 2H, CH$_2$-CH=CH$_2$), 2.04, 2.01, 1.95, 1.94 and 1.90 (5s, 15H, 5CH$_3$-COO), 1.74 (s, 6H, 2CH$_3$CONH), 1.35 (s, 9H, (CH$_3$)$_3$C).
[9] Procedure: A solution of fully protected chitobiosyl tripeptide ester **11b** (0.45 g, 0.39 mol) in a cold saturated solution of ammonia in methanol (20 mL) was stirred for 2 d at room temperature. The reaction mixture was then evaporated to dryness and the residual product (**15**) purified by two recrystallizations from methanol/chloroform. Yield 0.3 g (86%), m.p. 267°C; $[\alpha]_D^{22} = -14.4$ ($c = 0.1$, H_2O).—FAB mass spectrum: $m/z_{calc} = 885.8$, $m/z_{obs} = 887$ ($M+1$), 909 ($M+Na$)$^+$.—470-MHz ^{1}H NMR (D_2O): $\delta = 7.38$ (d, $J = 7.3$ Hz, 2H, 2*o*-H C$_6$H$_5$), 7.33 (t, $J = 6.7$ Hz, 1H, *p*-H C$_6$H$_5$), 7.29 (t, $J = 6.2$ Hz, 2H, 2*m*-H C$_6$H$_5$), 5.05 (d, J(H1/H2) = 9.5 Hz, 1H, H1), 4.59 (d, J(H1'/H2') = 8.4 Hz, 1H, H1'), 3.13 (dd, $J_{vic\,a} = 7.9$, $J_{vic\,b} = 8.4$ Hz, 2H, β-CH$_2$ Phe), 2.72 (dd, $J_{vic} = 16$, $J_{gem} = 5.6$ Hz, 1H, β-CHa Asn), 2.6–2.55 (m, 1H, β-CHb Asn), 2.06 and 2.02 (2s, 6H, 2CH$_3$-CONH), 1.41 (s, 9H, (CH$_3$)$_3$C), 1.16 (d, $J = 6.2$ Hz, 3H, CH(OH)-CH$_3$).

The First [2.1] Phane: a New Helical Molecular Skeleton**

By *Karl-Heinz Duchêne* and *Fritz Vögtle**

Of the chemically and optically stable helical molecules,[1] we have been interested in the low-molecular-weight compounds with rigidly twisted structures. Whereas several families of compounds of the helical [2.2]cyclophane type[2] have been described in the last few years,[3] the synthesis of phanes with shorter bridges, e.g., [2.1]phanes, has apparently not been seriously pursued[4] because of the expected ring strain. Interest in axially and helically chiral compounds has increased in connection with the transformation of nematic liquid-crystal phases into cholesteric phases.[5]

The route to the new 6,7-dihydrobenzo[*bc*]naphtho[2,1,8-*ghi*]oxecine **8** (m.p. = 94–96°C), which is highly strained according to molecular models, proceeds via six steps starting from **1**. The crucial cyclization could not be achieved directly by C–C bond formation (using phenyl or *n*-butyllithium), but rather indirectly via the sulfide **6** (m.p. = 115–118°C), obtained using Na_2S[6] with the assistance of Cs_2CO_3, and its photochemical ring contraction using triethylphosphite (with elimination of S).[7] The pyrolysis of the sulfone **7** [m.p. > 200°C (decomp.)] has not led to **8** under the standard conditions employed so far.



NBS: *N*-bromosuccinimide; DMF dimethylformamide

In the ^{1}H-NMR spectrum of **8**, the inner protons H_i (benzene ring) and H_i (naphthalene ring) are found, as anticipated, at high field strengths ($\delta = 4.66$ and 4.75, respectively). As expected, **8** is chiral: the complete enantiomeric

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[**] New Helical Molecules, Part 12. This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie. We thank *A. Aigner* and *W. Kissener* for help, in particular for the racemic separation, and Dr. *G. Eckhardt* for help in interpreting the mass spectra.—Part 11: [1].

resolution was achieved by HPLC on a column packed with (+)-poly(triphenylmethylmethacrylate) (PTrMA).[8] The pure (−)-enantiomer of **8** has a rotation of $[\alpha]_D^{20}$ −59.1. The UV and CD spectra are shown in Figure 1.

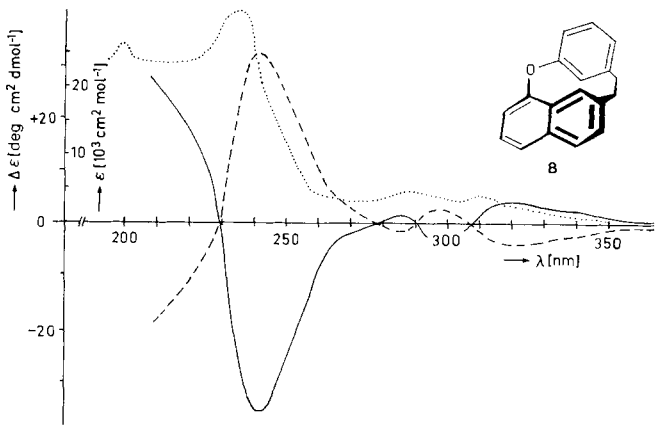


Fig. 1. CD spectra of (+)-**8** (---) and (−)-**8** (—) and UV spectrum (···) (in ethanol).

The enantiomers are stable to 200°C; only upon heating for 30 minutes at 250°C is **8** transformed into an optically inactive substance; according to the NMR and mass spectra, a transannular ring closure with loss of the two inner protons H_i and formation of benzophenanthrene and dihydrobenzophenanthrene rings occurs under these conditions.

Thus, a new framework[9] of highly strained and yet remarkably enantiomerically stable phanes and low-molecular-weight helices is available, which can be varied structurally for systematic chiroptical studies (heteroatoms S, NR, CR_2 instead of O; heterocycles instead of benzene and naphthalene; intra-annular substituents). The structural rigidification obtained here, namely, by annelation between molecular core and bridge, can be extended to other phane rings, especially in order to increase ring strain and racemization barriers.

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CAS Registry numbers:
1, 7511-27-5; **2**, 98331-27-2; **3**, 98360-88-4; **4**, 98331-28-3; **5**, 98331-29-4; **6**, 98360-89-5; **7**, 98360-90-8; (+)-**8**, 98360-91-9; (−)-**8**, 98462-55-6.

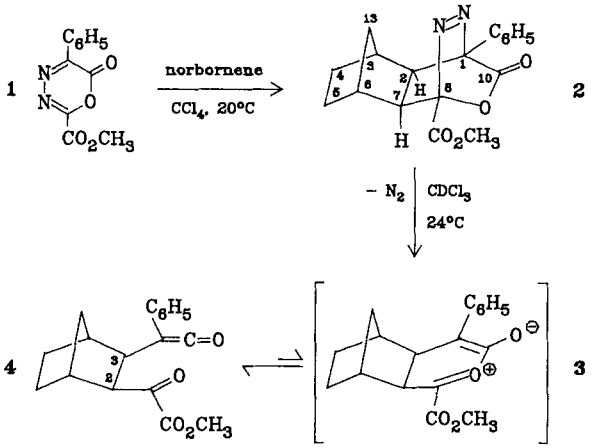
[1] W. Kissener, F. Vögtle, *Angew. Chem. 97* (1985) 227; *Angew. Chem. Int. Ed. Engl. 24* (1985) 222.
[2] K. Mislow, M. Brzechffa, H. W. Gschwend, R. T. J. Puckett, *J. Am. Chem. Soc. 95* (1973) 621.
[3] K. Meurer, F. Vögtle, A. Mannschreck, G. Stübler, H. Puff, A. Roloff, *J. Org. Chem. 49* (1984) 3484.
[4] The most strained [n.1]phanes so far known are [5.1]para- and [4.1]metacyclophane. a) H. A. Staab, A. Ruland, C. Kuo-Chen, *Chem. Ber. 115* (1982) 1755; b) M. Atzmüller, F. Vögtle, *ibid. 111* (1978) 2547; c) Review: H. Hopf, *Chem. unserer Zeit 10* (1976) 114; d) cf.: H. Günther, P. Schmitt, H. Fischer, W. Tochtermann, J. Liebe, C. Wolff, *Helv. Chim. Acta 68* (1985) 801.
[5] G. Solladié, R. G. Zimmermann, *Angew. Chem. 96* (1984) 335; *Angew. Chem. Int. Ed. Engl. 23* (1984) 348.
[6] K. Meurer, F. Vögtle, F. Luppertz, *Chem. Ber.*, in press.
[7] a) H. A. Staab, V. M. Schwendemann, *Liebigs Ann. Chem. 1979*, 1258; b) J. Bruhin, W. Jenny, *Tetrahedron Lett. 1973*, 1215.
[8] K. Meurer, A. Aigner, F. Vögtle, *J. Inclusion Phenom. 3* (1985) 51.
[9] Elemental analysis and mass spectrum are in accord with the structure of **8**. An X-ray structure analysis has not yet been possible due to the low quality of the crystals.

Primary Adduct, γ-Ketoketene, and Some Subsequent Products of the Reaction of Methyl 6-Oxo-5-phenyl-1,3,4-oxadiazinecarboxylate with Norbornene**

By *Manfred Christl,** *Ulrike Lanzendörfer, Maria M. Grötsch,* and *Joachim Hegmann*

2,5-Diaryl-1,3,4-oxadiazine-6-ones undergo Diels-Alder addition with activated olefins.[1] We have explained the remarkably rapid elimination of nitrogen from the primary adducts of type **2** in terms of a Diels-Alder cycloreversion with formation of dihydropyrylium 2-olates of type **3**,[1c] which, just like the primary adducts, could not be detected, and which should be in equilibrium with the frequently observed γ-ketoketenes of type **4**. Depending upon the nature of the olefin employed, the products isolated are derived either from intermediates analogous to **3** or to **4**. We report here on the first isolable primary product (**2**) and on unexpected reactions of the system **3** ⇌ **4**.

We have prepared the title heterocycle **1** from phenylglyoxylic acid and methyl oxalate-hydrazide according to the method described by *Steglich* et al.[2] for the diphenyl compound. That **1** is considerably more reactive than the diphenyl compound[1a,c] is demonstrated by the fact that it added norbornene in tetrachloromethane within 16 hours at 20°C, whereupon **2** crystallized. Due to this favorable circumstance, it was possible for the first time to isolate such a compound with two groups highly prone to elimination (N_2 and CO_2). Being dissolved in $CDCl_3$, **2** lost nitrogen with a half-life of about one hour at 24°C. On mechanistic grounds the intermediate **3** should be the precursor of the ultimate product **4**,[1c] which is stable in solution.



The γ-ketoketene **4**, a tri- or tetrachloromethane solution of which was employed in the following reactions, is attracting attention by virtue of the variety of transformations it can undergo. Reaction with anhydrous hydrogen chloride furnished, apparently via 1,4-addition to the intermediate **3**, the chloro substituted lactone **5**, which, upon heating in CH_3OH/H_2SO_4, was converted into the ketobisester **6**.

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[**] Cycloadditions of 1,3,4-Oxadiazine-6-ones (4,5-Diaza-α-pyrones), Part 4. This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.—Part 3: [1c].

Table 1. Selected data of **1**, **2**, and **4** through **9** [a]; IR [cm^{-1}], NMR ($CDCl_3$; δ values, coupling constants in Hz).

1: 54% yield in two steps, orange-yellow crystals, m.p. 125–126°C.—IR (KBr): 1782, 1745 (C=O)

2: 66% yield, colorless crystals, m.p. 105°C (dec.).—*IR* (KBr): 1780, 1750 (C=O).—UV (hexane): $\lambda_{max}=376$ ($\varepsilon\approx 50$).—^{1}H NMR: 0.76, 1.30 (each br. d, $J=11.8$; 13-H_2); 1.06, 1.22 (each dddd, $J=12.5$, 8.7, 4.3, 2.5; 4_{endo},5_{endo}-H); 1.43, 1.59 (each tt, $J=12.5$, 4.3; 4_{exo},5_{exo}-H); 2.06, 2.65 (each br. d, $J=4.3$; 3,6-H); 2.40, 2.70 (each d, $J=8.4$; 2,7-H); 4.13 (s; CH_3); C_6H_5: 7.51 (*p*-H), 7.59 (*m*-H), 8.00 (*o*-H)

4: IR (CCl_4, yellow solution): 2105 (C=C=O); 1730 (C=O).—^{1}H NMR: 3.10, 3.92 (each dd, $J=8.9$, 1.5; 2,3-H); 3.33 (s; CH_3) [b]

5: 90% yield (referred to **1**), colorless crystals, m.p. 153°C.—IR (KBr): 1757, 1780 (C=O).—^{1}H NMR: 2.57 (td, $J=8.5$, 1.4; 7-H); 2.82 (br. d, $J=8.6$; 2-H); 3.96 (s; CH_3); 4.69 (d, $J=8.4$; 6-H) [b].—^{13}C NMR: 28.40, 30.49, 33.64 (each t; C-9,10,11); 38.49, 42.19, 45.65, 46.31, 51.38 (each d; C-1,2,6,7,8); 53.83 (q; CH_3); 96.15 (s; C-3); 165.73, 168.79 (each s; C-5, CO_2CH_3); C_6H_5: 127.60 (d; *p*-C); 128.29, 130.18 (each d; *o*,*m*-C); 134.67 (*ipso*-C)

6: 83% yield (referred to **5**), colorless crystals, m.p. 118–120°C.—IR (KBr): 1745, 1732, 1720 (C=O).—^{1}H NMR: 3.00 (ddd, $J=12.3$, 9.2, 1.5; 3-H); 3.39, 3.63 (each s; $2CH_3$); 3.60 (br. d, $J=9.2$; 2-H); 3.62 (d, $J=12.3$; CHC_6H_5) [b]

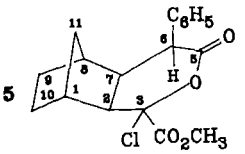
7: 17% yield (referred to **1**), colorless crystals, m.p. 111–112°C.—IR (KBr): *3480 (OH); 1742, 1710 (C=O).—^{1}H NMR:* 2.73, 2.86 (each br. d, $J=8.5$; 2,6-H); 3.24, 3.56 (each s; $2CH_3$); 3.99 (br. s; OH) [b]

8: 36% yield (referred to **1**), colorless crystals, m.p. 123–125°C.—IR (KBr): 1618 (C=C); 1728, 1751 (C=O).—^{1}H NMR: 1.24, 2.10 (each dquint, $J=10.5$, 1.5; 7-H_2); 1.30–1.48 (m; 2H); 1.56–1.78 (m; 8H); 2.02 (m, 2H); 2.21 (br. s; 1H); 2.29 (br. s; 1H); 2.34 (m; 2H); 3.09 (m; 2H); 3.14, 3.76 (each dd, $J=9.5$, 1.5; 2,3-H); 3.49 (s, CH_3); 7.12–7.26 (m; C_6H_5).—^{13}C NMR: 21.23, 24.59, 24.72, 25.59, 26.78, 29.06, 31.03, 31.24, 36.64 (each t; C-5,6,7,2′,3′,4′,5′,6′,7′); 38.34, 42.85, 51.13, 52.98 (each d; C-1,2,3,4); 52.44 (q; CH_3); 76.46 (s; C-10′); 150.16, 160.70 (each s; C-1′,8′); 179.47, 193.08, 196.03 (each s; C′-9, CO-CO_2CH_3); C_6H_5: 126.59, 128.45 (each d; *o*,*m*-C); 126.75 (d; *p*-C); 140.86 (s; *ipso*-C)

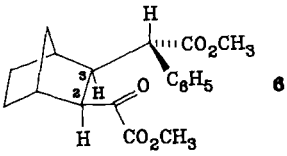
9: 50% yield (referred to **1**), colorless needles, m.p. 285°C.—IR (KBr): 1752 (several shoulders, C=O).—^{1}H NMR [c]: 0.97, 1.78 (each br. d; $J=11.5$; 17,18-H_2); 1.11, 1.26 (each m; 4,5,11,12-H_{endo}); 1.43–1.58 (m; 4,5,11,12-H_{exo}); 2.22 (br. s; 3,6,10,13-H); 2.36, 2.38 (br. AB spectrum, $J=9.0$; 2,7,9,14-H); 3.96 (s; CH_3); C_6H_5: 7.30–7.40 (m; 2H); 7.40–7.50 (m; 2H), 7.97 (br. d; 1 *o*-H).—^{13}C NMR [c]: 29.89 (double band), 34.00 (each t; C-4,5,11,12,17,18); 37.82, 38.46, 49.78, 53.06 (each d; C-2,3,6,7,9,10,13,14); 50.23 (s; C-8); 53.23 (q; *CH_3*); *85.45 (s; C-1); 170.47, 174.34 (each s; C-16, CO_2CH_3);* C_6H_5: *125.85*, 126.90, 127.28, 128.15, 131.86 (each d; 2 *o*-C, 2 *m*-C, *p*-C), 136.70 (s; *ipso*-C)

[a] Correct elemental analyses and mass spectra have been obtained for **1**, **2**, **5**–**9**. The isolation of **4** from the solution was not attempted. [b] The chemical shifts vary, but the multiplicities of the other signals are very similar to those of the corresponding signals of **2**. [c] Measurement at −50°C, since the restricted rotation of the phenyl group at 20°C gives rise to very broad phenyl signals.

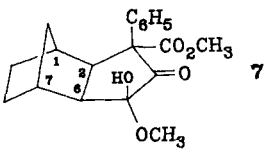
On reaction with methanol, **4** was transformed into a mixture, which, according to the number of OCH_3 signals in its ^{1}H-NMR spectrum, must consist of at least six components. So far it has only been possible to identify **6** (present in a relative amount of 10%) and the 1,2-cyclopentanedione derivative **7** (21%). Compound **7** crystallized on treatment of the mixture with CH_3OH/H_2O; the nature of **7** was disclosed by an X-ray structure analysis.[3] The ester enol presumably formed by addition of methanol to the ketene functionality of **4** could, on the one hand, isomerize to **6** and, on the other, undergo a Dieckmann condensation with the ester group that is present and thus finally give rise to **7**.



5

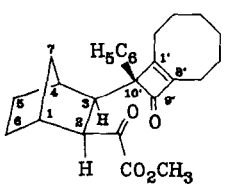


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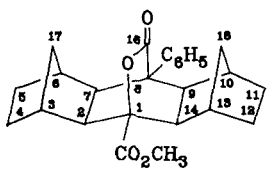


7

Cyclooctyne preferably reacted with the ketene moiety of **4** and afforded, in a [2+2]-cycloaddition, the cyclobutenone **8**, the nature of which could be confirmed by an X-ray structure analysis.[3] By way of contrast, when **4** was heated for twelve days in the presence of an excess of norbornene at 60°C the symmetrically *saturated* δ-lactone **9**



8



9

was obtained. Most likely, the well-known sluggish ketenophile norbornene[4] intercepts the heterodiene **3** in the equilibrium **3** ⇌ **4** in terms of a previously unknown variant of the Diels-Alder addition.—Some physical data of the compounds **1**, **2**, and **4** through **9** are listed in Table 1.

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CAS Registry numbers:
1, 98171-26-7; **2**, 98171-27-8; **4**, 98171-28-9; **5**, 98171-29-0; **6**, 98171-30-3; **7**, 98171-31-4; **8**, 98171-32-5; **9**, 98171-33-6; norbornene, 498-66-8; cyclooctyne, 1781-78-8.

[1] a) M. Christl, U. Lanzendörfer, S. Freund, *Angew. Chem. 93* (1981) 686; *Angew. Chem. Int. Ed. Engl. 20* (1981) 674; b) M. Christl, U. Lanzendörfer, K. Peters, E.-M. Peters, H. G. von Schnering, *Tetrahedron Lett. 24* (1983) 353; c) M. Christl, U. Lanzendörfer, J. Hegmann, K. Peters, E.-M. Peters, H. G. von Schnering, *Chem. Ber. 118* (1985) 2940.

[2] W. Steglich, E. Buschmann, G. Gansen, L. Wilschowitz, *Synthesis 1977*, 252.

[3] We thank Mrs. *E.-M. Peters*, Dr. *K. Peters*, and Prof. *H. G. von Schnering*, Max-Planck-Institut für Festkörperforschung, Heisenbergstrasse 1, D-7000 Stuttgart 80, for performing the X-ray structure analyses. The structural data will be published elsewhere.

[4] R. Huisgen, L. A. Feiler, P. Otto, *Chem. Ber. 102* (1969) 3444.

Methods of Enzymatic Analysis. Vol. 3: Enzymes 1. Oxidoreductases, Transferases. xxiv, 605 pp., bound, DM 224.00; **Vol. 4: Enzymes 2. Esterases, Glycosidases, Lyases, Ligases.** xxiv, 426 pp., bound, DM 198.00; **Vol. 5: Enzymes 3. Peptidases, Proteinases and Their Inhibitors.** xxvii, 558 pp., bound, DM 235.00 (prices when ordering all ten volumes). Edited by *H. U. Bergmeyer, J. Bergmeyer,* and *M. Grassl.* Verlag Chemie, Weinheim 1984.—ISBN 3-527-26040-4 (complete work)

Volume III follows the general trend of the two previous volumes and has been updated and considerably expanded.[*] It is the first volume in the 3rd edition to describe specific enzymes in detail, covering oxidoreductases and transferases.

Volume III begins with a general chapter—the first of seven chapters—which consists of three sections. The first section in Chapter I discusses enzyme determinations by various approaches and the limitations of these approaches. The second covers an area of increasing importance in clinical chemistry: determination of catalytic activities in body fluids other than blood. The third section discusses the principles and techniques of isoenzyme analysis.

Chapters 2 through 7 present detailed information on oxidoreductases and transferases. Each enzyme section begins with a general introduction to the enzyme and its history (general available assay methods for the enzyme, special applications of the enzyme, basic assay procedures, international reference methods and enzyme effectors or inhibitors). This information is followed by a detailed discussion of assay conditions, definitions of units of activity, temperature conversion factors for activity, equipment, preparation of reagents and stability of reagent solutions. These sections thus contain detailed descriptions of procedures for conducting assays and for analyzing the resulting data. Each section is completed by a part discussing the validity of the assay method; these sections are considerably expanded from the 2nd edition of "Methods of Enzymatic Analysis." The discussion of information concerning individual enzymes ends with approximately 20 literature references for each enzyme. These references provide the user ample opportunity for updated literature sources. Oxidoreductases are covered in detail in Chapters 2 and 3: assays available only in this edition include 3-hydroxy-3-methylglutaryl-coenzyme A reductase, "malic" enzyme, glutamate semialdehyde dehydrogenase, monoamine oxidase, glutathione reductase, cytochrome C oxidase and superoxide dismutase. Chapters 4 through 7 cover 21 transferases. New procedures are given for one-carbon group transferases (methionine synthase, thymidylate synthase), an acyltransferase (lecithin-cholesterol acyl transferase), glycosyl transferases (galactosyl transferase, purine-nucleoside phosphorylase, adenine phosphoribosyl transferase, hypoxanthine-phosphoribosyl transferase, sialyl transferase), an aminotransferase (tyrosine aminotransferase) and a phosphotransferase (adenylate kinase).

Even the enlarged 3rd edition of "Methods in Enzymatic Analysis" is not complete, and volume III has omitted detailed coverage of some enzymes described in the corresponding chapters in the 2nd edition: 6-phosphogluconate dehydrogenase, transketolase and D-glucose-1-phosphate phosphotransferase. The lack of extensive cross-references to the previous volumes can cause difficulties when attempting to obtain information on enzymes or reagents which are not described in volume III (6-phosphogluconate is covered in the reagent section of volume II). Several useful appendices, however, are maintained in each volume such as a list of symbols, abbreviations, mathematical formulae and NAD(P)H extinction coefficients.

Volume III of the 3rd edition of "Methods of Enzymatic Analysis" is a clearly written, amply referenced source of information focused on oxidoreductases and transferases and their assay procedures. The first chapter covering various kinds of enzyme determinations in water and body fluids other than blood is particularly useful. The section on isozymes is clear and well written. This volume has the form of an extensive handbook, whose size, organization and index system may cause problems for those less familiar with enzymology. Volume III provides an enormous amount of information which is not accessible in any other single source. This volume should be regarded as a basic reference on oxidoreductases and transferases. It is strongly recommended for everyone who uses enzymatic analysis.

Volume IV describes analyses for esterases, glycosidases, C–N and anhydride splitting enzymes, lyases and ligases. It continues in the spirit of volume III by providing descriptions of enzyme assays in a well-organized, strict format. Each section concerning a specific enzyme begins with a general introduction of the enzyme and its history, and continues with descriptions of available assay methods for the enzyme, special applications of the enzyme, international reference methods and enzyme effectors or inhibitors. Information concerning assay conditions, definitions of units of activity, temperature conversion factors for activity, equipment, preparation and stability of reagents follows.

The literature on each enzyme in the General Section, although expanded and updated from the previous edition, still provides information relevant only to analysis—enzyme structure and mechanisms are not discussed. A new section entitled "Enzyme Properties Relevant in Analysis" emphasizes pitfalls dependent on variables such as the source of the enzyme. The Methods of Determination section provides a new emphasis on comparison of methods, describing the limitations and applications of each. The heart of each section is a detailed, step-by-step description of the enzyme assays. The language is concise and frank; the authors reassure readers with comments such as "these assays are precise, cheap and quick" as well as providing caveats where needed. Assays which are apparently cumbersome and outdated, such as the photometric assay for lipase, are omitted from the 3rd edition. Additional sections are added where appropriate, such as "Details for Measurement in Other Body Fluids, Cells and Tissues."

Chapter I describes esterases and is divided into nine sections, each section describing one enzyme. A few new enzymes are included in the 3rd edition including cyclic nucleotide phosphodiesterase and serum ribonuclease. Chapter 2 presents glycosidases and is split into 13 sections, each section describing one enzyme or enzyme group. This chapter has been considerably expanded from the 2nd edition and now includes specific descriptions of α-amylases, cellulase, lysozyme, β-galactosidase, α-D-mannosidase, β-D-mannosidase, β-D-glucuronidase, α-L-fucosidase and β-*N*-acetylhexosaminidase. Chapter 3 covers C–

[*] Cf. *Angew. Chem. Int. Ed. Engl. 24* (1985) 797.

N bond and anhydride splitting enzymes. It consists of five sections of which three are an expansion from the 2nd edition. The newly included enzymes are arginase, β-lactamase and adenosine triphosphatases. Urease is described separately in the 3rd edition.

The final chapter consists of seven sections. This chapter is expanded with six new enzymes; two enzymes previously covered are omitted. The enzymes described in this chapter are orotidine-5-phosphate decarboxylase, citrate synthetase, fumarase, δ-aminolaevulinate dehydratase, adenylate cyclase, guanylate cyclase and fructose-1,6-biphosphate aldolase (the only enzyme also described in the 2nd edition). The two enzymes omitted are 1-phosphofructoaldolase and tetrahydrofolate formylase.

The enlarged 3rd edition provides extensive coverage of esterases, glycosidases, lyases and ligases. It is not a complete handbook; it is, however, an updated and enlarged improvement of the 2nd edition. Useful appendices follow each volume, and the lack of cross-referencing is somewhat made up for by the clear sectioning of the volumes. Volume IV is a basic source of information and is strongly recommended for everyone who uses enzymatic analysis.

Volume V describes analytical procedures for assaying proteolytic enzymes. The format is similar to the previous two volumes. Each section covering a specific enzyme begins with some general background (source and function of the enzyme, applications, special properties relevant in analysis, methods of determining activity, international reference methods and standards, and known enzyme effectors). One or two assay procedures, chosen on the basis of simplicity and reliability are then described in detail. The assays are presented in a uniform, rigidly organized, format, making them easy to follow. In many cases, a procedure for assaying enzyme inhibitors is also included.

The strength of the text lies in the attention to detail. Each assay procedure includes a discussion of the principles behind it. Information on assay conditions, equipment, preparation and stability of reagents and samples, temperature conversion factors, and calculation of results are also included. A validation of methods section following each assay discusses the reliability of the procedure, clearly warning the reader about possible sources of error or problems involving specificity.

The volume is divided into four chapters. Chapter I covers peptidases and their inhibitors. Three enzymes not discussed in the 2nd edition (angiotensin I converting enzyme, proline carboxypeptidase, and carboxypeptidase N) have been added to this edition, and angiotensinase and glycyl-glycine dipeptidase have been dropped. In total, procedures are given for assaying eight different peptidases. Chapter 2 covers proteinases and their inhibitors. Besides the sections dealing with specific enzymes, a general review is provided, covering unique features of proteinase analysis, for example: quantitation of pro-enzymes design of synthetic substrates, and differentiation of related enzymes by inhibitors. Many of the specific assays include methods for assaying pro-enzymes and inhibitors. The reader is warned when the existence of iso-enzymes or related enzymes can affect results. Eighteen proteinases are covered in this chapter. Sections on enterokinase, gelatinase, subtilisin, and the cathepsin have been added in this edition, as have sections on proteinase determination by hydrolysis of proteins and active site titrations of proteinases. Another improvement in this edition has been the replacement of a general assay for elastases with assays specific for pancreatic and leukocyte elastase as well as for the elastase-α_1-proteinase inhibitor complex.

Chapters 3 and 4 cover blood coagulation factors and complement enzymes respectively. Both of these chapters are new, neither topic being covered in the 2nd edition. Probably for this reason the introductions to these two chapters go into much more biological detail than is usual for the series. Concise descriptions of activation and regulation of the haemostatic process and the complement system are provided, as are discussions of their biological significance.

In addition to assays for fourteen enzymes and pro-enzymes involved in haemostasis, Chapter 3 provides assays for heparin, fibrinogen, and various important effectors. Two coagulation methods are also described.

Chapter 4 includes assays for six components of the complement system. For those readers interested in assaying for complement enzymes, an important caveat is included in the editor's preface to the volume. Bergmeyer notes that procedures in this rapidly growing field are too new to be proven by time and use, therefore, "these methods represent a departure from the principle of describing only well-proven methods suitable for routine use." However, the importance of the field clearly merits inclusion of the chapter.

Volume V greatly expands the coverage given peptidases and proteinases in the 2nd edition. The number of enzymes discussed is more than doubled. The increase in scope has fortunately not led to any decrease in clarity or ease of use. Volume V is the obvious first reference to turn to for analysis of proteolytic enzymes and their inhibitors.

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Polymers. Properties and Applications. Vol. 8: Polymer Degradation and Stabilization. By *W. L. Hawkins*. Springer-Verlag, Berlin 1984. xii, 120 pp., bound, DM 88.00.—ISBN 0-540-12851-4

This book[*] deals in eight main chapters with the problems of polymer degradation under various influences and possible methods of polymer stabilization. Each main chapter begins with a short introduction, in which the synoptic and clearly related subsections are summarized for the reader in an easily comprehensible fashion.

A short review of the historical development of the stabilization of rubber is the subject of the introduction for example. Quite early on it is pointed out that the explanation of the degradation mechanism of polymers is a necessary prerequisite for the development of suitable stabilizers. Thus, as a result, the following most comprehensive chapter is devoted to polymer degradation.

Pyrolysis reactions, i.e. thermal degradation in the absence of oxygen, is discussed for some chosen polymers and the mechanisms are explained. In this the hydrocarbon polymers polyethylene and polypropylene are treated preferentially. A deal of space is devoted to thermal oxidation and photooxidation, which are naturally of particular importance for the behaviour in applications. Degradation by high energy radiation, ozone, and physical effects is also dealt with briefly. Some comment about the energetic situation which leads to the coupling of two radical chains in the crystalline areas of polyolefins would have been apposite. The chapter closes with some new results on the

[*] Cf. *Angew. Chem. Int. Ed. Engl. 24* (1985) 717.

oxidative degradation of polyolefins, polystyrene, polyethylene-polypropylene blends, polycarbonates and polyacetals. On the other hand, only the hydrolytic degradation is discussed for the polyamides which serve as examples of polycondensates.

A further short chapter describes stabilization by means of structural changes, copolymerization and cross-linking, demonstrating that there are very few possibilities for stabilization in cases of purely thermal degradation without drastically changing the structure of the polymer. In this book the author quite rightly places most emphasis on stabilization against thermal oxidation and UV radiation. The mode of operation of short-term and long-term antioxidants, peroxide decomposers, metal deactivators, of antioxidant combinations, of non-migrating antioxidants such as carbon black and incorporable antioxidants is explained using polyolefins as an example. Amongst the light stabilizers an exhaustive discussion is devoted to the hindered amines as the most recent radical quenchers. Naturally the reader also obtains a quick look at the mechanism of photostabilization by benzophenones and benzotriazoles (without the Jablonski diagrams which are usually employed for this purpose). The practising synthetic organic chemist is provided with the structural modifications to UV absorbents and their effects.

The discussion of the mode of operation of anti-ozone agents is worthy of mention in the chapter on stabilization against ozone, which is the last of the stabilization chapters.

The importance of test processes as well as their advantages and disadvantages when used to determine the thermo-oxidative and photo-oxidative degradation are brought together in a separate section. Information is also given about the importance of tests which are not yet in use for the recognition of degradation in the early stages by employing chemoluminescence tests.

This book is of less use to the stabilization researcher who is not working in the polyolefin field. On the other hand the compact and logical format of the book make it very suitable for readers who wish to become familiar with the field of stabilization and degradation of polymers with polyolefins as an example.

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Practical Analytical Electron Microscopy in Materials Science. By *D. B. Williams*. Verlag Chemie International, Deerfield Beach, FL, USA 1984. vii, 153 pp., bound, $ 34.95.—ISBN 3-527-26224-5

The term Analytical Electron Microscopy (AEM) is in use for the analysis of elemental composition and crystal structure in submicron areas by means of a transmission electron microscope (TEM). This book is an introduction to elemental analysis by energy-dispersive X-ray spectrometry (EDS) and by electron energy-loss spectroscopy (EELS) and to crystal structure analysis by microdiffraction methods.

Chapter 1 introduces the different modes of AEM; it gives an overview of electron sources and detectors for X-ray quanta. Illustrative examples demonstrate AEM capabilities. Chapter 2 deals with alignment procedures for different imaging modes and for EDS and EELS. The success of AEM in the last decade has its origin in the development of the production of small electron probes with diameters of 2–100 nm by means of the prefield of the objective lens in front of the specimen foil. For localizing the electron probe, the scanning transmission electron microscope (STEM) mode has been introduced as an additional imaging mode of a TEM. Therefore, Chapter 3 compares the conventional TEM and the STEM modes for bright and dark field imaging. Quantitative X-ray microanalysis is first introduced in Chapter 4 with a brief review of the physics of X-ray production. The author discusses the optimization of an AEM for X-ray microanalysis, including the elimination of spurious X-ray signals. Quantification by the k-factor method and by thin film standards is then outlined and is followed by a discussion of the limits for minimum detectable masses and concentrations and for spatial resolution. Chapter 5, concerning EELS demonstrates the possibilities of getting information from the low-loss region (plasmon losses) and from the high-loss region (ionization edges), including the fine structure of the ionization edges. Background subtraction and deconvolution methods are discussed for both EDS and EELS. Chapter 6, which deals with microdiffraction, concentrates mainly on convergent beam diffraction patterns, including the fine structure from Bragg diffraction with reciprocal lattice points at high-order Laue zones (HOLZ). It is demonstrated how much more information is available from these HOLZ patterns than from conventional selected-area diffraction patterns.

Considering that the book has only 150 pages, it contains a wealth of information. The reference lists at the end of the Chapters are also representative and up to date. Because of its size, one cannot expect such a book to give a complete discussion of the physics of these methods. For example, the book contains nothing about the dynamic theory of electron diffraction, and one has to ask how one can understand and use convergent beam patterns, not being familiar with the basic physics of dynamic theory. Furthermore, the formation of Kikuchi lines and bands is oversimplified.

The book is expensive when compared with other text books about TEM which run to a few hundred pages and give more detailed information for the same price. It does not require just the copyright (by Philips Electronic Instruments) to give one the feeling of advertizing on many of the pages.

Nevertheless, the book is well written and contains many practical examples and excellent illustrations.

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Beilstein Handbook of Organic Chemistry, 4th Edition, 5th Supplementary Series, Volume 17/1. Edited by *R. Luckenbach*. Springer Verlag, Berlin 1984, lxxxvii, 858 pp., bound, DM 1620.00.—ISBN 3-540-13418-2

In this volume are covered heterocyclic compounds of class 10, parent compounds $C_nH_{2n}O$, $C_nH_{2n-2}O$, $C_nH_{2n-4}O$, $C_nH_{2n-6}O$ and $C_nH_{2n-8}O$. But that is not what matters and that is not why this particular Beilstein volume is singled out for review. What matters and what makes this volume of signal importance is that it is the first Beilstein volume to appear in the English language. Since World War II, like it or not, English has become the *lingua franca* of science. In general, those national journals not published in English have had diminishing impact, in large part because of the language problem outside of their home country. It has become a common complaint of

those scientists who publish in such journals that their work is insufficiently cited.

For the preparative chemist as well as for those scientists who have a need to know about the properties and reactivities of chemical compounds, three handbooks of chemistry which were published in German have been indispensable almost from the day of their respective founding: the "Beilstein Handbuch der Organischen Chemie", the "Gmelin Handbuch der Anorganischen Chemie" and "Houben-Weyl Methoden der Organischen Chemie". Of these, the Gmelin Handbook already has made the switch from German to English. And now the Beilstein Handbook has done so as well. A comparison of the present volume with a previous one written in German shows that this is not really such a very great change. There is little text in a Beilstein volume and for many of the German scientific words the English counterparts often are quite similar. Nonetheless, this change from German to English will be welcomed by all Beilstein users whose native language is not German for it will facilitate their use of the Handbook. It will be welcomed especially by the, alas, many who cannot read German at all.

The Beilstein Handbook celebrated its 100th birthday in 1981: in 1881 the first volume of the initial two volume set appeared. With the publication of the second volume in 1883 the organic chemists of the day had available a register of about 15,000 compounds. In these two volumes which totaled about 2200 pages they could find carefully selected information about the preparation and properties of these organic compounds, together with references to the original literature, an immense help to anyone active in organic research. *F. K. Beilstein,* the founder of the Handbook, born in Russia of German parents, spent his student and early professional years in Germany, but returned to Russia in 1866, at age 27, to become the successor of *Mendeleev* at the Imperial Technical Institute in St. Petersburg. However, his Handbook was published in Germany in the German language. By the time of his death in 1906, the third edition of his Handbook had just been published. There is no doubt that it fulfilled an important need when it first appeared and it won immediate acceptance by the organic chemists of that time. Chemists of the latter part of the 19th century were more literate in foreign languages than the chemists of today and that the Beilstein Handbook was written in German presented no problems.

In the succeeding years, through good times and bad, the Beilstein Handbook has continued and grown. Its impact in the world of chemistry has been, right from the start, considerable and it has become an indispensible aid to the organic chemist. It is no exaggeration to say that no library that services organic chemists can be considered complete without a set of "Beilstein". Nowhere else can one find such a comprehensive coverage of critically selected data of organic compounds of all kinds. It would appear that no stone is left unturned in this search for facts. These are culled from original research publications, patents, the review and monograph literature and theses. The information provided for a given organic compound may include its preparation, occurence in nature and isolation, physical properties, an indication of what spectroscopic properties have been reported, chemical reactivity and transformations, key literature references. It is important to note that this coverage is not exhaustive in the sense that *all* such information on a given compound is provided. As the present director of the Beilstein Institute has pointed out, it is the task of the Beilstein workers to clarify the inconsistencies found in the original research literature and omit incorrect data, to critically note ambiguous results, to ignore reported findings that are trivial in nature. Thus, the Beilstein Handbook has as its commendable objective a *critical* evaluation of the organic literature. And what a task this is! As noted already, the first two-volume edition of the Beilstein Handbook of 1883 contained about 15,000 compounds. By 1940 about 400,000 compounds had been reported in the research literature; in the 50's, already one million. Today, one may estimate a count of nearly five million! The Beilstein Institute at this point is nearing completion of the Supplementary Series IV of the Fourth Edition which covers the literature of the period 1950–1959. The next Supplementary Series V, which will cover the period 1960–1980, will truly be a challenge since these two decades have seen a veritable explosion of the organic literature. We may be certain that the members of the Beilstein Institute will rise to this difficult challenge. The continuation of the life's work of *Friedrich Beilstein* is in good hands!

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Smectic Liquid Crystals, Textures and Structures. By *G. W. Gray* and *J. W. Goodby,* Leonard Hill, Glasgow 1984. xvi, 162 pp., bound, £ 46.00.—ISBN 0-249-44168-3

Textbooks on the liquid crystalline state or on liquid crystals are a rarity. It is thus even more pleasing that this new publication gives the first comprehensive survey. The book has been written by internationally recognized experts for the practically oriented reader and for those interested in working with liquid crystals. It will contribute significantly towards ending the uncertainty still dominating the original literature concerning the nomenclature of smectic phases and thus could become the standard work on smectic liquid crystals.

The book consists of a textual section of 157 pages and another portion with 124 photographs of the characteristic textures of liquid crystalline phases taken under the polarizing microscope.

The text is clearly arranged. Nine chapters treat smectic phases A to J and the 10th chapter additionally deals with the most recent developments in phase classification and structure. The nine chapters are largely uniformly set out. A short *introduction* gives a general overview of the particular smectic phase followed by a description of the historical development of the investigations. The intelligibility of the detailed discussion of the *structure* of the phase that then follows is made easier by the large numbers of very clear schematic presentations. Finally, there is a description of the *textures* of the phase with a direct reference to the diagrams in the second part of the book. It is here that the intention of the authors is particularly clearly expressed: Reading this part of the book encourages one to sit at a polarizing microscope with the book and to investigate a known or new liquid crystal. Finally under the heading "*Identification and Classification*" significant aspects of the textures are summarized, standard substances are introduced for mixture experiments, the characteristics of X-ray diffraction data are mentioned briefly, and details are given of the thermochemical data of phase transformations. A detailed list of references is attached to each chapter.

The polarization micrographs reproduce typical texture pictures that were obtained without specific preparation techniques. The colored plates are of good quality.

This book is recommended without any reservations to all those who are concerned with or wish to concern themselves with liquid crystals. It will be an indispensable laboratory manual for the classification and identification of smectic phases.

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Analytiker-Taschenbuch. Band 5. Edited by *W. Fresenius, H. Günzler, W. Huber, I. Lüderwald, G. Tölg,* and *H. Wisser.* Springer-Verlag, Berlin 1985. xi, 348 pp., bound, DM 118.00.—ISBN 3-540-13770-X

Organic Reactions. Vol. 33. Edited by *A. S. Kende.* John Wiley, Chichester 1985. xvii, 347 pp., bound, £ 57.00.—ISBN 0-471-80229-8

Pictorial Orbital Theory. By *J. M. Tedder* and *A. Nechvatal.* Pitman Publishing Ltd., London 1985. viii, 120 pp., paperback, £ 4.95.—ISBN 0-273-01902-3

Lecture Notes in Chemistry. Series Editors: *G. Berthier, M. J. S. Dewar, H. Fischer, K. Fukui, G. G. Hall, H. Hartmann, H. H. Jaffe, J. Jortner, W. Kutzelnigg, K. Ruedenberg,* and *E. Scrocco.* **Vol. 37: Potential Energy Functions in Conformational Analysis.** By *K. Rasmussen.* Springer-Verlag, Berlin 1985. xiii, 231 pp., paperback, DM 48.00.—ISBN 3-540-13906-0

Annual Reports on Analytical Atomic Spectroscopy. Vol. 13. Reviewing 1983. Edited by *K. W. Jackson* and *L. Ebdon.* The Royal Society of Chemistry, London 1985. xii, 415 pp., bound, £ 55.00.—ISBN 0-85186-687-5

Organotin Compounds in Modern Technology. By *C. J. Evans* and *S. Karpel.* Elsevier, Amsterdam 1985. x, 280 pp., bound, HFl. 195.00.—ISBN 0-444-42422-9

Chemical Analysis Series. Vol. 74: Auger Electron Spectroscopy. By *M. Thompson, M. D. Baker, A. Christie,* and *J. F. Tyson.* John Wiley, Chichester 1985. vii, 394 pp., bound, £ 95.00.—ISBN 0-471-04377-X

Orbital Interactions in Chemistry. By *T. A. Albright, J. K. Burdett,* and *M.-H. Whangbo.* John Wiley, Chichester 1985. xv, 447 pp., bound, £ 63.25.—ISBN 0-471-87393-4

IUPAC Solubility Data Series. Series Editor: *A. S. Kertes.* **Vol. 16/17: Antibiotics I: β-Lactam Antibiotics.** Volume Editors: *E. Tomslinson* and *A. Regosz.* Pergamon Press, Oxford 1985. xxii, 790 pp., bound, £ 125.00.—ISBN 0-08-029235-6

Analytische Chemie des Mangans. Edited by *W. Fresenius.* By *O. G. Koch.* Springer-Verlag, Berlin 1985. xvi, 266 pp., bound, DM 168.00.—ISBN 3-540-13588-X

The Handbook of Environmental Chemistry. Edited by *O. Hutzinger.* **Vol. 1, Part D: The Natural Environment and the Biogeochemical Cycles.** Springer-Verlag, Berlin 1985. xi, 246 pp., bound, DM 168.00.—ISBN 3-540-15000-5; **Vol. 2, Part C: Reactions and Processes.** 1985. xiii, 145 pp., bound, DM 98.00.—ISBN 3-540-13819-6

Chromatographic Science Series. Marcel Dekker, Basel 1985. **Vol. 30: Modern Chromatographic Analysis of the Vitamins.** Edited by *A. P. De Leenheer, W. E. Lambert,* and *M. G. M. De Ruyter.* 576 pp., bound, SFr. 255.00.—ISBN 0-8247-7221-0; **Vol. 31: Ion-Pair Chromatography: Theory and Biological and Pharmaceutical Applications.** Edited by *M. T. W. Hearn.* 1985. 312 pp., bound, SFr. 195.00.—ISBN 08247-7272-5

Polysaccharide. Eigenschaften und Nutzung. Eine Einführung. Edited by *W. Burchard.* Springer-Verlag, Berlin 1985. ix, 314 pp., paperback, DM 88.00.—ISBN 3-540-13931-1

The Chemistry of Functional Groups. The Chemistry of the Metal-Carbon Bond, Vol. 2: The Nature and Cleavage of Metal-Carbon Bonds. Edited by *F. R. Hartley* and *S. Patai.* John Wiley, Chichester 1985. xiii, 904 pp., bound, £ 155.00.—ISBN 0-471-90282-9

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Arene Complexes of Univalent Gallium, Indium, and Thallium

By Hubert Schmidbaur*

Dedicated to Professor Max Schmidt on the occasion of his 60th birthday

Arene complexes of main-group metals were, until recently, rare species—in contrast to the now classical, analogous complexes of transition metals. In systematic investigations, it has been possible to prepare and structurally characterize arene complexes of the univalent elements gallium, indium, and thallium, which directly follow the d-block elements in the periodic table. This new type of compound is characterized by centric (η^6) coordination of the metal to the arene; both mono- and bis(arene) complexes are known. The interaction can be explained by the perfect agreement between the HOMO/LUMO symmetry of the arene and of the low-valent metal. The electronic states of the $nd^{10}(n+1)s^2$ configuration, which are partially modified by relativistic effects, play a particularly important role. The relationship to the few known complexes of the neighboring elements (Sn^{II}, Pb^{II}) becomes plausible via the isoelectronic principle. The arene/Ga^I, In^I, Tl^I systems are of potential significance as homogeneous reducing agents and as agents for the activation of aromatic compounds, the purification of metals, and the separation of metals from non-aqueous media.

1. Introduction

Common alkali metal salts are virtually insoluble in aromatic hydrocarbons, which, of course, is not unexpected. The rule of thumb for solvation processes, as well as detailed thermodynamic calculations, make it very unlikely that the ionic lattices of alkali metal salts should yield to hydrocarbon solvation. It is only in the presence of very bulky anions having complicated substructures or after efficient anion chelation that uncomplexed alkali metal cations are dissolved readily as solvated ion pairs in an organic liquid phase. The salts that can be precipitated from such solutions may contain, e.g., "crystal benzene." These solvent molecules,[1,2] however, are distributed more or less randomly in the lattice with no specific coordination to the alkali metal component. In such cases, alkali metal cations are rarely found in what is referred to as η^6 coordination to arenes, i.e., perpendicular to the ring center. On the contrary, the crystal benzene appears non-centered, most frequently η^2 or η^3 bonded[1,2] (cf. **A1**, **A2**).

It is therefore very intriguing that salts of low-valent metals of the third main group, such as Ga^I, In^I, or Tl^I, are often readily soluble in aromatic solvents.[3–6] For instance, $Ga[GaCl_4]$ forms a 7% (w/w) solution in benzene at room temperature, whereas $K[GaCl_4]$ is insoluble. Since the ionic radii of univalent gallium, indium, and thallium are very similar to those of the heavier alkali metals (Table 1), the coulombic terms of the lattice energy and the classical

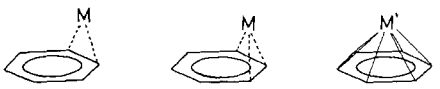
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Table 1. Ionic radii r of univalent alkali metals and of heavy metals of the third main group.

M	r [Å]	M	r [Å]
Li	0.76		
Na	1.02		
K	1.38	Ga	1.20
Rb	1.52	In	1.40
Cs	1.67	Tl	1.50

solvation energies are unlikely to be responsible for this difference in solubilities. Other factors, specific for the electronic configuration of the low-valent post-transition metals must be invoked, but until recently a complete lack of information regarding stoichiometry and structure made theoretical approaches difficult if not impossible.



A1 **A2** **A3**

A similar discrepancy exists between alkaline earth metals and divalent metals of the fourth main group. Complex halides of the latter exhibit surprisingly high solubility in aromatic hydrocarbons, whereas analogous calcium, strontium, or barium salts are completely insoluble in such solvents.[7-9]

In contrast to research in gallium, indium, or thallium chemistry, structural work on the benzene adducts of compounds like $Sn[AlCl_4]_2$ was initiated as early as 1957 by *Rundle* et al.[11] and continued later by *Amma* et al.[10] The results of these studies have established that tin(II) and lead(II) form discrete 1:1 arene complexes exhibiting η^6 coordination (cf. **A3**). No 1:2 complexes, i.e., bis(arene) complexes, were detected with metals of the fourth main group, however. On the basis of the isoelectronic principle, predictions were made as to the structures of the related hypothetical In^I or Tl^I compounds, but none of these were substantiated by experimental evidence.[11b]

Like the ions Ge^{2+}, Sn^{2+}, and Pb^{2+}, the Ga^+, In^+, and Tl^+ ions have the electronic configurations $3d^{10}4s^2$, $4d^{10}5s^2$, and $5d^{10}6s^2$, respectively. Their filled d shells require a description of bonding in arene complexes quite different from that for the d-block elements, in which incompletely filled d orbitals are available as acceptor orbitals.[12] Moreover, they also differ from the d^{10} metal ions of the elements at the end of the transition series, like Ag^+ ($4d^{10}5s^0$) or Hg^{2+} ($5d^{10}6s^0$) in that their outer s orbital is also filled (Table 2).

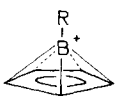
Table 2. Electronic configuration of metal cations on the borderline between p-block and d-block elements and the resulting arene coordination.

Electronic configuration	$d^{10}s^0$		$d^{10}s^2$	
Metal ions	Cu^+	Zn^{2+}	Ga^+	Ge^{2+}
	Ag^+	Cd^{2+}	In^+	Sn^{2+}
	Au^+	Hg^{2+}	Tl^+	Pb^{2+}
Arene coordination	η^2 (η^3)		η^6	

For the coinage metals (copper, silver, and gold), η^2 (or η^3) coordination is known to be the exclusive mode of arene complexation.[13] This observation is consistent with the findings for the alkali metals. It is easily explained on the basis of the analogous LUMO configurations: an empty (alkali metal) or filled (coinage metal) d shell, is followed by vacant s and p orbitals, respectively.

On account of their filled outer s orbitals, the univalent metals and divalent metals of the third and fourth main groups, respectively, are left with the outer p orbitals as the vacant acceptor orbitals (LUMO's), the energy and symmetry characteristics of which determine the strength and orientation of the arene interaction. There is little doubt, therefore, that, e.g., In^I and Sn^{II} coordination will be similar, but many questions remain unanswered, including the number of arenes that can be bonded, the relative strength of bonding, the geometrical details of the complexes, and the role of the counterions.

Of the lighter homologues, aluminum has never been observed in the univalent state, with the exception of a few high-temperature species. Boron, however, is known to form *nido*-clusters,[14a] which could also be referred to as arene complexes of boron(I) (cf. **B**). Sandwich clusters with a larger number of carbon atoms remain to be prepared.



$[BF_4]^-$ **B**

In the course of preparative and structural studies, the first mono- and bis(arene) complexes of Ga^I, In^I, and Tl^I have now been isolated and structurally characterized. The gap existing between the two blocks (Table 2) has thus been closed. Moreover, the first "bent" arene sandwich compounds of non-transition elements have also been detected. Their structural features are particularly important, since no such complexes had been reported for the neighboring isoelectronic metals of the fourth main group, or for any other main group element.

2. Practical Aspects

Solutions of low-valent gallium and indium compounds in aromatic hydrocarbons are of great interest for several reasons. First, these solutions are powerful reducing agents for a large variety of substrates. In this connection it is important that gallium, like aluminum, is neither a poisonous, hazardous element, nor an element of environmental concern. In contrast to the situation with thallium, there are no reservations about the laboratory or large-scale use of gallium. Moreover, the price of gallium metal is in an acceptable range. There also exist recent reports on the oxidation of arenes with gallium(III) to give gallium(I) complexes.[15a] Second, it is reasonable to assume that gallium(I) complexation to arenes should activate the hydrocarbon for nucleophilic substitution reactions. It is only due to the reactivity of the counterions present in most of the conventional systems (e.g., $[GaCl_4]^-$) that this possibility has not yet been exploited. The changes in the elec-

tronic states of the arene complexes have not yet been studied by, e.g., spectroscopic techniques, whereas extensive information is available on arene adducts of other metal halides.[14b] Finally, current trends in electrical conductor, semiconductor, and superconductor technologies are responsible for a growing demand for ultrahigh-purity metals. Gallium and indium are important in this context. The unusual solubility behavior of Ga^{I} and In^{I} salts may well be significant for new purification processes involving redistribution and extraction in nonaqueous solvents. Electrolytic recovery of the metal from these solutions is an established method.[15b]

3. Crystal Structures of the Arene-Free Gallium Subhalides, and ^{69}Ga,^{71}Ga-NMR Spectra of the Solids and Melts

A starting point for the discussion of the structures and NMR spectra of the arene complexes is an examination of the data for the arene-free subhalides. Of the $M^{I}[M^{III}X_4]$ phases, the structures of $In[InI_4]$,[16] $Ga[GaCl_4]$,[17] and $Ga[GaI_4]$[18] have been determined so far. Of these, the first two crystallize in the same orthorhombic space group Pnna. M^{I} occupies the center of an only slightly distorted dodecahedron formed by eight halogen atoms. M^{III} occupies the positions of a distorted tetrahedron. The Ga^{I}–Cl and In^{I}–I distances are relatively large, indicating large ionic radii for the univalent cations. $Ga[GaI_4]$ crystallizes rhombohedrally (acentric space group R3c). There is a hexagonal close packing of tubes formed from $[GaI_4]$ tetrahedra, the interstices of which are filled by the Ga^{+} ions. The environment of the Ga^{+} ions consists of eight nearest I neighbors with a large spread of Ga···I distances (3.281 to 3.020 Å). This geometry approximates a bicapped trigonal prism.

Only the last of the three structures is compatible with stereochemical activity of the lone pair of electrons of the M^{+} ions. The dodecahedra, in particular, give no indication for such an effect, since the very minor reduction in their symmetry is not directed towards the generation of a halogen-free corner in the polyhedron, where such a lone pair of electrons could be accommodated.

The small deviation from dodecahedral symmetry observed for $Ga[GaCl_4]$ is just sufficient to allow observation, even in the solid state, of surprisingly intense Ga^{I}-NMR signals without the use of special procedures such as magic angle spinning.[19] The appearance of a complex ^{69}Ga signal (Fig. 1a, b) is in agreement with the theoretical resonance calculated for asymmetry parameters $\eta > 1/3$. Signal-form analysis according to this model yields a quadrupole coupling constant $e^2qQh^{-1}(^{69}Ga) = 1.7 \pm 0.1$ MHz and an η value of 0.44 ± 0.05.[20] In contrast, the ^{71}Ga resonance shows no resolvable structure (Fig. 1c), as expected from the relations $Q(^{69}Ga) > Q(^{71}Ga)$ and $\eta(^{69}Ga) < \eta(^{71}Ga)$: The value calculated for $e^2qQh^{-1}(^{71}Ga)$ from the existing data is only 1.1 ± 0.1 MHz. The resulting maximum splitting (1500 Hz) is well below the experimental line width ($\Delta B = 3070$ Hz).

The quadrupole coupling constants found for crystalline $Ga[GaCl_4]$ therefore confirm that there is only a very small distortion of the dodecahedral environment of the Ga^{+} ions. It also follows from the asymmetry parameter that the symmetry of the tensor of the electric field gradient at the Ga^{+} centers is reduced only according to the orthorhombic crystal symmetry. Both results are in agreement with the notion that the $4s^2$ lone pair of electrons deviates only very little from spherical symmetry. Any significant hybridization should lead to much more drastic effects. Resonances of the Ga^{III} nuclei cannot be observed in the ^{69}Ga,^{71}Ga-NMR spectra of crystalline $Ga[GaCl_4]$. The distortion of their tetrahedral environment is too strong, so that the condition for the NMR experiment $e^2qQh^{-1} \ll \mu B$ is no longer fulfilled.[20]

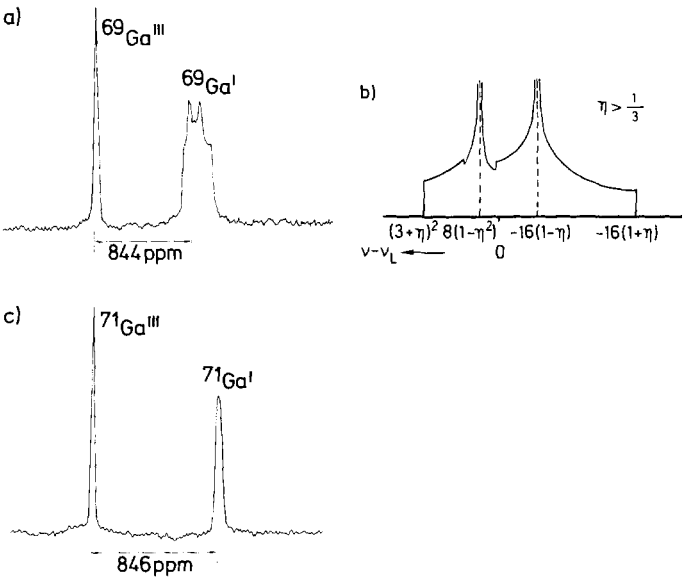


Fig. 1. a) Solid-state ^{69}Ga-NMR spectrum of $Ga[GaCl_4]$. Crystal powder at 30°C, Larmor frequency $\nu_L = 47.987$ MHz, sweep width 180 kHz, pulse 4 μs. Reference: $GaCl_3$ in aqueous hydrochloric acid. b) Calculated spectral pattern for the central transition ($m = 1/2, -1/2$) for half integral spin I in frequency units $\nu_Q^2(144\nu_L)^{-1}[I(I+1)-0.75]$ with $\nu_Q = 3e^2qQ[2I(2I-1)h]^{-1}$ [20]. c) Solid-state ^{71}Ga-NMR spectrum of $Ga[GaCl_4]$. Conditions as in a), $\nu_L = 60.790$ MHz.

The $Ga[GaCl_4]$ melt (at 200°C), in contrast, shows an extremely noteworthy ^{71}Ga-NMR spectrum:[21] Not only are separate signals detected for Ga^{I} and Ga^{III}, but the resonance of the univalent ion is characterized by its sharpness and large high-field shift (Fig. 2). These observations again suggest a very symmetrical environment of the Ga^{I} nuclei in the melt and an extremely strong shielding due to a reduction of paramagnetic effects through the presence of the $4s^2$ lone pair of electrons. The results for $Ga[GaBr_4]$

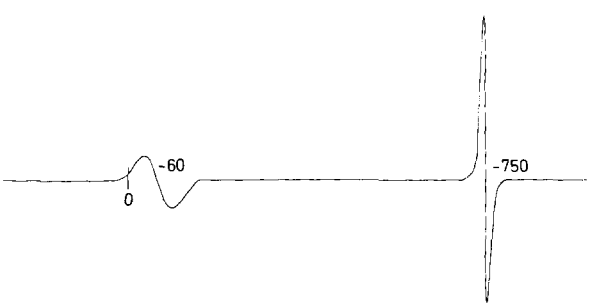


Fig. 2. ^{71}Ga-NMR spectrum of the $Ga[GaCl_4]$ melt at 200°C. Reference: $[Ga(H_2O)_6]^{3+}$ in aqueous solution. δ values.

melts are qualitatively analogous, but broader resonances and smaller shift differences are to be noted. These differences are not unexpected because of the lower electronegativity and higher polarizibility of the bromine atoms. Both spectra provide important reference data for the Ga-NMR spectra of the arene complexes.

4. Earlier Studies on Ga^I, In^I, Tl^I/Arene Systems

The discovery more than 50 years ago that $Ga[GaCl_4]$ dissolves readily in benzene prompted investigations of the colligative properties of the resulting solutions. Cryoscopic molecular weight determinations indicated a pronounced concentration dependence with the value for the undissociated monomer being reached only at infinite dilution.[22] Between 0.05 and 0.1 M, dimeric species appear to prevail.[22] The dielectric constants of the solutions are strongly temperature-dependent, indicating solvated ion pairs and a high dipole moment for the solute.[22] The solutions are electrically nonconducting, again strong evidence for tight ion-pair formation.[23, 24]

For $Ga[GaBr_4]/C_6H_6$,[25] phase diagram studies showed the existence of two discrete phases, with compositions $Ga_2Br_4 \cdot C_6H_6$ and $Ga_2Br_4 \cdot 3\,C_6H_6$. The complete phase diagram of the $Ga[GaCl_4]/C_6H_6$ system is not known, but a phase 1 : 1 with a molar ratio could also be identified under certain work-up conditions.[26] Preliminary X-ray analysis of one of these phases gave the approximate cell constants $a = 11.89$ and $c = 30.05$ Å ("pseudohexagonal," $Z = 12$), but the structure could not be solved.[10]

Vibrational spectroscopy was successfully employed to verify the presence of quasitetrahedral $[GaX_4]^-$ anions (X = Cl, Br). However, no definite conclusions could be drawn regarding the mode of interaction between Ga^+ and the benzene molecule.[22] Nevertheless, the η^6 model was favored, and it was pointed out that *Mulliken*'s charge transfer concept could be used to account for such a ring-centered metal/arene interaction.[10, 27, 28]

^{71}Ga-NMR spectra of solutions of $Ga[GaCl_4]$ and $Ga[GaBr_4]$ in benzene[21] exhibit separate signals for Ga^I and Ga^{III}. Conclusions drawn from the analyses of line widths and chemical shifts, however, were limited by the small number of known examples. Among other models, an anion-association with benzene was also considered.

For indium(I) the experimental investigations were comparatively meager and evidence for benzene complex formation was only mentioned in passing.[11b] For thallium(I), however, the isolation of two compounds, $2\,Tl[AlCl_4] \cdot C_6H_6$ and $Tl[AlCl_4] \cdot 2\,C_6H_6$, was reported (supported by elemental analysis data). The materials were described as extremely labile, the benzene being partly lost on drying. For these species, a "ferrocene sandwich-type structure" and an "inverted ferrocene structure," respectively, were discussed, again with reference to *Mulliken*'s theory, but could not be supported by further details.[11b]

Thus, there has been ample evidence for over half of a century for compounds having the compositions $[M^+(C_6H_6)M^+]$, $[(C_6H_6)M]^+$, and $[(C_6H_6)_2M]^+$ for all three elements of the third main group in their univalent state.

5. Structural Chemistry of the Arene Complexes

5.1. The Bis(benzene)gallium(I) Tetrachlorogallate(III) Dimer 1[5]

When crystals are grown at 20 °C from an anhydrous benzene solution saturated previously with $Ga[GaCl_4]$ at elevated temperatures, a transparent colorless material is obtained which loses benzene rapidly under vacuum or when purged with dry nitrogen or argon. According to elemental analysis, this phase contains benzene in excess of a 3 : 1 molar ratio C_6H_6/Ga_2Cl_4. (The alleged 1 : 1 complex is reported to be formed upon removal of the solvent by pumping at −5 °C[11]).

An X-ray diffraction study of the benzene-rich phase revealed the presence of the dimeric units $[\{(C_6H_6)_2Ga\}^+\{GaCl_4\}^-]_2$, **1**, with three additional molecules of benzene trapped in the triclinic lattice. The overall stoichiometry is thus 3.5 : 1, in good agreement with the analytical data. There is also a remarkable parallel to the 3 : 1 phase detected in the phase diagram of the system C_6H_6/Ga_2Br_4.[25] The two Ga^+ centers in **1** form two "bent" sandwich moieties with the benzene molecules (Fig. 3), which are linked together by two bridging

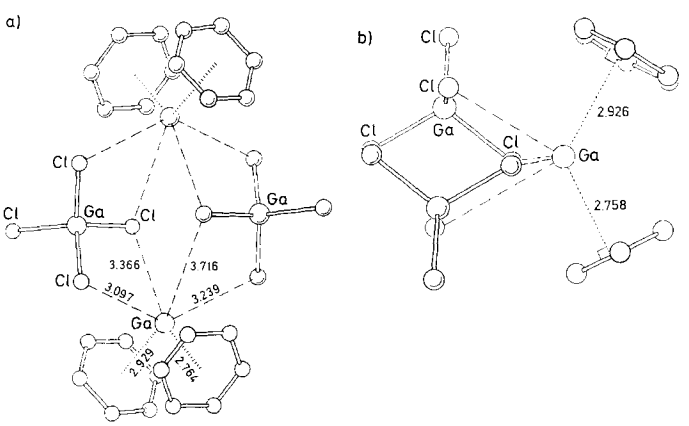


Fig. 3. a) The centrosymmetric unit of $[\{(C_6H_6)_2Ga\}(GaCl_4)]_2$ **1** projected perpendicular to the plane of the four gallium atoms. b) View showing the arrangements of ligands around the Ga^I center in **1**. Distances [Å].

$[GaCl_4]^-$ tetrahedra. Most important, the Ga^+ ions are located over the centers of the benzene rings. The normals to the rings form angles of only 2.8 and 3.7°, respectively, with the corresponding lines connecting the metal atom and the ring centers. Four chlorine atoms surround Ga^+ irregularly, two of which lie roughly in the plane that bisects the angle between the benzene rings. This structure is probably also present in solution. At high dilution, however, solvated monomers are more likely, as suggested by the colligative properties.[22–24]

The bis(benzene)–metal coordination is an unexpected and unparalleled phenomenon for p-block elements. The two benzene rings are not equidistant, however, from the Ga^+ center. If no other corroborative example had been found, the results would therefore have remained in doubt.

5.2. The Bis(1,3,5-trimethylbenzene)gallium(I) Tetrachlorogallate(III) Chain Polymer 2[29]

$Ga^+[GaCl_4]^-$ also dissolves readily in hot mesitylene, which on cooling affords monoclinic, colorless, transparent crystals. Elemental analysis indicates a 2 : 1 molar ratio mesitylene/Ga_2Cl_4, which is retained even after exposure to a vacuum at 20°C. The single-crystal X-ray analysis of **2** showed that "bent" sandwich moieties are again present in this phase; however, they are linked by $[GaCl_4]^-$ tetrahedra into chains rather than rings (Fig. 4a). As in **1**, the bridging chlorine atoms approach the Ga^+ centers in a plane bisecting the angle between the two arenes (Fig. 4b). In **2**, these arenes are equidistant from the Ga^+ ion (Fig. 4c), and thus there is no ambiguity about equivalent bond-

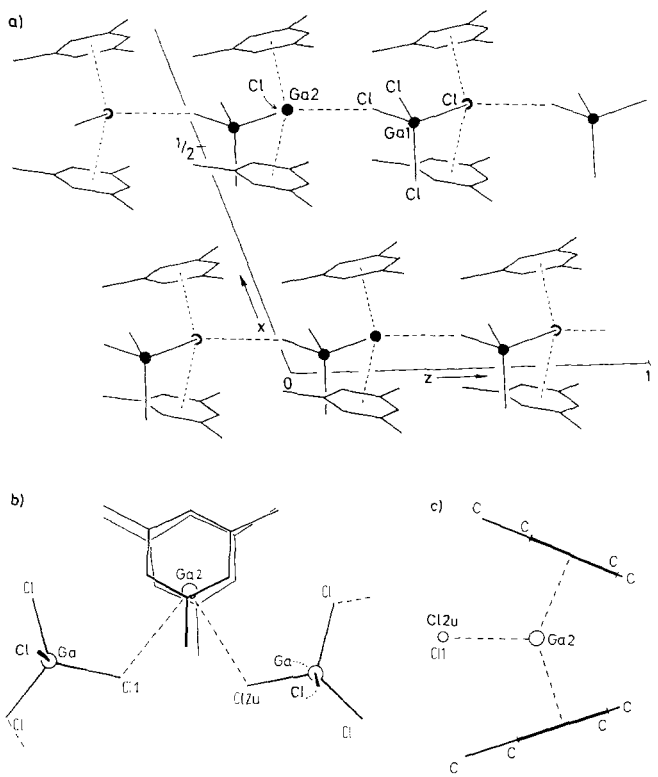


Fig. 4. a) Crystal structure of $[\{1,3,5\text{-}(CH_3)_3C_6H_3\}_2Ga(GaCl_4)]$ **2**. Projection along the *y* axis. b, c) Environment of the Ga^1 center in **2**. Projection onto the Ga2C11Cl2u plane (b). Projection along the Cl1–Cl2u vector (c).

ing of the two hydrocarbon rings. The metal is again centered over the mesitylene rings as in the benzene analogue. The sterically more demanding mesitylenes prevent a closer approach of the $[GaCl_4]^-$ tetrahedra and the coordination number of Ga^+ is essentially 4.

In mixtures of benzene or toluene with mesitylene, only the latter is taken up as a ligand by the Ga_2Cl_4 solute. Apparently, increasing methyl substitution strongly favors the Ga^+ complexation.

5.3. The (Hexamethylbenzene)gallium(I) Tetrachlorogallate(III) Tetramer 3[30]

Solutions of Ga_2Cl_4 in a mixture of toluene and hexamethylbenzene yield a crystalline phase on cooling, which has the analytical stoichiometry of a 1 : 1 complex of $[(CH_3)_6C_6]$ and Ga_2Cl_4 [m.p. = 168°C (decomp.)]. Purging with dry nitrogen does not change the composition. The rhombohedral crystals are very soft and extremely difficult to manipulate. The X-ray diffraction analysis showed the presence of four formula units in the unit cell in the form of a tetrameric cluster with crystallographic C_{3v} symmetry (Figs. 5a, b). One unique Ga^+ ion lies on the threefold axis and is coordinated to a hexamethylbenzene ring that is perpendicular with respect to the C_3 axis. The distance from the metal to the ring center is only 2.43 Å. The inner core of the cluster is composed of four $[GaCl_4]^-$ tetrahedra, from which, altogether, seven chlorine atoms in the form of a regular hexagonal pyramid are directed toward the unique Ga^+. The three remaining symmetry-related Ga^+ ions are also attached to a hexamethylbenzene molecule, each at a distance of 2.51 Å, and are coordinated to six chlorine atoms which form a cap in the shape of a pentagonal pyramid (Fig. 5c).

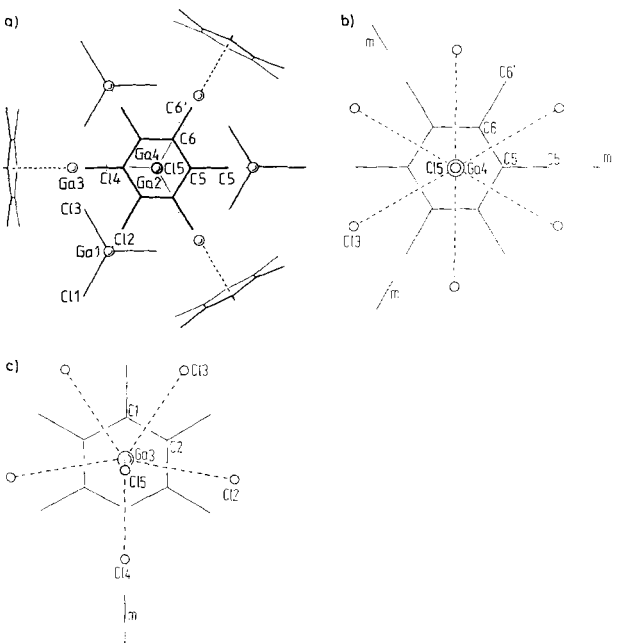


Fig. 5. a) Crystal structure of $[\{(CH_3)_6C_6\}Ga(GaCl_4)]_4$. Projection of a unit of **3** along the [111] axis (Ga2, Ga4, and Cl5 lie on this axis). b) Projection of the coordination sphere of Ga4 (cf. a) onto the corresponding hexamethylbenzene plane. A hexagonal pyramid of seven chlorine atoms is staggered relative to the hydrocarbon. c) Projection of the coordination sphere of Ga3 (cf. a) onto the corresponding hexamethylbenzene plane. Six chlorine atoms form a distored pentagonal pyramid.

The overall structure may be described as consisting of four $[(CH_3)_6C_6]Ga^+$ cations and four $[GaCl_4]^-$ anions, generating a hydrocarbon surface around an inorganic Ga_8Cl_{16} skeleton. Each arene can be assigned to a discrete Ga^+ center as an η^6 ligand.

5.4. The (Hexamethylbenzene)gallium(I) Tetrabromogallate(III) Network 4[31]

A solid phase of composition $[\{(CH_3)_6C_6\}Ga]^+[GaBr_4]^-$ **4** can be crystallized from solutions of Ga_2Br_4 in a mixture

of toluene and hexamethylbenzene. The colorless, transparent material, which is stable at room temperature in a vacuum (m.p. = 146 °C), contains no toluene. Hexamethylbenzene is therefore clearly preferred as a ligand for Ga^+, regardless of whether $[GaBr_4]^-$ or $[GaCl_4]^-$ counterions are present (**3** and **4**, respectively).

The X-ray analysis of the monoclinic phase **4** revealed a complicated network of interacting $[(CH_3)_6C_6]Ga^+$ and $[GaBr_4]^-$ ions. In the former the metal atoms are located perpendicularly above the arene ring center at a distance of 2.52 Å, which is shorter than in the bis(arene) complexes (**1** and **2**) and similar to that in the tetrameric cage of the $[GaCl_4]^-$ analogue **3**. The coordination sphere around Ga^+ is completed by a distorted tetragonal pyramid of five bromine atoms (Fig. 6). This geometry complements the pentagonal and hexagonal pyramids detected in **3**, in which the smaller chlorine atoms permit higher coordination numbers. One monodentate and two bidentate $[GaBr_4]^-$ tetrahedra are the origins of the five nearest bromine atoms.

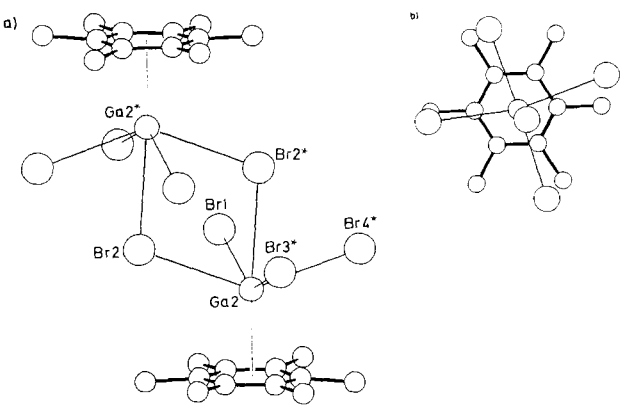


Fig. 6. a) Crystal structure of $[\{(CH_3)_6C_6\}Ga]^+[GaBr_4]^-$ **4**. The gallium(III) atoms of the $[GaBr_4]^-$ tetrahedra have been omitted for clarity. b) The coordination sphere of Ga^1 in **4**, projected onto the hexamethylbenzene plane. Five bromine atoms form a distorted tetragonal pyramid.

5.5. The Bis(1,3,5-trimethylbenzene)indium(I) Tetrabromoindate(III) Chain Polymer 5[32] and Related Compounds

Arene-indium(I) complexes are more difficult to obtain than their gallium analogues. With many complex subhalides and many hydrocarbons, no reaction takes place.[33] However, a combination was found in the system In_2Br_4/mesitylene, from which a 1:2 phase was easily obtained.

The structure of the bis(1,3,5-trimethylbenzene)indium(I) tetrabromoindate(III) **5**, which precipitates from saturated In_2Br_4 solutions containing excess hydrocarbon, is closely related to the mesitylene/Ga_2Cl_4 analogue **2**. The crystalline phase contains chain-like coordination polymers of $[InBr_4]^-$-linked bis(arene)indium(I) moieties (Fig. 7a). The aromatic rings are positioned nearly equidistantly from the metal (at 2.83 and 2.89 Å, respectively), and form an angle of 47.3°. In the plane bisecting this angle, there are three bromine atoms contributed from monodentate and bidentate $[InBr_4]^-$ tetrahedra (Fig. 7b, c). The In^+ ions in **5** are thus pentacoordinate, whereas only tetracoordinate Ga^+ ions are found in **2**. The difference of the ionic radii (Table 1) offers a straightforward explanation for this structural difference.

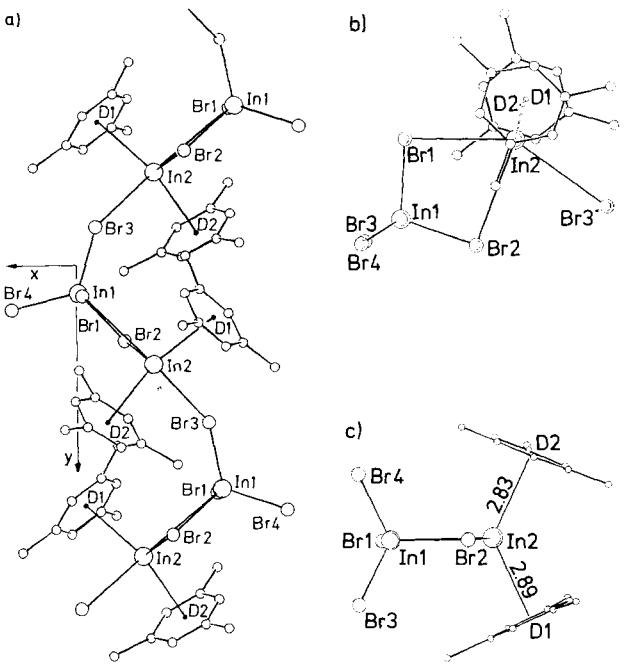


Fig. 7. a) Crystal structure of $[\{(CH_3)_3C_6H_3\}_2In(InBr_4)]$ **5**. Projection onto the xy plane. b, c) The coordination sphere of In^1 in **5**. Projection onto the In2Br1Br2Br3* plane (b). Side view of the same unit (c). Distances [Å].

A hexamethylbenzene complex of In_2Br_4 has also been obtained, but not yet structurally characterized. Benzene forms only very labile adducts with the subhalides of indium, and no discrete products could be isolated. There is little doubt, however, that the arene coordination chemistry of indium resembles that of the gallium congener; however, both the higher lattice energies of the indium halides and the reduced tendency of indium to complex with arenes are responsible for the more limited scope of its chemistry.

5.6. The Mixed Mono- and Bis(arene)thallium(I) Complex $[\{1,3,5\text{-}(CH_3)_3C_6H_3\}_6Tl_4(GaBr_4)_4]$ 6[34]

Thallium(I) tetrahalometalates(III) such as $Tl[AlCl_4]$, $Tl[AlBr_4]$, $Tl[GaCl_4]$, and $Tl[GaBr_4]$ are soluble in hot benzene, mesitylene, or hexamethylbenzene. The arene complexes that are present in solution are very unstable, and isolation of discrete phases often involves enormous experimental difficulties. To date only the title compound **6** has been fully characterized.[35]

The X-ray diffraction analysis of the triclinic crystals obtained from mesitylene in hot benzene or toluene gave a very unexpected result: centrosymmetric tetrameric units were found in which both mono- and bis(arene)thallium moieties are present in the same cluster (Fig. 8a). In the monoarene ions, the metal atom is located 2.94 Å above the ring center of the mesitylene, while in the bis(arene) ions, the two arenes are displaced by 3.00 and 3.02 Å, respectively, with a mutual inclination of 60.5° (Fig. 8b, c).

The cationic units are linked via tetrahedral $[GaBr_4]^-$ ions into a complicated network of thallium-bromine contacts.

An analogy to the mono(arene)gallium(I) species **3** and **4** exists only insofar as the metal atom of the (mesitylene)thallium units is also coordinatively saturated by a pentagonal pyramid of six bromine atoms, donated from three chelating $[GaBr_4]^-$ ions, two bisequatorial and one axial/equatorial (Fig. 8a, c). The bromine contacts of the metal atom in the bis(mesitylene)thallium(I) unit are irregular, but the geometry of **6** is reminiscent of that of **1**.[5]

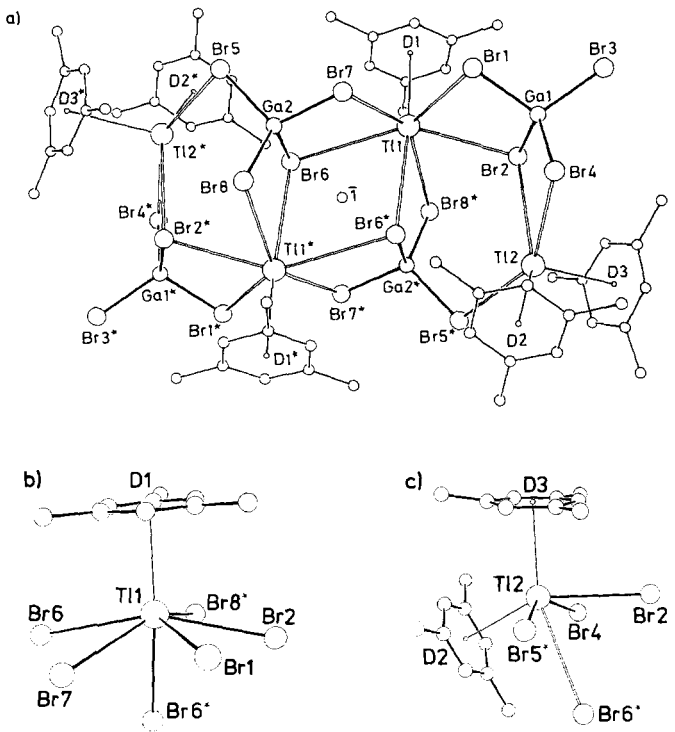


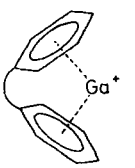
Fig. 8. a) Projection of the centrosymmetric unit of $[(1,3,5\text{-}(CH_3)_3C_6H_3)_6Tl_4(GaBr_4)_4]$ **6** onto the plane of the thallium atoms. b, c) View of the coordination sphere of the Tl^I atoms in **6**: cationic monoarene unit (b), cationic bis(arene) unit (c).

6. Relative Stabilities and Possible Modifications

The addition of the arenes to the Tl^I salts is based on relatively weak interactions and is therefore readily reversible. Thermogravimetric analyses proved that the hydrocarbon is liberated completely and unchanged from the solid on heating at temperatures below 150°C. Experiments with the gallium(I) and indium(I) analogues gave similar results.

Semiquantitative observations suggest that the arene complex stability decreases as the radius of the metal increases from gallium to thallium. The role of the counterion is less obvious, but it is particularly noteworthy that no examples have been found with anions other than tetrahalometalates. All attempts to synthesize species with (thio)phosphates, halophosphates, halosilicates or other anions have failed. This situation is not unlike the state of affairs with the subvalent arene complexes of the fourth main group, with the exception of a tin(II) diphenyldithiophosphate, in which an intramolecular coordination of one of the phenyl rings to the Sn^{II} center was observed.[8]

Increased arene substitution with electron releasing groups provided the expected stabilization of the arene complexes, as shown in numerous reactions in which different arenes were allowed to compete for the M^I centers (see above). In order to exploit additional entropy effects, linked bis(arenes) were reacted with Ga^+ salts. Surprisingly, the introduction of a hydrocarbon bridge between the two phenyl rings did not increase the stability of the bis(arene)metal complexes (*cf.* **C**). Experiments carried out with the potentially chelating arenes $C_6H_5\text{-}(CH_2)_n\text{-}C_6H_5$ (where $n = 1\text{-}4$) as ligands for Ga^I, In^I, or Tl^I gave no well-defined products.[33,35] Cleavage reactions or intermolecular bridging led to intractable materials. Formula **C** is a possible model for the desired structures, as yet unrealized.



C

Due to the flexibility of the alkyl chains, the position of the two arene substituents in α,ω-diphenylalkanes is not fixed. In experiments aimed at positioning the arenes in a sandwich-type arrangement in the free ligand, the ligand *cis*-1,2-diphenylcyclopropane was chosen, based on the optimum dimensions derived from the complexes **1** and **2**, and experimentally tested. The ligand, which is accessible via a known procedure,[36] was first structurally investigated,[35] and the expected geometry confirmed (Fig. 9). On

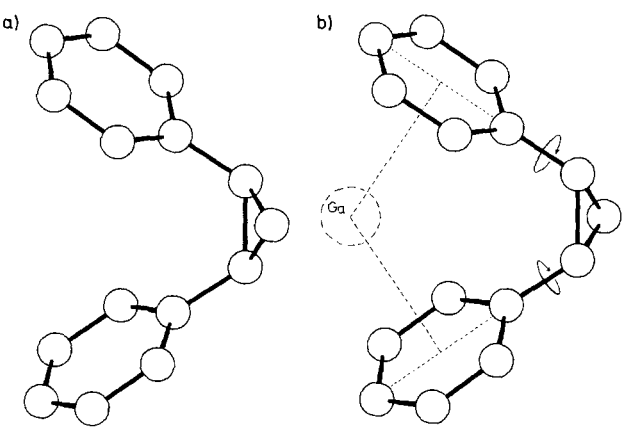
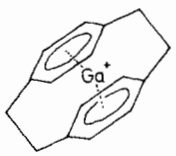


Fig. 9. a) Molecular structure of *cis*-1,2-diphenylcyclopropane; b) expected geometry of the corresponding gallium(I) complex; The calculated distances and angles are in excellent agreement with those in other bis(arene)gallium complexes.

introduction of a Ga^+ ion between the two phenyl rings, metal-ring bonds should be formed that are in satisfactory agreement with those observed for **1** and **2**. However, no crystalline products could be isolated from solutions containing the ligand and $Ga[GaX_4]$ salts, although, according to NMR data, complex formation must indeed have occurred.[35]

Experiments with cyclophanes appeared to be more successful.[35] Colorless, microcrystalline 1:1 complexes are formed immediately on addition of [2,2]paracyclophane to

solutions of Ga_2Cl_4 or Ga_2Br_4 in benzene, toluene, or xylenes. These complexes are much less sensitive to air and moisture than the analogous complexes with non-bridged arenes. (Hydrolysis with coloration to brown takes place only after hours.) In the solutions treated with the cyclophane, no gallium(I) can be detected. Complex formation with the cyclophane is specific for Ga^I, since no In^I or Tl^I can be precipitated from benzene solutions of In_2Cl_4 or $TlGaCl_4$. Attempts to crystallize a product yield again the benzene complexes. These results suggested that the Ga^I complexes of the cyclophane have a double-bridged sandwich structure (Formula **D**), one already proven for the chromium(0) complex.[37,38] The estimated atomic radii for Cr^0 and Ga^I are, in fact, almost equal.[39]



D

The X-ray structure analysis of the Ga_2Br_4 complex showed very surprisingly, however, that the gallium(I) ions have not entered the cyclophane interstices, but have become attached from the outside to the bridged arene rings of the hydrocarbon. Each Ga^I center is thereby coordinated to two different cyclophane molecules, and each cyclophane bears two η^6-coordinated gallium atoms. In the resulting endless, slightly folded stacks, the centers of the cyclophane molecules represent centers of symmetry (Fig. 10a). The two benzene rings of each cyclophane remain parallel to each other (as required by symmetry) and form an angle of 56.7° with the benzene rings of the following cyclophanes in the "polydecker" arrangement. This folding corresponds to the geometry found in other bis(arene)metal complexes (**1**, **2**, **5**, and **6**). The coordination sphere of Ga^I is complemented by two bromine atoms which belong to two different $[GaBr_4]^-$ tetrahedra. These bromine atoms lie on a crystallographic mirror plane together with the Ga^{III} centers (Fig. 10b), and they form bridges between the Ga^I atoms. Consequently, coordination polymer chains $-Ga^I-Br-Ga^I-Br-$ are formed perpendicularly to the (cyclophane)Ga^I stacks and interconnect the system to give a three-dimensional lattice (Fig. 10c). It is conceivable that other cyclophane complexes, e.g., of silver(I), obey a similar structural principle. However, no structural data are available as yet.[40]

It is hoped that cyclophanes with larger arene-arene separations will be able to accommodate the gallium(I) cations within the molecular cavity.

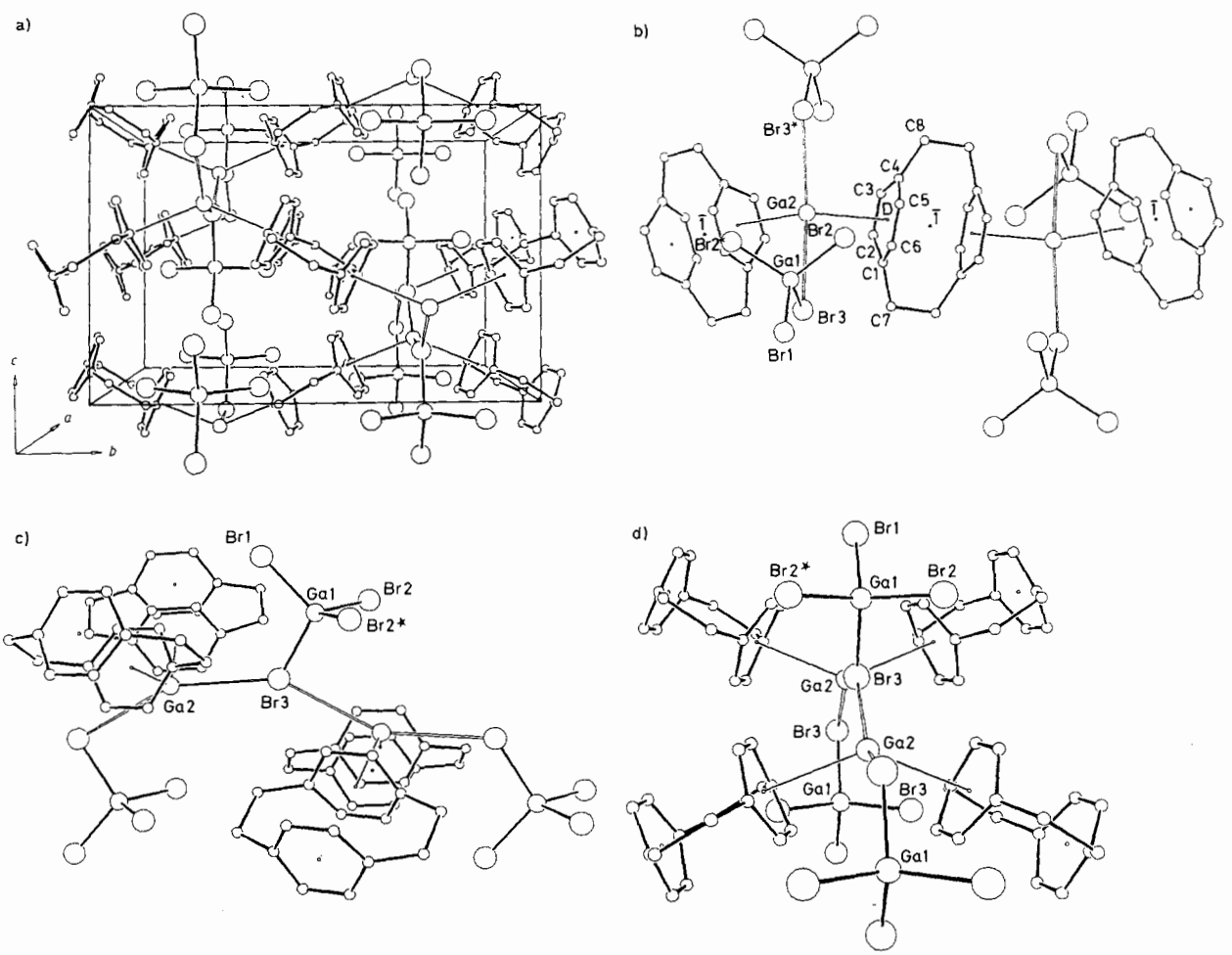


Fig. 10. a) View of the crystal structure of [2.2]paracyclophane-gallium(I) tetrabromogallate(III). b) View along the stacks formed from alternating cyclophane and gallium(I) units. The chains are folded periodically at the metal centers. c) View down the cyclophane/gallium(I) stacks, but perpendicular to the mirror planes formed by the gallium and the bromine atoms Br1 and Br3. d) View almost perpendicular to the cyclophane stacks and almost parallel to the mirror plane referred to in c (d).

7. ^{71}Ga-NMR Spectra of Solutions of Gallium(I) Compounds in Aromatic Hydrocarbons

The isolation of crystalline arene complexes and the elucidation of their crystal structure provided a much better basis for the discussion of the solution NMR spectra of these materials. From a variety of measurements on solutions of Ga_2Cl_4 and Ga_2Br_4 in benzene, toluene, p-xylene, and mesitylene, and in mixtures of these solvents, in suitable ranges of temperature and concentration, the following new and essential aspects emerged:[41]

a) The ^{71}Ga nucleus (abundance 39.6%, spin 3/2, quadrupole moment 0.112×10^{-24} cm^2) affords sharp signals with high sensitivity for Ga^I-containing structural elements (and, therefore, for the arene complex moieties) of all systems investigated. These signals show the largest high-field shift ever observed for a gallium compound. The δ values (Table 3) are higher (more negative) by 200 ppm than those of the molten Ga[GaX$_4$] salts.[21] The introduction of arenes into the coordination sphere of the metal, which had contained only GaX_4 tetrahedra in the melt, leads to a further reduction of paramagnetic contributions to the chemical shift. Since the arenes are clearly kept at a considerable distance, only weak interactions are possible (Fig. 11).

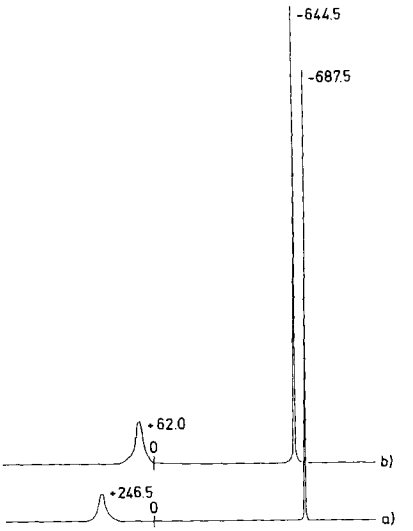


Fig. 11. ^{71}Ga-NMR spectra of benzene solutions of a) Ga[GaCl$_4$] and b) Ga[GaBr$_4$] at 30°C. δ values.

Table 3. ^{71}Ga-NMR spectra of solutions of the salts Ga[GaX$_4$] in aromatic hydrocarbons [41] [a] (Bruker CXP 200, ν=60.99 MHz; standard 1 M Ga(NO$_3$)$_3$, in diluted aqueous HNO$_3$, corresponding to [Ga(H$_2$O)$_6$]$^{3+}$).

	Solvent [a]	Conc. [wt. %]	δ(Ga$^+$)	δ(Ga^{3+})
Ga[GaCl$_4$]	benzene	1	−650	+247
	benzene [b]	3	−669	+247
	toluene	1	−668	+247
	toluene [b]	4	−673	+247
	p-xylene [b]	7	−674	+247
	mesitylene	sat.	−675	br.
	mesitylene/benzene	sat.	−675	+247
Ga[GaBr$_4$]	benzene	3	−609	+ 62
	mesitylene	sat.	−624	br.

[a] The line widths for Ga$^+$ lie between 50 (127°C) and 100 Hz (27°C), for Ga^{3+} between 1700 und 4700 Hz. [b] With too little solvent, two-phase mixtures are formed, the heavier of which show δ(Ga$^+$) = −687 for Ga[GaCl$_4$] in benzene, −686 in toluene, and −688 ppm in *p*-xylene (at constant δ(Ga^{3+}) = +247).

b) In mixed solvents a chemical shift is observed for Ga$^+$ that corresponds to a complex with the better donors among the arenes present in the mixture (hexamethylbenzene > mesitylene > xylene > toluene > benzene). Thus, there is also a preference for specific components in solution.

c) The line width of the ^{71}Ga$^+$ resonance of arene complexes, which typically is ca. 100 Hz at 20°C and 50 Hz at 130°C, is of the same order of magnitude as that of the highly symmetrical [Ga(H$_2$O)$_6$]$^{3+}$ ion. Since the environment of Ga$^+$ in arene complexes cannot attain the high symmetry of point group O$_h$, it is necessary to assume that the conservation of spherical symmetry of the outer electron shell, combined with the large distances to the ligand, is responsible for a relaxation behavior which corresponds to that of complexes of high symmetry.

d) The resonances of the [GaX$_4$]$^-$ anions are largely constant in their δ value and have large line widths (Table 3). It follows that these counterions do not attain their full tetrahedral symmetry in solutions of Ga[GaX$_4$] salts in arenes even at high dilution, but remain coordinated to the (arene)Ga^I centers. It has been noted repeatedly that other M$^+$[GaX$_4$]$^-$ salts, when fully dissociated in polar solvents, do indeed give rise to sharp signals. This is because the relaxation behavior of ^{71}Ga^{3+} is modified by the T$_d$ symmetry of the free GaX_4^- anions so that small line widths result.[41-43] This conclusion is also in agreement with the colligative properties of the solutions, which show no significant dissociation of the ions.[23,24]

e) The ^{71}Ga-NMR spectra give no indication of the simultaneous presence of mono- and bis(arene)Ga^I complexes in solution. Even at low temperatures (−50°C), only one Ga$^+$ resonance is observed. Similarly, only one Ga$^+$ signal is detected in mixed arene solvents. Arene exchange processes between Ga$^+$ centers probably have very low activation barriers, so that a separate recording of the individual states is not possible. This result supports the view that the bonding of the arenes to the metal is weak. ^{1}H- and ^{13}C-NMR spectra lead to the same conclusion.

f) Two separate liquid phases are formed if an excess of a Ga[GaX$_4$] salt is dissolved in benzene, toluene, or mesitylene. This phenomenon is especially apparent with *tert*-butyl- and trimethylsilylbenzenes.[41] Even if the phase boundary remains invisible to the naked eye, because phase separation is incomplete, this situation becomes immediately obvious in the NMR spectra through a doubling of all signals. These additional signals disappear as more solvent is added, until homogeneity is reached.

8. The Nature of the Bonding in Arene Complexes of the Third Main Group

Arene complexes of metals are best referred to as donor-acceptor adducts, the hydrocarbon π-system being the donor component. Qualitative observations have also consistently shown that, for metals of the third main group, an increased arene donor strength through electron-releasing substituents leads to enhanced stability of the complexes. The resulting metal-ring bond distances are shorter for hexamethylbenzene or mesitylene than for benzene (Table 4). The interactions are not strong enough, however, to induce significant distortions of the six-membered ring, or to bend hydrogens or methyl groups out of the ring planes. None of the deviations from the original ligand symmetry exceeds the standard deviations of the X-ray diffraction analysis. These findings are in accord with the extremely low thermal stability of the complexes and with the exchange processes observed by NMR.

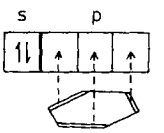
Table 4. Metal-carbon bond lengths [Å] and hydrocarbon interplane angles [°] in arene complexes **1**–**6**.

M	M–C in [(arene)M]$^+$ (average)		M–C in [(arene)$_2$M]$^+$ (average)		Angles
Ga	**4**: 2.887		**1**: 3.08	3.23	55.6
	3: 2.79	2.88	**2**: 3.01	3.02	39.7
In	—		**5**: 3.15	3.21	47.3
Tl	**6**: 3.28		**6**: 3.32	3.34	60.5

A molecular orbital description of the mono(arene) complexes can use a model previously suggested for (benzene)tin(II)[9] analogues. In Figure 12, the MO's of a benzene molecule and the valence orbitals of a Ga^+ ion are combined under the assumption of local C_{6v} symmetry. The lowest unoccupied atomic orbitals of the metal and the highest occupied molecular orbitals of the arene have the same symmetry (e_1) and lead to bonding and antibonding linear combinations. The four HOMO electrons of the arene are thus just sufficient to fill the two new bonding MO's of the complex (e_1 symmetry). This situation accounts for the ligand-metal bonding. Owing to the significant energy gap between arene and metal orbitals, however, the energy of complex formation is limited. It is therefore not surprising that the stability of the metal-arene bond is hardly high enough to compete with other metal-ligand interactions.[44]

The metal-halogen coordination in complexes **3**, **4**, and **6** does not appear to be geometrically specific, as evidenced by the very different arrangement of chlorine or bromine atoms in the coordination sphere. Therefore, it is probably pointless to include details of this coordination in the MO diagrams. A largely electrostatic description of this part of the coordination should lead to at least equally acceptable predictions.

A simple picture of the arene-metal interaction, in which the six electrons of the benzene π system fill the three vacant p orbitals of the metal, is of little value since symmetry criteria are ignored in such a model of localized bonding.[45] Although an inert gas shell is formally reached in



this formalism, a closed-shell state is not present.[46] This reasoning is further supported by the fact that more than one arene can engage in bonding to the same metal atom, as in compounds **1**, **2**, **5**, and **6**. The MO scheme for these bis(arene) complexes with local C_{2v} symmetry is, on the other hand, straightforward (Fig. 13).

A closely related scheme has previously been proposed for bent bis(cyclopentadienyl) complexes of germanium(II) and tin(II).[47] For these prototypes the origin of the interplane angle between the two cyclopentadienyl rings has

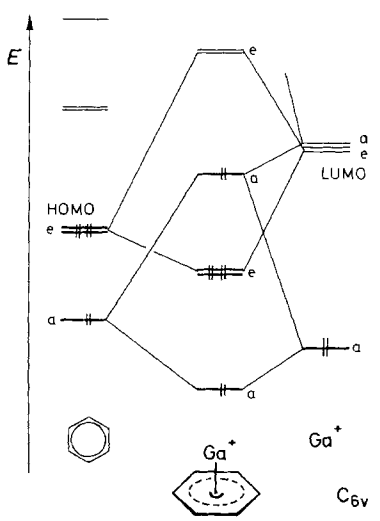


Fig. 12. Qualitative MO diagram of [(arene)Ga]$^+$ complex ions (C_{6v} symmetry) [48].

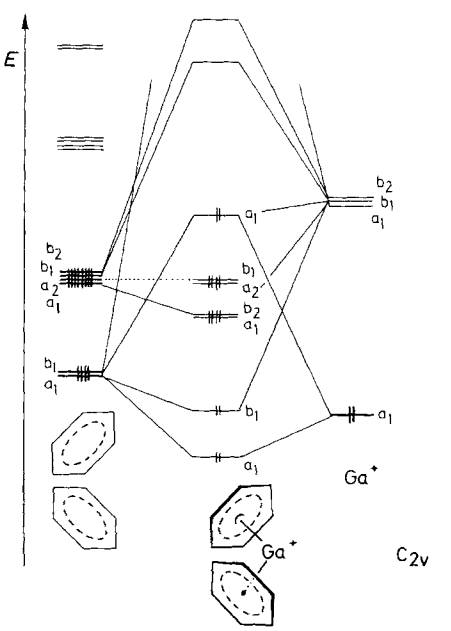


Fig. 13. Qualitative MO diagram of [(arene)$_2$Ga]$^+$ complex ions (C_{2v} symmetry) [48].

been considered in some detail. It was pointed out that mixture of the s orbital into the relevant metal p orbitals leads to a significant gain in energy, even in the absence of stabilizing ligands. In the case discussed here, the bis(arene)metal tetrahalometalates (Fig. 14), direct metal-halogen coordination, which is made possible by the increased interarene angle, is likely to afford additional stabilization.[48]

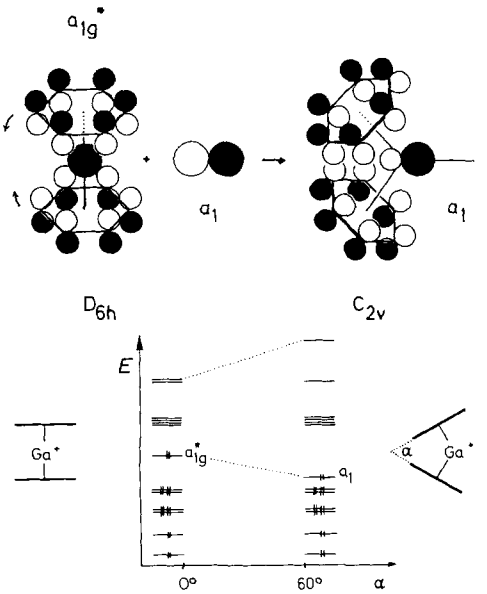
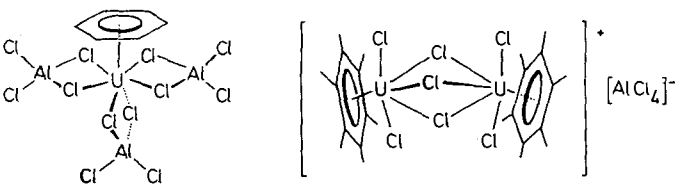


Fig. 14. Dependence of the MO diagram of $[(arene)_2Ga]^+$ complex ions on the angle α between the two arene planes [48].

In summary, the qualitative MO schemes can account for most of the new experimental data. The metal complexes of the third main group can be viewed as the missing links in the existing series of arene-metal complexes. They are unique in that the LUMO set of p orbitals of the low-valent metal can interact perfectly with the HOMO set of an arene, whereas in most classical cases the d orbitals play the key role.[12]

Both the (Ga)-NMR data and the structural features of the arene complexes indicate only a slight deviation from a spherical arrangement of the two outer electrons of the univalent M^+ cations. Due to large shielding effects and lack of stereochemical activity, these electrons appear to be in a "dehybridized" state.[49-51] In fact, indications of directed effects of the free electrons are rarely found in the structural chemistry of trivalent elements of the third main group.[18] However, this effect becomes pronounced with the divalent (Ge, Sn, Pn) and trivalent (As, Sb, Bi) neighboring elements, indicating a lowering of the energy through hybridization. Especially in the case of heavy atoms (Tl, Pb, Bi), the stabilization of the $6s^2$ state, known as the "inert pair effect," may be interpreted as a relativistic phenomenon.[51] After completion of the two d shells of Zn ($3d^{10}$) and Cd ($4d^{10}$), a significant influence on $4s^2$ and $5s^2$ of gallium and indium, respectively, seems to be present, manifested by an unusually strong binding of these electrons. Therefore, hybridization becomes more unfavorable as the p states become higher in energy, and directed bonds arise only with less electronegative and more polarizable partners. Experiments in this direction have always led to rapid disproportion of the Ga^I and In^I compounds, however, and as a consequence, almost no distinctly covalent Ga^I, In^I, or Tl^I compounds are known so far.

Recent reports on the first complexes of actinide metals with neutral arenes show that these elements, in low oxidation states, are also capable of η^6-arene coordination.[52,53] In the two compounds **E** and **F**, which have been studied by X-ray diffraction, tri- and tetravalent uranium is bound to arene and halide ligands in a very similar way as in the low-valent third and fourth main-group metal ions of the complexes presented above.



E **F**

9. Outlook

Several decades after the discovery of the polar In^I and Tl^I cyclopentadienyl complexes, the coordination chemistry of these metals with neutral arenes is now being developed. The arene complexes of p-block metals differ from the analogous complexes of d-block metals, especially in the strongly decreased binding interaction between metal and hydrocarbon. This is evident not only in the easy cleavage of the complexes into their components, but also in the large metal-ring separations and the apparently small change in the electronic states of the arenes. For example, no absorption in the visible region is observed, and the IR bands and NMR signals are changed only slightly. Although thermodynamic data are lacking, these observations place these complexes in the class of substances exhibiting "weak interactions." Both the dissolution of gallium(I) compounds in aromatic hydrocarbons and their separation from these media involve only small energy changes, which means that solution, extraction, and recovery processes can be carried out reversibly with a minimum amount of energy under mild conditions. The position of the equilibrium can be easily influenced by modifications of the ligands. These considerations can also be of considerable advantage for stoichiometric reductions using low-valent metals of the third main group.

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Mechanisms of Biological Ion Transport— Carriers, Channels, and Pumps in Artificial Lipid Membranes

By Peter Läuger*

The cell membrane contains specific systems for passive and active transport of ions between the cytoplasm and the extracellular medium. For a number of small and medium-sized transport molecules like valinomycin and gramicidin A, extensive structural and kinetic data are available and it is possible in these cases to understand the transport function on the basis of their molecular structure. Incorporation into artificial bimolecular lipid membranes opens up the possibility of studying the kinetic properties of biological transport systems in detail.

1. Introduction

The basic structure of biological membranes consists of a bilayer of lipid molecules with their polar head groups oriented toward the aqueous phase and their hydrophilic hydrocarbon chains forming the interior of the membrane (Fig. 1). The lipid structure contains protein molecules, some of which span the whole membrane. A particular feature of biological membranes is the fact that their structure is predominantly held together by noncovalent bonds such as van der Waals and coulombic interactions, so that a high degree of flexibility with respect to their chemical composition and dynamic properties is achieved.

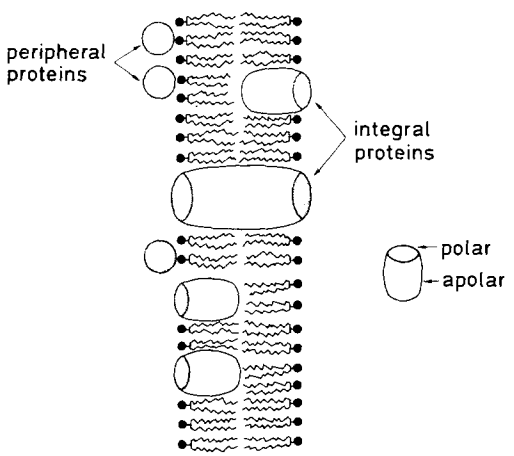


Fig. 1. The structure of a biological membrane (schematic). The basic structure of the membrane consists of a lipid bilayer. Peripheral proteins are bound to the membrane mainly by electrostatic interactions. Integral proteins are incorporated into the lipid matrix.

At physiological temperatures cell membranes are in a *fluid* state.[1] Exchange of lipid molecules between neighboring positions within a monolayer takes place in the time range of 10^{-8}–10^{-7} s.[2] (The exchange of lipid molecules in *transversal* direction, i.e., between two adjacent monolayers is, however, much slower, from seconds to days.) For some proteins a high diffusion rate within the plane of the membrane was observed[3] (diffusion coefficients of 10^{-11}–10^{-9} cm^2/s); other membrane proteins are probably fixed in the membrane by interactions with the cytoskeleton.

Lipid membranes are extremely impermeable to small ions such as Na^+ or Cl^-. A protein-free bilayer of phosphatidylcholine (lecithin) in 0.1 M NaCl has a specific conductance of 1–10 nS/cm^2,[4] a value that corresponds (at a membrane thickness of 5–10 nm) to the conductivity of an excellent insulator. The origin of the small ion permeability is the high energy necessary to transfer an ion from the aqueous phase into the apolar, hydrocarbon-like interior of the membrane. This barrier is important for the functioning of the cell membrane, since it allows the selective passage of certain types of ions and enables the cell membrane to regulate the ionic permeability by chemical or electrical means.

2. Ion Carriers and Ion Channels

The ionic permeability of cell membranes depends on certain specialized transport molecules. With respect to mechanism it is possible to distinguish two classes of transport systems: carriers and channels.[5] An ion carrier is a molecule that binds the ion and transports it in its bound form through the membrane (Fig. 2). The binding site is

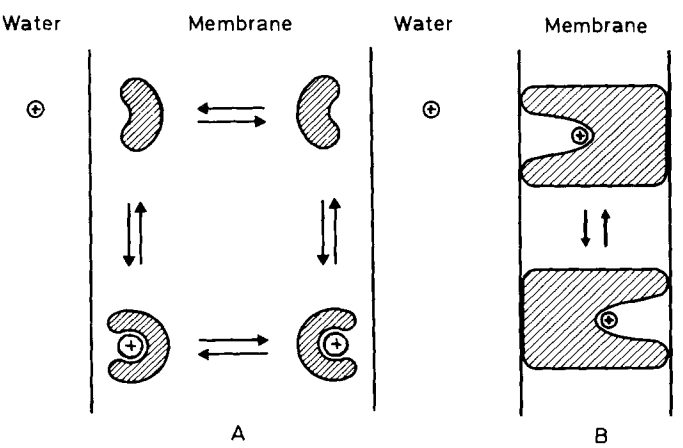


Fig. 2. Two mechanisms of carrier-mediated ion transport through lipid membranes. A: Translation of the carrier molecule relative to the membrane; B: alternation between a left-exposed and right-exposed form of the ion binding site due to conformational changes.

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accessible alternately from the left-hand or from the right-hand side but not from both sides simultaneously. The transition between states with left-exposed and right-exposed binding sites is achieved either by movement of the entire carrier molecule relative to the membrane or via a conformational change of the carrier molecule (Fig. 2).

An ion channel is a protein molecule that spans the entire membrane and contains in its interior a tunnel-like pathway for ions (Fig. 3). Entry of ions into the channel is

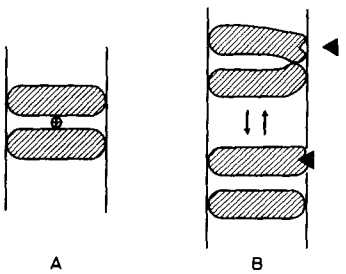


Fig. 3. A: Permanently opened ion channel; B: regulation of an ion channel by binding of an effector molecule.

energetically favored by electrostatic interactions with polar groups of the protein (e.g., peptide carbonyl groups). Certain ion channels in cell membranes are either open always or open and close at statistically determined time intervals. In other cases the channel opens only upon binding of an effector molecule (Fig. 3). This mechanism for regulating ion channels is the basis of signal transmission at neuromuscular synapses; the presence of transmitter molecules at nerve junctions results in an activation of ion channels in the muscle membrane.[6] The opening and closing of Na^+ and K^+ channels in the nerve membranes is regulated by the electrical field in the membrane.[7]

3. Artificial Lipid Membranes

Numerous laboratories are presently engaged in the isolation and purification of transport proteins from biological membranes. In the study of isolated transport proteins a fundamental difficulty arises since the transport function can no longer be tested once the protein is present in homogeneous solution. This is quite different from the situation for an enzyme, whose activity can easily be studied in vitro. This difficulty can be overcome by incorporating the isolated transport molecule into an artificial lipid membrane.[8] For this purpose, two artificial membrane systems may be used: planar lipid bilayers and lipid vesicles.

3.1. Planar Lipid Bilayers

Planar lipid bilayer membranes with diameters up to 10 mm can be formed in aqueous solution by a variety of techniques.[9,10] The method introduced by *Montal* and *Mueller*[10-12] starts with the formation of monomolecular lipid films on the water surfaces in a cell containing two compartments separated by a teflon diaphragm with a circular opening in the middle. After formation of the monolayers the liquid is raised, first in one chamber then in the other, above the level of the opening. In this way a lipid bilayer is formed across the opening in a zipper-like manner (Fig. 4). By the use of different lipids for the formation of the two monolayers, asymmetric membranes may be obtained.[13,14]

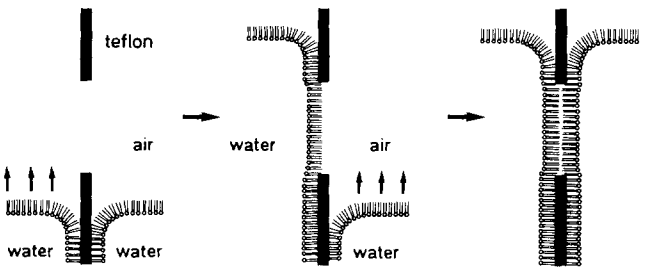


Fig. 4. Formation of artificial lipid bilayers. A monomolecular lipid film is formed on the water surface by spreading from an *n*-hexane solution. By subsequent raising of the aqueous solutions, a bimolecular lipid membrane is formed across the opening of the teflon support.

The electrical properties of lipid bilayers can be investigated in the measuring cell illustrated in Figure 5. The specific electrical capacitance of a dioleoyl phosphatidylcholine membrane formed according to the method of *Montal* and *Mueller* is $C_m = 0.72\ \mu F/cm^2$.[15] Using the relationship for a plate condensor, $C_m = \varepsilon_0 \varepsilon / d$, one can calculate the membrane thickness d ($\varepsilon_0 = 8.85 \times 10^{-12}\ CV^{-1}\ m^{-1}$ is the electrical field constant and ε is the dielectric constant of the membrane). Using $\varepsilon = 2.1$, a value appropriate for a hydrocarbon, one obtains a membrane thickness of $d = 2.6$ nm. This value is smaller than twice the chain length $2l$ of oleic acid ($2l \simeq 4.0$ nm), which indicates that the hydrocarbon chains are not completely extended within the membrane.

The electrical conductivity of simple lipid bilayers is, as already mentioned, very small. Thus it is possible to measure changes in conductivity that are caused by incorporation of biological ion transport systems with high sensitivity. A further considerable advantage of using planar lipid membranes is the small series resistance between electrodes

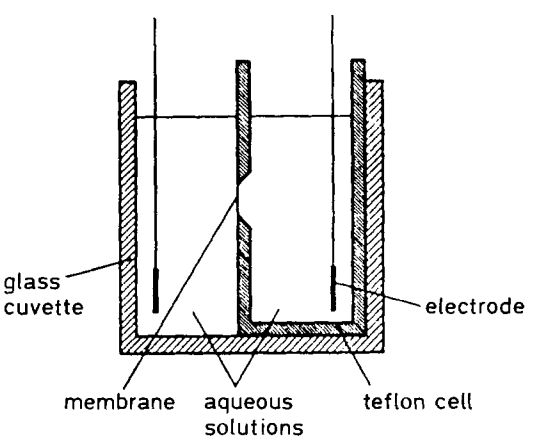


Fig. 5. Measuring cell for the investigation of the electrical properties of lipid bilayers. Platinized platinum electrodes or silver/silver chloride electrodes are used.

and membrane. This makes it possible to investigate fast electrical processes within the membrane by relaxation techniques with high time resolution (Section 4.1).

Recently *Hanke* et al. described a method of producing membranes with a small surface area (a few μm^2) which are ideally suited for the incorporation of proteins.[16-19] A glass micropipette (tip diameter ca. 1 μm) filled with an electrolyte solution is placed with its tip beneath the water surface (Fig. 6). After formation of a lipid monolayer on

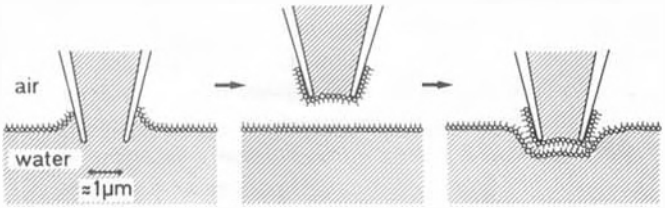


Fig. 6. Formation of lipid bilayers having small areas. The tip of a glass micropipette is initially located below the water surface. After formation of a monomolecular lipid film, the pipette is pulled out of the aqueous phase and then reinserted.

the water surface, the pipette is lifted out of the water, resulting in the formation of a monolayer on the pipette tip. Reinsertion of the pipette into the liquid results in the apposition of two monolayers and the formation of a bimolecular membrane. Ion channels isolated from biological membranes may be incorporated into the monolayer, and thus subsequently into the bimolecular membrane by spreading protein-containing lipid vesicles on the water surface.[16-20] Since the membrane area is fairly small, it is possible to achieve the incorporation of only one channel molecule into the artificial membrane. Thus it is possible to measure single-channel currents with high sensitivity.

3.2. Lipid Vesicles

Planar lipid membranes, which have a limited area, are not well suited for the study of transport systems with small rates of transport. Such systems can be more easily studied using suspensions of artificial lipid vesicles, which may be produced with diameters of between 30 nm and 1 μm in aqueous electrolyte solutions.[21,22] Lipids such as phosphatidylcholine swell in contact with water and form so-called liposomes consisting of concentric layers of lipids. Ultrasonic treatment of these large liposomes (with diameters of several μm) results in the formation of single-shelled spherical vesicles with an outer diameter of approximately 30 nm. Such single-shelled vesicles have an aqueous core in which water-soluble substances can be trapped.

Another method of producing single-shelled lipid vesicles consists in solubilizing the lipid in micellar form in water by detergents with subsequent removal of the detergents by dialysis or gel chromatography. The diameter of the vesicle may be varied in the range of 50–200 nm by the proper choice of the detergent and by the experimental conditions used to remove the detergent. Dialysis of cholate leads to dioleoyl phosphatidylcholine vesicles with a mean outer diameter of 90 nm.[23] 1 mL of a vesicle suspension with a lipid concentration of 10 g/L corresponds to a membrane area of $\approx 3\ m^2$; the enclosed aqueous volume is approximately 1% of the total volume of the suspension.

Interesting possibilities arise through the use of synthetic amphiphilic compounds in the formation of vesicles. Using polymerizable lipid analogues or analogues containing functional groups, membrane vesicles with novel properties can be obtained.[24-26]

Transport proteins isolated from biological membranes can be introduced into artificial lipid vesicles.[27] This is achieved by adding the detergent-solubilized protein to a lipid/detergent mixture and subsequently removing the detergent by dialysis. In this way, the protein is incorporated into the membrane of the lipid vesicles. Ion fluxes through the vesicle membrane can be studied either using radioactive isotopes or with optical indicator molecules.

4. Ion Carriers

A variety of compounds are now known that function in biological membranes or artificial lipid membranes as mobile ion carriers (Fig. 2A).[24-28] Best characterized are macrocyclic compounds such as valinomycin and enniatin B and macrotetrolides like monactin (Fig. 7). Valinomycin and enniatin B are depsipeptides formed from alternating amino acids and α-hydroxy acids. Valinomycin forms a 1:1 complex with K^+ ions in which the ion is surrounded by the six oxygen atoms of the ester carbonyl groups[31] (Fig. 8). The exterior of the complex, formed by methyl and isopropyl groups, is strongly hydrophobic.

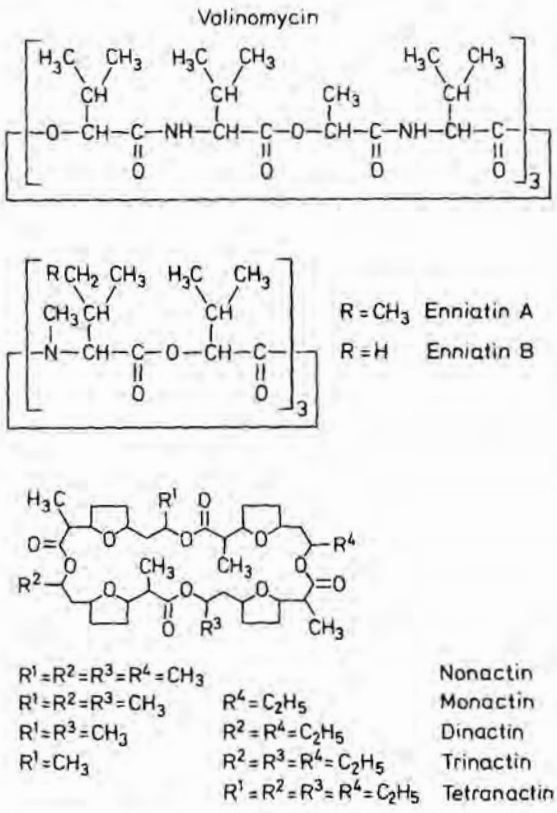


Fig. 7. Macrocyclic ion carrier. Valinomycin, enniatin A, and enniatin B are depsipeptides which consist of alternating α-amino acids and α-hydroxy acids.

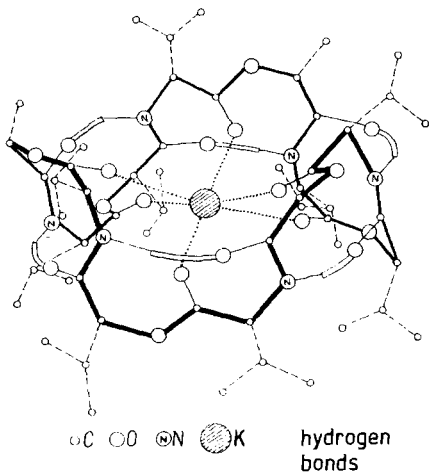


Fig. 8. Structure of the valinomycin/K^+ complex [31]. The central K^+ ion is encaged by six oxygen atoms of the ester carbonyl groups. The complex is stabilized by six hydrogen bonds between NH and CO groups of the six amino acids.

The structure of the valinomycin/K^+ complex (Fig. 8) was determined by X-ray analysis[32–36] as well as from spectroscopic data.[31,37–48] The backbone of the molecule is folded into six loops which are held together by six hydrogen bonds between NH and C=O groups of the amino acids. UV, IR, circular dichroism (CD), and NMR studies have shown that the noncomplexed valinomycin molecule can adopt a variety of conformations in solution, depending on the nature of the solvent. In nonpolar solvents the molecule exhibits a closed conformation similar to that of the K^+ complex, whereas in polar solvents an open conformation with a smaller number of intramolecular hydrogen bonds predominates (Fig. 9).[29,30] Transitions between these two conformations take place in the time range of 10^{-9}–10^{-7} s, as was shown by ultrasound absorption measurements.[29] Fast conformational equilibria seem to be a necessary precondition for the high rates of complexation of macrocyclic ion carriers in homogeneous solution.[41,49–52]

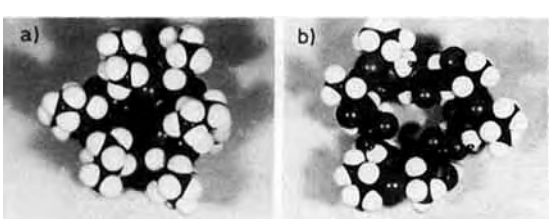


Fig. 9. Structure of valinomycin in solution. (a) Closed conformation with six intramolecular hydrogen bonds; (b) semi-open conformation with three intramolecular hydrogen bonds. Conformation (a) predominates in apolar solvents, whereas conformation (b) is adopted in polar solvents (from *Grell* et al. [29]).

The mechanism of carrier-mediated transport of alkali-metal ions through membranes has been studied in detail using planar lipid bilayers.[53–82] In a 1 M KCl solution containing 0.1 μM valinomycin, the membrane conductivity is about 10 mS/cm^2, six orders of magnitude greater than the conductivity of the membrane in the absence of valinomycin.[59] This enormous increase of the conductivity is practically solely due to the transport of K^+ ions; this is deduced from the observation that the membrane potential in asymmetric KCl solutions agrees with the Nernst potential for K^+.[53] The specificity of valinomycin is extremely high; the ratio of the membrane conductivity in a solution containing K^+ to that in a solution containing an equivalent concentration of Na^+ is about 2000.[84,85] Valinomycin may be added to the aqueous phase or directly to the lipid. It then undergoes distribution between the aqueous phase and the membrane with a partition coefficient of about 5×10^4 in favor of the membrane.[60]

The observed concentration dependence of the membrane conductivity can be explained by the assumption that both valinomycin and enniatin B as well as macrotetrolides act according to a translational mechanism as illustrated in Figure 2A. The transport process consists of four steps: 1) formation of a complex between the ion M^+ and the carrier molecule S at the membrane surface; 2) translocation of the complex MS^+ to the opposite side of the membrane; 3) liberation of the ion; 4) back-transport of the free carrier molecule S. The kinetics of the transport process can be described in a first approximation by the introduction of rate constants for each reaction step (Fig. 10). This is self-evident in the case of association and dissociation steps (rate constants k_R and k_D); k_R and k_D are overall rate constants which may include several intermediate reactions (e.g., conformational changes of the carrier or stepwise replacement of water molecules by ligand atoms of the carrier within the hydration shell). The description of the translocation steps of MS^+ and S by the unimolecular rate constants k_{MS} and k_S is only an approximation which is based on the assumption that the residence times of MS^+ or S in the membrane–solution interfaces are much longer than the time required for the actual translocation.[60]

The reaction scheme illustrated in Figure 10 leads to a number of interesting questions. Is there a rate-limiting step that determines the rate of the overall reaction? Is the high specificity of valinomycin dominated by thermodynamic factors (equilibrium constants of complex formation) or by kinetic parameters? Which kinetic factors are important for the optimal functioning of a carrier? In order to answer these questions the kinetics of the transport system must be studied in detail. Such an analysis is made possible by the use of relaxation measurements.

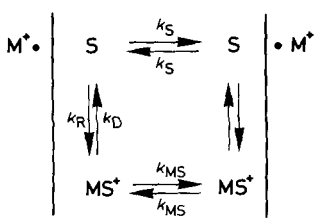


Fig. 10. Transport of an ion M^+ by the carrier S. k_R and k_D are the association and dissociation rate constants, k_{MS} and k_S the rate constants for translocation of the complex MS^+ and the free carrier S.

4.1. Relaxation Methods for the Study of Ion Transport Processes in Membranes. Kinetic Analysis of Carrier Systems

Relaxation methods were first developed for the study of fast chemical reactions in homogeneous phase.[83] The system under investigation is perturbed by the sudden change of an external parameter such as pressure or temperature, and the time course of the approach to a new equilibrium state is followed. Relaxation methods have also proved to be useful tools for the kinetic study of ion transport processes in membranes.[60-63, 67-72, 75-81]

The voltage-jump relaxation method (Fig. 11) consists in rapidly applying a voltage to the membrane and then recording the current relaxation.[60, 78, 79] For the carrier mechanism illustrated in Figure 10 it is possible to describe the time dependence of the membrane current by the sum of three (or, in some simple cases, two) exponential functions. From the experimental time constants and the amplitudes of the exponential functions, the rate constants k_R, k_D, k_S, and k_{MS} can be calculated.

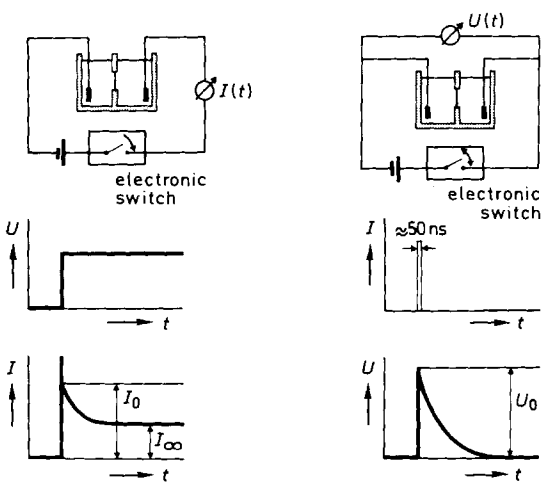


Fig. 11. Electrical relaxation methods for the study of ion transport processes in membranes. In the voltage-jump method (left), a voltage is rapidly applied to the membrane and the relaxation of the membrane current I is measured. In the charge-pulse method (right), the membrane capacitance is charged by a 50-ns electrical pulse to a starting potential of U_0. At the end of the pulse the outer electrical circuit is interrupted and the decrease in voltage due to charge transport within the membrane is recorded.

The time resolution of the voltage-jump method is limited by the charging time of the membrane capacitance and is approximately 1 μs. A considerably better time resolution is obtained with the charge-pulse relaxation method (Fig. 11).[68, 78, 86] In this case, the membrane capacitance is charged to starting voltage of approximately 10 mV by a current pulse of 10–50 ns duration. The outer electrical circuit is then interrupted and the relaxation of the voltage resulting from the movement of ions within the membrane is monitored. Using the charge-pulse relaxation method it is possible to achieve a time resolution of 40 ns.[87]

A further relaxation method consists in changing the temperature of the membrane and the surrounding solutions in a stepwise fashion. The temperature jump can be achieved by absorption of an intense flash of light.[88, 89] If a light source emitting in the visible region is used, an appropriately absorbing dye has to be added to the external medium.[71] Because of its small thickness, the membrane responds to the temperature changes in the medium within less than 1 ns. An improved version of this method makes use of an IR laser pulse to heat the solution (Fig. 12).[76] For the wavelength of the Nd glass laser ($\lambda = 1.06$ μm) the absorption coefficient of water is 0.063 cm^{-1}. This allows temperature jumps of approximately 0.3–0.4 K within 0.4 ms using the fixed Q-mode of the laser. In practice, a constant voltage is usually applied to the membrane prior to the temperature jump. The T-jump leads to an almost instantaneous increase in membrane conductivity, corresponding to the temperature dependence of the ion-transport system. This rapid increase in the membrane current is followed by a slower relaxation process due to translocation of carrier molecules within the membrane and changes in the degree of complexation.

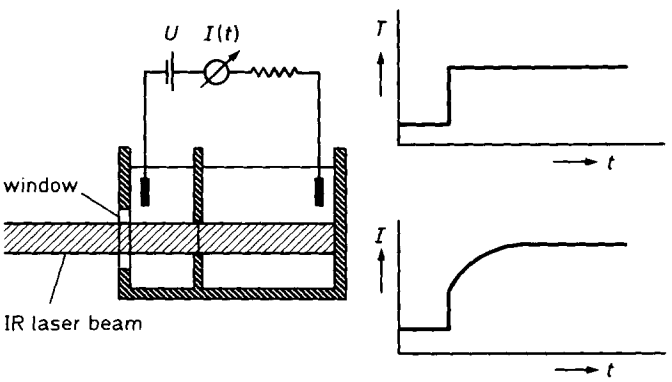


Fig. 12. Principle of the temperature-jump relaxation method. The membrane and the surrounding solutions are rapidly heated by absorption of an infrared laser pulse. A voltage U is applied to the membrane prior to the T-jump. The T-jump leads to a practically instantaneous increase in membrane conductivity (according to the temperature dependence of the rate constants), followed by slow relaxation processes.

The kinetic analysis of a carrier system such as valinomycin (Fig. 10) involves the determination of four rate constants (k_R, k_D, k_S, and k_{MS}). By the use of the voltage-jump method[60, 62, 63, 65, 67, 75, 90, 91] and the charge-pulse relaxation method,[68-70, 73] the ion carriers valinomycin, enniatin A and B, and beauvericin as well as the macrotetrolides have been studied in artificial lipid membranes. As a typical example, the rate constants for valinomycin-mediated K^+ transport through monooleate membranes at 25°C are given below:

$k_R \approx 3 \times 10^5\ M^{-1}\ s^{-1}$
$k_D \approx 3 \times 10^5\ s^{-1}$
$k_{MS} \approx 2 \times 10^5\ s^{-1}$
$k_S \approx 4 \times 10^4\ s^{-1}$

At a K^+ concentration of 1 M ($c_M = 1$ M) the rate constants for the association ($c_M k_R$), dissociation (k_D), and translocation of the charged carrier (k_{MS}) are approximately equal (2×10^5–$3 \times 10^5\ s^{-1}$). The rate-limiting step in this case is determined by the back-transport of the free carrier ($k_S \approx 4 \times 10^5\ s^{-1}$). $k_{MS} \approx 2 \times 10^5\ s^{-1}$ is the frequency with which the charged carrier crosses the membrane; its

reciprocal value, $1/k_{MS} \simeq 5\ \mu s$, is the average residence time of the complex in the energy minimum at the membrane-solution interface.

A useful parameter for the kinetic description of carriers (and other transport systems) is the maximum turnover number f, which is defined as the limiting value of the transport rate reached under short-circuit conditions with an infinitely high ion concentration on the left-hand side and a negligible ion concentration on the right-hand side of the membrane.[61] f is the maximum number of transport cycles that a carrier molecule can carry out per second. From the known values of the rate constants, the turnover number can be calculated using the following equation:

$$f = \left(\frac{1}{k_{MS}} + \frac{1}{k_S} + \frac{2}{k_D}\right)^{-1} \quad (1)$$

For the above example, $f \simeq 2 \times 10^4\ s^{-1}$ is obtained, which means that a single valinomycin molecule is able to transport 10^4–$10^5\ K^+$ ions per second through the membrane. The high efficiency of valinomycin as an ion carrier is mainly determined by its high turnover number. In contrast, the stability constant $K = k_R/k_D \simeq 1\ M^{-1}$ of the K^+ complex in the membrane-solution interface is remarkably small. Considerably higher values for the stability constant ($K \simeq 3 \times 10^4\ M^{-1}$) were found in methanol.[29] In methanol/water mixtures, however, K is smaller and at 70% (v/v) water in methanol reaches a value of approximately $1\ M^{-1}$.[29] A mixture of 30% methanol and 70% water is thus comparable to the membrane interface with respect to complex stability.[30] The same is true for the association and dissociation rate constants. In pure methanol $k_R \simeq 4 \times 10^7\ M^{-1}\ s^{-1}$ and $k_D \simeq 1.2 \times 10^3\ s^{-1}$ are found,[29] while for 70% water in methanol the extrapolated values are $k_R \simeq 1.4 \times 10^5\ M^{-1}\ s^{-1}$ and $k_D \simeq 1.8 \times 10^5\ s^{-1}$, similar to those found for the membrane.[30] From CD measurements, the stability constant of the valinomycin/K^+ complex in artificial dimyristocyl lecithin vesicles was found to be $K \simeq 1\ M^{-1}$.[29] This value agrees with that determined from relaxation experiments with planar lipid membranes.

4.2. Optimization Principles for Carrier Systems

The kinetic analysis described above leads to the general question of how to optimize carrier systems. In particular, it is interesting to ask how close nature has come to an optimal solution in the evolution of ion carriers. In order to achieve high transport rates it is advantageous to make all rate constants large, within the physical limits imposed on the system. The translocation rate constant k_S of the free carrier is limited by its size, by the microviscosity of the membrane, and by the binding of the amphiphilic carrier molecule at the membrane-solution interface. k_{MS} is also limited by membrane viscosity as well as by the height of the dielectric energy barrier of the membrane. It is therefore unlikely that, for a mobile carrier, k_S and k_{MS} will exceed the value of ca. $10^5\ s^{-1}$ observed for valinomycin. The association rate constant k_R, however, lies far below the limiting value for a diffusion-controlled reaction. The small value of k_R probably results from the fact that the carrier molecule at the membrane interface is stabilized in an open conformation which is less favorable for complex formation.

How large is the optimum value of the dissociation rate constant k_D for a given set of values of k_R, k_{MS}, and k_S? A very large value of k_D would obviously be a disadvantage since it would result in a decrease of the stability constant $K = k_R/k_D$. For a very small value of k_D, on the other hand, the transport rate would be limited by the slow dissociation of the complex MS^+ at the membrane interface. The optimum value of k_D can be calculated under the condition that for given values of k_R, k_{MS}, and k_S the membrane conductivity induced by the carrier should reach a maximum. This results in the following equation:[78]

$$k_D^* = [c_M k_R k_{MS}(2 + c_M k_R/k_S)]^{1/2} \quad (2)$$

Using the experimental values for k_R, k_{MS}, and k_S given above, $k_D^* \simeq 1 \times 10^5\ s^{-1}$ for $c_M = 0.1\ M$ is obtained, which agrees approximately with the observed value of $k_D \simeq 3 \times 10^5\ s^{-1}$. All macrocyclic peptide and depsipeptide analogues of valinomycin synthesized up to now have been found to be less efficient carriers than valinomycin itself.[27,72,92,93]

4.3. Influence of Membrane Structure on the Kinetics of Carrier Systems

Biological membranes contain a variety of lipids, which differ in the structures of their polar head groups, the lengths of their hydrocarbon chains, and the number of C=C double bonds. The functional significance of this diversity is not yet well understood. Using artificial bilayers prepared from chemically uniform lipids, it is possible to study the influence of membrane structure on the kinetics of carrier systems.[62,63,69,70,72,73,94–96]

The electrical charges and dipole moments of the headgroups influence the ion transport rates. Membranes consisting of phosphatidylserine or phosphatidylinositol have a negative interfacial potential; this results in an accumulation of cations at the membrane interface and in an increase in cation transport rates.[96] Oriented dipole layers at the interface result in an additional difference in the potential between the interior of the membrane and the aqueous solution.[95,97] From experiments with positively and negatively charged lipophilic ions, for example, it may be estimated that the potential of the interior of a phosphatidylcholine membrane is about +0.3 V relative to the external solution.[97] This electrostatic energy barrier inhibits the transport of cations and favors that of anions.

Variation in the length of the hydrocarbon chains of the lipid molecules and in the number of double bonds has a marked effect on the rate constants of ion carriers. Table 1 summarizes the kinetic parameters for the valinomycin/Rb^+ system in membranes formed from different monoglycerides.[69] An increase in chain length from C_{16} to C_{22} results in a decrease of the translocation rate constants k_S and k_{MS} by a factor of 8 to 10, whereas k_R and k_D remain almost constant. Increasing the number of C=C double bonds from one to four results in a marked increase of k_S

Table 1. Influence of the chain length and the number of double bonds of lipids on the rate constants for the valinomycin-mediated Rb^+ transport [69]. The membranes were formed from α-monoglycerides (MG) containing the following fatty acid residues: palmitoleoyl (16:1), oleoyl (18:1), 11-eicosenoyl (20:1), erucoyl (22:1), 11,14-eicosadienoyl (20:2), 11,14,17-eicosatrienoyl (20:3), and arachidonoyl (20:4). The membranes were spread from *n*-decane. $T=25°C$.

Lipid	k_R [10^4 M^{-1} s^{-1}]	k_D [10^4 s^{-1}]	k_{MS} [10^4 s^{-1}]	k_S [10^4 s^{-1}]
Variation of the chain length				
(16:1)-MG	43	13	74	8.5
(18:1)-MG	37	24	27	3.5
(20:1)-MG	23	12	10	1.8
(22:1)-MG	24	13	7	1.1
Variation of the number of double bonds				
(20:1)-MG	23	12	10	1.8
(20:2)-MG	34	9	39	3.2
(20:3)-MG	34	5	136	9.4
(20:4)-MG	42	3	240	12

and k_{MS}. This increase in translocation rate constants is probably due to the decreased order and smaller microviscosity of membranes consisting of highly unsaturated lipids.

5. The Gramicidin Channel

The simplest known molecule that forms ion channels in a lipid membrane is gramicidin A (Fig. 13), a linear pentadecapeptide with the sequence

HCO-NH-L-Val-Gly-L-Ala-D-Leu-L-Ala-D-Val-L-Val-D-Val-L-Trp-D-Leu-L-Trp-D-Leu-L-Trp-D-Leu-L-Trp-CO-NHCH$_2$CH$_2$OH

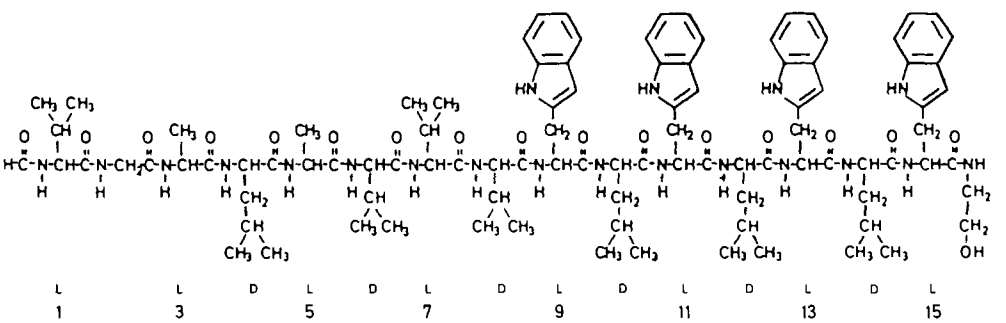


Fig. 13. Structure of valine-gramicidin A [98].

isolated from *Bacillus brevis* and exhibiting antibiotic activity.[98] Gramicidin A consists mainly of hydrophobic amino acids, and the end groups are blocked. In the presence of gramicidin A the permeability of biological membranes or artificial lipid membranes is strongly increased for small monovalent cations such as alkali metal ions, Ag^+, Tl^+, NH_4^+, and H^+.[53,54,99-102]

5.1. Single-Channel Experiments

The first evidence that gramicidin A acts as an ion channel and not as a carrier came from experiments in which an extremely small amount of the peptide was added to a lipid bilayer. Under these conditions, when a constant electrical voltage is applied to the membrane, discrete, stepwise variations of the membrane current are observed with amplitudes of approximately 8×10^{-12} A in 1 M Cs^+ solution and at 0.1 V (Fig. 14).[103] When increasing amounts of gramicidin A are added to the membrane, more and more current fluctuations superimpose until eventually the membrane reaches a macroscopic conductivity. The simplest explanation of these observations is to assume that the observed current fluctuations result from the formation and disappearance of single ion channels. The height of the current step corresponds to a single-channel conductivity of 80 pS (in 1 M Cs^+ solution), which is equivalent to the transport of 5×10^7 Cs^+ ions per second (at a voltage of 0.1 V). This transport rate is 3-4 orders of magnitude greater than the maximum transport rate of an ion carrier of the valinomycin type (Section 4.1). Therefore, gramicidin A presumably does not act as a carrier; the high transport rates observed, however, are perfectly compatible with a channel mechanism.[103]

The possibility of directly observing single molecular events within a membrane by current measurements is a consequence of the extremely small intrinsic conductivity of a lipid membrane. Recently, it has been possible to electrically isolate small areas of cell membranes with the aid of glass micropipettes and to monitor single-channel currents through biological ion channels.[105]

Detailed analysis of the experiment illustrated in Figure 14 shows that the amplitudes of the fluctuations in conductivity are not completely uniform but rather distributed about a mean value. The width of the distribution depends on the nature of the lipid.[106] Furthermore, gramicidin channels occasionally show single-channel events with much smaller amplitudes.[107] A possible explanation for these observations is to assume that the gramicidin channel may adopt several long-lived conformations (see Section 5.2) which have different ionic permeabilities.[107-110]

Single-channel experiments yield, apart from the channel conductivity, the life-time of the open state of the channel. Experimentally, one obtains for the probability dP of finding a channel with a lifetime between t and $t+dt$ the relation $dP=\exp(-t/\tau)dt$ as one would expect for a system of independent particles with a constant rate of decay.[103] The constant τ is the mean lifetime of the channel.

Although the channel conductivity is almost independent of the nature of the lipid (if the lipid is electrically neutral), the mean lifetime τ decreases rapidly with increasing chain length of the lipid (i.e., with increasing membrane thickness).[102, 111, 112] τ varies from milliseconds to seconds. A further parameter influencing the mean lifetime is the interfacial potential of the membrane.[112, 114–116]

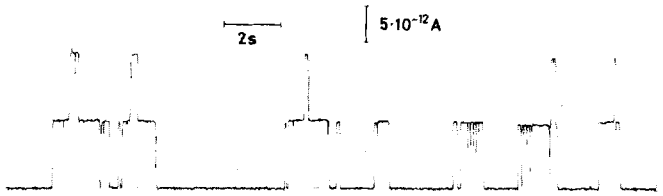


Fig. 14. Fluctuations in membrane current at very low gramicidin concentration [104]. 1 M CsCl, 25°C, membrane potential 0.1 V. The membrane was formed from monoolein. The base line represents the membrane conductivity in the absence of gramicidin.

5.2. The Structure of the Gramicidin Channel

A structural model for the gramicidin channel has been proposed by *Urry* based on calculations of the conformational energies.[117–119] It consists of a hydrogen-bond-stabilized helical dimer in which the two monomers are connected head-to-head at their formyl ends (Fig. 15 and 16). The hydrophobic amino acids side chains are located on the outside of the helix.[120] In the center of the helix, along the axis, a 0.4-nm-wide tunnel is present which is lined with the oxygen atoms of the peptide carbonyl groups. The diameter of 0.4 nm is sufficient to allow the passage of non-hydrated alkali metal ions. The total length of the dimer is 2.5 to 3.0 nm, which is somewhat less than the thickness of the hydrocarbon layer of a bimolecular lipid membrane. Conformational energy calculations show that the peptide carbonyl groups can tilt with their oxygen end toward the helix axis.[117–119] This "libration" allows the channel width to adjust to the diameter of the ion; the close approach of the negative end of the carbonyl dipole to the cation results in an energetically favorable interaction between ion and channel.

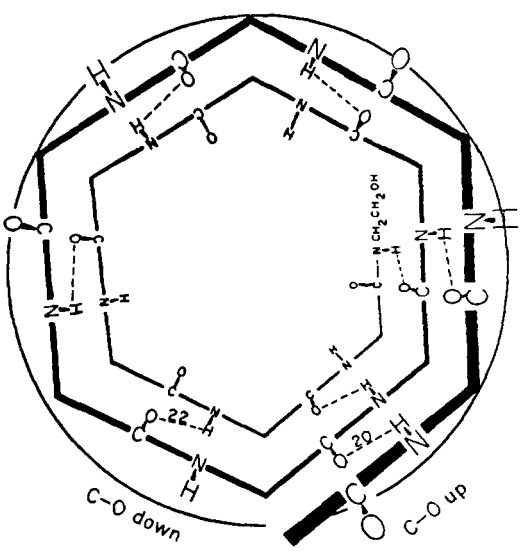


Fig. 15. Helical structure of the gramicidin A channel [121]. The 0.4-nm wide channel along the helix axis is lined with the oxygen atoms of the peptide carbonyl groups. The amino acid side chains, which are located at the outside of the helix, are not shown. The transmembrane channel consists of two helixes joined at their formyl ends.



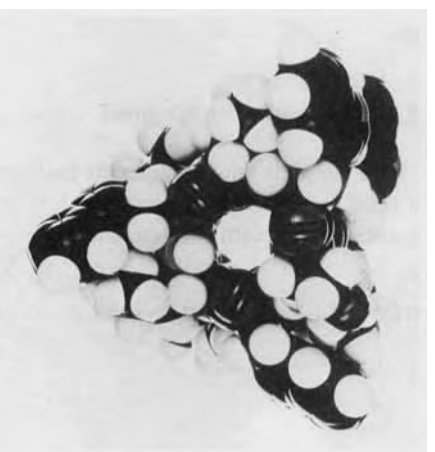


Fig. 16. Space-filling model of the gramicidin channel, according to *Urry* [118]. Left: the outside of the dimeric channel. The two monomers are joined by hydrogen bonds. Right: view along the helix axis. The central tunnel has a diameter of 0.4 nm.

Energy considerations also indicate that the channel can adopt a variety of stable conformations which differ in the orientation of the amino acid side chains.[108–110] The channel conformation may influence the channel conductivity, for example, due to the dependence of the electrostatic energy of the ion inside the channel on the orientation of the dipolar tryptophan residues. In addition, the libration of the carbonyl groups may be restricted to different extents for different side chain conformations.

X-ray diffraction studies of gramicidin have been possible to date only at low resolution,[122, 123] the results being compatible with a helical structure. It is interesting to note that the structure is different for the free dimer and the dimer occupied by a cation (K^+ or Cs^+). The helix diameter increases from 0.5 to 0.68 nm upon binding of a cation, and the length decreases from 3.2 to 2.6 nm.

Evidence for the dimeric structure of the channel was obtained from kinetic studies of channel formation (Section 5.3) as well as from experiments with pyromellityl derivatives of gramicidin (Section 5.4). A further test of the dimer hypothesis was performed by combining fluores-

cence and conductivity studies on membranes containing dansylated gramicidin.[133] In these experiments, a quadratic dependence of the membrane conductivity on the fluorescence intensity, and thus the concentration of the incorporated gramicidin, was observed, in accordance with the dimer model.

Spectroscopic investigations show that gramicidin A forms helical dimers in organic solvents.[124-132] Apart from head-to-head dimers, double-stranded helixes are observed in which both peptide chains are wound around a common axis and joined by intermolecular hydrogen bonds. The double-stranded helix was originally proposed as an alternative to *Urry*'s channel model.[127] The evidence for *Urry*'s model is based on measurements of membrane conductivity (Section 5.4) as well as on nuclear magnetic resonance experiments.[134-136] In particular, it was possible to prove via distance measurements based on spin-spin interactions that the carboxyl terminal end of the peptide is localized at the membrane interface whereas the amino terminal end is buried deep inside the hydrophobic part of the membrane.[134] Nuclear magnetic resonance experiments in which ^{13}C-NMR chemical shifts were measured in the presence of cations in the channel support the model of a left-handed β-helix.[136, 137]

5.3. Kinetics of Channel Formation

On the basis of the dimer model (Section 5.2) it is possible to describe channel formation as a bimolecular reaction:

$$G + G \underset{k_D}{\overset{k_R}{\rightleftharpoons}} G_2 \qquad (3)$$

The kinetics of this reaction can be investigated by relaxation measurements.[138, 140] The basis for the application of the voltage-jump or charge-pulse relaxation method lies in the fact that the number of active channels in the membrane is dependent on the transmembrane electrical field strength. If a voltage is rapidly applied at time $t=0$ to a membrane doped with gramicidin, an initial current is observed which is determined by the number of channels initially present. Subsequently, the current increases asymptotically toward a limiting value which corresponds to the voltage-induced shift in the equilibrium constant of channel formation. For the channel-formation reaction given by Equation (3), the reciprocal of the time constant τ_c for the increase in current should be linearly related to the square root of the stationary membrane conductivity λ_∞:

$$1/\tau_c = k_D + 4\sqrt{k_R k_D \lambda_\infty / L\Lambda} \qquad (4)$$

L is Avogadro's number and Λ the conductivity of a single channel. Equation (4) has been experimentally verified: measurement of τ_c and λ_∞ for a variety of gramicidin concentrations and plotting of $1/\tau_c$ versus $\sqrt{\lambda_\infty}$ results in a straight line.[138] Channel formation thus can be described as a second-order reaction in agreement with Equation (3). This does not exclude, however, more complicated mechanisms such as an equilibrium between inactive and active forms of the dimer or the association of inactive dimers to form an active tetramer.[142]

On the basis of the dimer model [Eq. (3)], the rate constants k_R and k_D can be determined from a plot of $1/\tau_c$ versus λ_∞. $1/k_D$ agrees within experimental error with the mean lifetime τ of the channel determined by single-channel experiments.[138, 139]

A totally independent method of studying the kinetics of channel formation consists in the analysis of electrical noise.[113, 143, 144] A bimolecular lipid membrane is thermodynamically a small system and is therefore subject to large fluctuations. In accordance with the statistical nature of channel formation, the number of channels and thus the membrane conductivity varies with time. Measurement of the correlation function or the spectral intensity of the current fluctuations allows the kinetic parameters of the channel system to be determined. Noise analysis provides the same information as a combination of relaxation experiments and single-channel measurements; furthermore, this method yields information on single-channel conductivity at high channel density. Thus, noise analysis offers the possibility of studying interactions between neighboring ion channels.[113]

5.4. Derivatives and Analogues of Gramicidin A. Effects of Electric Charges at the Channel Opening

Experiments with gramicidin channels open up the possibility of studying the relationship between structure and permeability properties of ion channels. To this end, a variety of derivatives and analogues of gramicidin A have been investigated.[104, 121, 141, 145-161] Synthetic analogues with a simplified sequence, e.g., HCO-NH-(L-Trp-D-Leu)$_7$-L-Trp-CO-NHCH$_2$CH$_2$OH, also form ion channels, but these exhibit different conductivities and altered selectivities.[152] Replacement of a single amino acid may lead to a considerable change in single-channel conductivity. For instance, replacement of tryptophan in position 11 by phenylalanine (see Fig. 13) results in a decrease in K^+ conductivity by a factor of 1.4.[106] Simultaneous changes in two different positions change the conductivity even more.[158] The variations in conductivity are likely to result from local effects of amino acid side chains on the geometry and flexibility of the ligand system. Furthermore, as discussed above, the potential energy of the ion inside the channel can be influenced by the introduction of side chains with electrical dipole moments.

Of particular interest are gramicidin derivatives carrying charged groups at the carboxyl or amino terminal ends.[148, 152, 154, 159, 162] Esterification of the ethanolamine residue at the carboxyl terminal end with pyromellitic acid results in the introduction of three negative charges at the mouth of the channel opening.[148] *O*-Pyromellitylgramicidin A (Fig. 17) forms ion channels in planar lipid membranes that exhibit opening and closing behavior similar to gramicidin A itself. Other properties of the neutral and negatively charged gramicidins, however, differ considerably, as described below.

Addition of *O*-pyromellitylgramicidin to one of the aqueous solutions bathing the membrane results in only a mar-

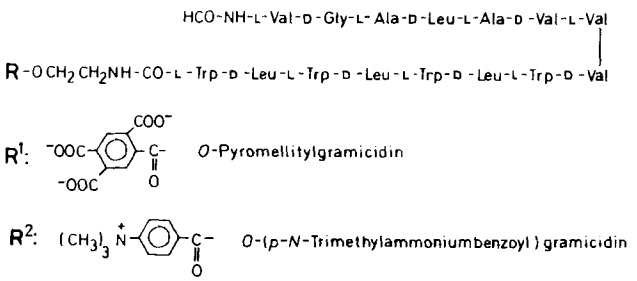


Fig. 17. Gramicidin derivatives with positively and negatively charged groups at the carboxyl terminal end, which is located at the opening of the channel.

ginal change in membrane conductivity. If the compound is subsequently added to the other solution, however, an increase in conductivity by several orders of magnitude is observed.[148] This result is in marked contrast to the behavior found for neutral gramicidin, where addition of the peptide to one side or to both sides simultaneously results in almost the same conductivity. These observations can be explained on the basis of the dimer model, assuming that both half-channels can combine only if they are located on opposite sides of the membrane. Unmodified gramicidin A can probably cross the membrane easily due to its highly hydrophobic character, whereas the negatively charged derivative remains on the side of the lipid bilayer to which it has been added. Simultaneous addition of *O*-pyromellitylgramicidin to both outer solutions leads to an increase in membrane conductivity proportional to the square of the peptide concentration,[148] in accordance with the dimer model.

Marked differences between neutral and negatively charged gramicidin are also observed in their single-channel conductivity Λ.[148] Whereas at high ion concentrations (1 M) the Λ values of the neutral and negatively charged channels are almost equal, at low ion concentrations (0.1 M) the conductivity of the negatively charged channel is 5 to 6 times higher (Fig. 18). This result is consistent with the notion that the negative charges at the channel opening should lead to an accumulation of cations capable of permeating the membrane. This accumulation effect is most pronounced at low ionic strength according to the Debye-Hückel theory of ionic interactions. Even greater electrostatic effects are observed when neutral gramicidin A is introduced into a negatively charged membrane.[163]

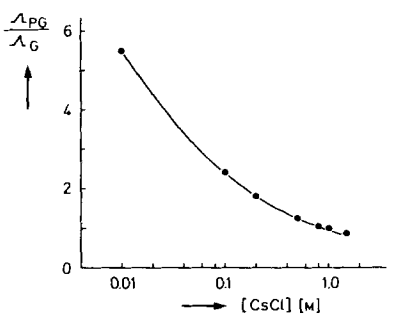


Fig. 18. Single-channel conductivity Λ_{PG} of the negatively charged *O*-pyromellitylgramicidin channel divided by the channel conductivity Λ_G of neutral gramicidin [148]. At low ionic strength, the negatively charged channel has a five- to sixfold greater conductivity than the neutral channel.

In the presence of a mixture of neutral and negatively charged gramicidin three types of channels with different conductivities are observed.[148] The channel with the highest conductivity is identical to the *O*-pyromellitylgramicidin channel and that with the smallest conductivity to the normal gramicidin channel. Presumably, therefore, the channel with intermediate conductivity is a hybrid consisting of one neutral and one negatively charged half-channel. Such hybrid channels, whose existence is predicted from the dimer model, have also been observed with other derivatives and analogues of gramicidin.[151,158]

A gramicidin derivative with a positive charge at the channel opening may be prepared by introduction of a *p*-trimethylammoniumbenzoyl group (Fig. 17). In this case the conductivity is less than that of the neutral channel.[152]

Channels exhibiting novel properties can be obtained by adding the positively charged peptide to one aqueous phase and the negatively charged peptide to the other. In this case hybrid channels, which consist of one positive and one negative half-channel, are formed inside the membrane.[152] This structural asymmetry is reflected in an asymmetric current-voltage behavior (Fig. 19). The channel

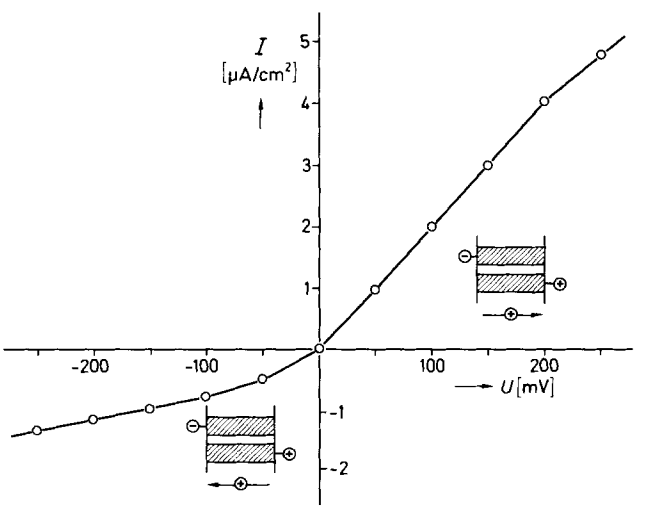


Fig. 19. Asymmetric current-voltage characteristic of hybrid channels, which are formed from a positively and a negatively charged half-channel (Fig. 17) [152]. The membrane current I was measured 1 ms after the voltage U was applied. The current is larger in the forward direction (cation flux from the negative to the positive channel end) than in the backward direction.

current increases much more in the "forward" direction (cation flux from the negative to the positive end of the channel) than in the "backward" direction. Chemical modifications thus allow preparation of ion channels with intrinsic rectifying properties.

Experiments with ionic derivatives of gramicidin may also be used to distinguish between different channel models. To this end, the membrane activity of the *N*-pyromellityl derivative of desformylgramicidin A, in which the formyl group at the amino terminus is replaced by a pyromellityl residue was studied.[162] In a double-stranded helix, both the amino terminal ends as well as the carboxyl terminal ends should lie at the membrane interface. Since the *O*-pyromellityl derivative is able to form channels, one

would expect, on the basis of the double-strand model, the *N*-pyromellityl derivative also to be active. For the *Urry* model, in which the amino terminal ends are located in the interior of the membrane (Section 5.2), a membrane activity would not be predicted since the localization of the negatively charged pyromellitic acid group in the apolar interior of the membrane is energetically unfavorable. Experimentally, channel formation is not observed with the *N*-pyromellityl derivative, in agreement with *Urry*'s model.[162]

5.5. Mechanism of Ion Transport through the Channel

Compared to an ion carrier such as valinomycin, the gramicidin channel exhibits a much smaller selectivity. Within the series of alkali-metal ions, the order of permeability is identical with the order of mobility of these ions in water ($Li^+ < Na^+ < K^+ < Rb^+ < Cs^+$). The permeability ratio $P(K^+)/P(Na^+)$ is only 3–4,[102] whereas for valinomycin $P(K^+)/P(Na^+)$ is greater than 10^3. The channel is virtually impermeable to anions and higher-valent cations. Ca^{2+} and Ba^{2+}, at high concentrations, block the passage of monovalent cations.[164–166]

The selectivity of an ion channel is influenced by the geometry and flexibility of the ligand system.[167] The preference for cations over anions can be explained by the favorable electrostatic interactions of the cation with the negatively charged oxygen atoms of the carbonyl groups. The fact that all alkali metal ions have comparable permeabilities (within a factor of 10) is probably connected to the aforementioned libration of the carbonyl groups. Presumably, a cation entering the channel loses only part of its hydration shell and migrates together with two water molecules, one preceding and one following, through the channel.[168, 179, 180]

Permeation experiments suggest that the gramicidin channel normally contains several water molecules. The water permeability of a gramicidin-doped membrane can be measured in two ways, either by application of an osmotic gradient or by isotope flux experiments.[169, 170] For small pores in which water molecules cannot exchange positions, the theory predicts that the ratio of the two permeability coefficients P_{osm}/P_{iso} is equal to the number N of water molecules inside the pore.[170] Experimentally, $N=6$ is obtained. This value of N was independently confirmed by measuring the so-called streaming potential.[170–172] A pore that simultaneously contains water molecules and ions should exhibit coupling between ion transport and water transport, and in a narrow pore such as the gramicidin channel (0.4 nm) the coupling should be rather strong.[178, 179] Any osmotically induced transport of water should therefore result in a transport of charge and should create (under open-circuit conditions) an electrical potential difference across the membrane. The experimentally measured streaming potential yields, under appropriate assumptions, a value for N of 6–7.[170]

The interaction of the ion with the ligands results in a series of local minima and maxima of potential energy along the transport pathway in the channel.[173–177] Superimposed on this potential is the dielectric interaction of the ion with the aqueous phase and the lipid. The dielectric interaction creates a broad energy barrier with a maximum in the middle of the membrane.[181, 182] This analysis gives a potential profile with one binding site at either end of the channel (Fig. 20). The energy barrier at the channel opening takes into account the existence of energetically unfavorable transition states between the fully hydrated and the ligand-bound states of the ion.

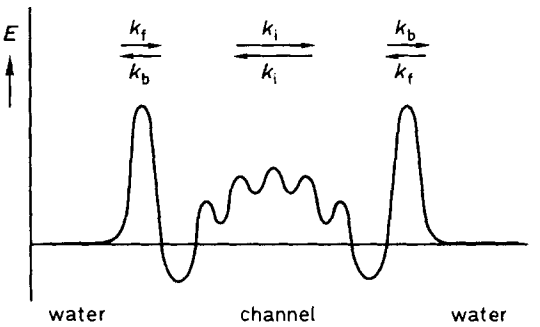


Fig. 20. Hypothetical potential-energy profile of a cation in the gramicidin channel. The potential profile results from a superposition of a broad dielectric energy barrier and local potential variations caused by interactions with the ligand system. The energy barriers at the openings take into account the (probable) existence of energetically unfavorable transition states between the completely hydrated and the ligand-associated states of the ion. k_i is the rate constant for ion jumps across the central barrier; k_f and k_b are the on and off rate constants for ion binding (when the second binding site is unoccupied).

The model illustrated in Figure 20 leads to the following predictions: if one binding site is occupied, the on and off rates for the other binding site should be altered by electrostatic ion-ion interaction. Furthermore, an ion should be able to leave one binding site and cross over the central barrier only if the other binding site is free. In fact, several experimental observations indicate ion-ion interactions inside the channel, e.g., the concentration dependence of permeability ratios,[102, 183] the blocking by Tl^+ ions,[183, 186] the exact form of the concentration dependence of channel conductivity,[103, 183, 185, 187] isotope interactions in flux experiments,[188] and the conductivity of short-chain gramicidin analogues.[189] Important information on the transport mechanism can also be deduced from the current-voltage characteristics of the channel.[103, 173, 190] These observations can be largely explained on the basis of the model in Figure 20 if one assumes that at high ion concentrations both binding sites can be occupied. The model is characterized by five rate constants (Fig. 20): k_i (crossing of the central barrier), k_f and k_b (on and off rate when the second binding site is unoccupied), and k_f^* and k_b^* (on and off rate when the second binding site is occupied). The values for the kinetic parameters summarized in Table 2 were obtained by fitting the model to the experimental data.[191, 192] According to the data given in Table 2, the first binding site is already occupied at ion concentrations of 1–10 mM ($k_b/k_f \simeq 8$ mM for Na^+). An interesting result is the large increase in the dissociation rate constant after occupancy of the second binding site ($k_b^*/k_b \simeq 600$). This agrees with the predicted electrostatic repulsion between the two ions. It is unclear, however, why a similar effect is not found for the association rate constants k_f and k_f^*. The data listed in Table 2 show that for high ion concentrations the channel

Table 2. Rate constants for ion transport through the gramicidin channel according to the model illustrated in Figure 20 [191]. k_i: rate constant for crossing over the central energy barrier; k_f, k_b: on and off rate constants when the second binding side is unoccupied; $k\dagger$, $k\ddagger$: on and off rate constants when the second binding site is occupied. The values in the first three columns were determined from conductivity and permeability measurements [191], the values in the last column from nuclear magnetic resonance studies [194].

	Cs^+	K^+	Na^+	Na^+ (NMR)
k_f [10^8 M^{-1} s^{-1}]	1.8	1.6	0.55	0.3
k_b [10^5 s^{-1}]	2.9	3.9	4.5	3
$k\dagger$ [10^8 M^{-1} s^{-1}]	1.6	1.4	0.53	0.12
$k\ddagger$ [10^8 s^{-1}]	1.6	2.1	2.6	0.4
k_i [10^7 s^{-1}]	8.2	2.7	1.3	>0.03

conductivity is limited by the rate constant for crossing the central barrier ($k_i \cong 10^7\ s^{-1}$). Values for k_i of this order of magnitude were also obtained from dielectric relaxation experiments.[196]

Nuclear magnetic resonance spectroscopy can also be used to study the transport kinetics of ions in the gramicidin channel.[193-195] For this purpose gramicidin A was introduced into lysolecithin micelles. From the concentration dependence of the rate of longitudinal relaxation of $^{23}Na^+$, the presence of one high-affinity and one low-affinity binding site for Na^+ was deduced. From the chemical shift of the ^{23}Na resonance and from relaxation data, an estimate for the binding constants $K = k_f/k_b$ and $K^* = k\dagger/k\ddagger$ was obtained. As shown in Table 2, the rate constants obtained by nuclear magnetic resonance agree within an order of magnitude with those obtained by conductivity measurements.

6. Introduction of Channel Proteins into Artificial Lipid Membranes

Biological membranes contain ion channels that are regulated by the electrical field in the membrane or by effector molecules such as acetylcholine. Examples are the Na^+ channel[197] of nerve membrane and the acetylcholine-activated channel in neuromuscular synapses.[6] The Na^+ channel of the nerve membrane is a glycoprotein whose main polypeptide chain has a molecular weight of $M \approx 260000$ g/mol. The acetyl-choline-activated channel has a molecular weight of 270000 g/mol and consists of five polypeptide subunits.

Channel proteins can be isolated from biological membranes by detergent solubilization. During the last few years methods have been developed to incorporate isolated membrane proteins into artificial lipid membranes.[8, 198] A phospholipid is added to the detergent-solubilized protein and the detergent is subsequently removed by dialysis. In this way, closed lipid vesicles are formed in which the protein is incorporated into the membrane. Addition of these lipid/protein vesicles to the external medium of a planar lipid membrane results, under appropriate conditions, in fusion of the vesicles with the membrane and incorporation of the protein. If the vesicle membrane and the planar membrane contain negatively charged lipids, the fusion can be induced by the addition of Ca^{2+} ions. An osmotic pressure inside the vesicle further promotes fusion.[199] An increased rate of fusion is observed at the characteristic temperature of the transition between the liquid crystalline phase and the gel-like phase of the membrane lipid.[200, 201]

An alternative to the fusion method consists in spreading lipid/protein vesicles on a water surface. From the monolayer obtained in this way, a bimolecular membrane can be formed by the technique described in Section 3.1. This method was applied to the incorporation of the acetylcholine-activated channel into planar bilayer membranes.[202-205]

It is also possible to incorporate channel proteins into planar lipid membranes without previous purification. This is achieved by mechanical fragmentation of cells followed by density gradient centrifugation. A membrane-vesicle fraction is thus obtained that can be fused with a planar membrane. Since, in general, a large number of different membrane proteins are incorporated into the planar membrane by this method, the desired channel protein must be identified either by its electrical properties or by its pharmacological behavior. This technique was used for the incorporation of Cl^- channels from the electric organ of the electric eel into an artificial membrane[206, 207] as well as for the incorporation of K^+ channels from sarcoplasmic reticulum[208-211] and from nerve endings,[212, 213] Ca^{2+}-dependent K^+ channels from muscle,[214, 215] and Na^+ channels from nerves.[216, 217] By the use of highly sensitive measurements of current (Section 5.1), the electrical properties of single channels can be studied after incorporation into the membrane (Fig. 21). Such reconstitution experiments also allow channels to be studied that are not accessible in situ due to an unfavorable cell geometry. This is the case, for instance, for the voltage-dependent Ca^{2+} channel from nerve endings (Fig. 21).[218] In the future, experiments using artificial membrane systems may become increasingly important for the study of structurally modified ion channels.

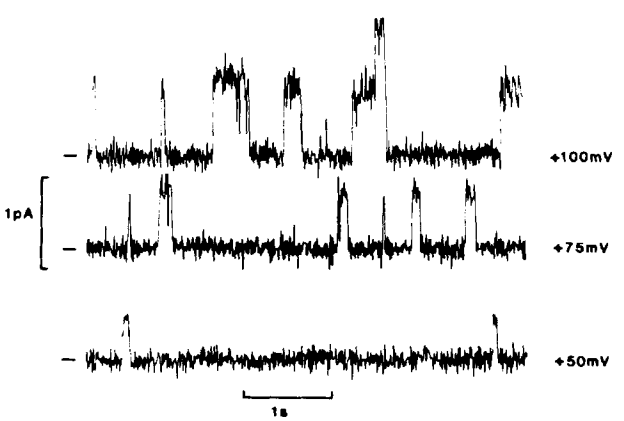


Fig. 21. Single-channel currents of Ca^{2+} channels from nerve endings at three membrane potentials [218]. The ion channels were incorporated into planar lipid membranes by fusion of nerve membrane vesicles. The probability for spontaneous opening and closing of channels depends on the applied voltage. The current level of the closed channel is marked by the horizontal line. The channels are permeable for Ca^{2+}, Sr^{2+}, and Ba^{2+}; in the experiment shown here, 0.25 M $BaCl_2$ was present in the aqueous phase.

7. Ion Pumps

The ion carriers and channels discussed so far are strictly passive transport systems; net transport is observed when a difference $\Delta\tilde{\mu}$ in the electrochemical potential of the permeable ion is present across the membrane as a driving force. $\Delta\tilde{\mu}$ can either be a concentration difference and/or a difference in electrical potential. Most biological membranes also contain active transport systems, which have the ability to transport ions against a thermodynamic potential gradient when energy is supplied. Depending on the kind of energy source, several types of active transport systems may be distinguished. In secondary active transport systems, the "uphill" transport of one substance is thermodynamically made possible by coupling it to the "downhill" transport of a second substance. The following discussion will only deal with primary active transport systems (ion pumps), which either use light, redox processes, or the free energy generated by the hydrolysis of adenosine triphosphate (ATP) as energy sources.

7.1. Light-Driven Proton Transport: Bacteriorhodopsin

Bacteriorhodopsin, a protein with a molecular weight of 26000 g/mol in the cell membranes of halobacteria, contains retinal as a chromophore and acts as a light-driven proton pump.[219,220] The protein is integrated into the bacterial membrane in the form of distinct patches which are two-dimensional protein lattices. These membrane areas can be isolated from the cells in the form of "purple-membrane fragments." After absorption of a photon, bacteriorhodopsin undergoes a cycle of conformational changes in the course of which one to two protons are transported from the cytoplasm into the extracellular medium. At the end of the cycle (after ca. 10 ms) the protein is again present in its initial state.

The individual states of the protein were at first characterized spectroscopically.[219] For instance, a fast *cis/trans* transition of the retinal was observed as an early event in the cycle. Still open is the question how the spectroscopically detected intermediates are correlated with the actual transport steps. Information about the transport kinetics is provided by experiments in which the purple membrane is associated in an oriented manner with a planar lipid membrane (Fig. 22).[221-227] After laser-pulse excitation at 575 nm (pulse length 10 ns), transient current signals are observed in the external circuit which originate from a charge redistribution within the bacteriorhodopsin molecule.[226] The first detectable signal has a time constant of $\tau \simeq 1$ µs and corresponds to a shift of the positive charge inside the purple membrane from the extracellular to the cytoplasmic side, i.e., in a direction opposite to that of stationary proton transport under constant illumination. This negative signal probably results from intrinsic charge displacements within the protein associated with a conformational change.[226-232] It is followed by charge displacements in the positive direction (from the cytoplasmic side to the extracellular medium) with time constants $\tau_2 \simeq 20$, $\tau_3 \simeq 60$, and $\tau_4 \simeq 400$ µs. On the basis of the pH dependence and H/D isotope effects, it is possible to assign the different charge displacements to specific spectroscopically detected transitions. From the amplitudes of the observed photoelectric signals, information can be obtained about the relative contributions of the individual events to the total charge displacement.

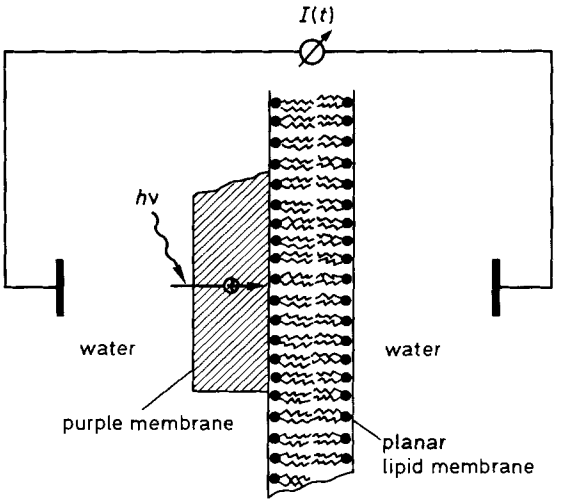


Fig. 22. Arrangement for carrying out photoelectric experiments with bacteriorhodopsin [226]. The purple membrane contains bacteriorhodopsin in the form of a two-dimensional lattice. After addition to the aqueous phase, the purple membrane binds with the extracellular side to the lipid bilayer. Charge transport within the bacteriorhodopsin molecule after flash excitation creates a current signal in the outer circuit.

7.2. Reconstitution of the Sodium-Potassium Pump

Most animal cells have the ability to maintain a high K^+ concentration and a low Na^+ concentration in the cytoplasm relative to the concentration of these two ions in the external medium. Responsible for the active transport of Na^+ and K^+ ions is a protein embedded in the cell membrane, the Na^+,K^+-ATPase, which transports K^+ into the cytoplasm and Na^+ into the extracellular medium at the expense of the free energy of ATP hydrolysis.[233-235] Under physiological conditions, the hydrolysis of one ATP molecule leads to the transport of three Na^+ ions to the outside and two K^+ ions to the inside. The Na^+,K^+ pump is thus (like bacteriorhodopsin) electrogenic, i.e., the pumping activity is associated with net charge transport. Using detergents it is possible to isolate the Na^+,K^+ pump from the cell membrane. The protein, which consists of an α subunit ($M \simeq 110000$ g/mol) and a β subunit ($M \simeq 40000$ g/mol), most likely has the dimeric structure $\alpha_2\beta_2$ inside the membrane.

Reconstitution of the Na^+,K^+-pump in planar lipid membranes has not yet been achieved. It is possible, however, to incorporate the Na^+,K^+-ATPase in a functional form into lipid vesicles.[236-246] Solubilization of the protein in a detergent (e.g., cholate) and removal of the detergent by dialysis after addition of a phospholipid (e.g., phosphatidylcholine) leads to the formation of lipid vesicles formed from monolayers and containing the protein incorporated into the membrane (Fig. 23). Whereas the Na^+,K^+-ATPase is always present in the cell membrane with its ATP binding site oriented toward the cytoplasm, it exhibits both orientations in reconstituted vesicles. Addition of ATP to the external medium leads only to activa-

tion of those ATPase molecules whose ATP binding site faces toward the outside (Fig. 23).

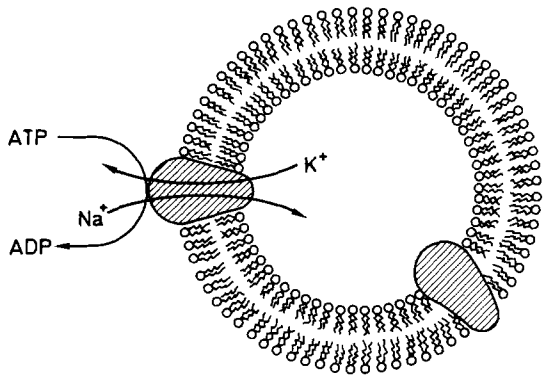


Fig. 23. Reconstitution of the Na^+, K^+ pump in artificial lipid vesicles [246]. Protein-containing vesicles form spontaneously when the detergent is removed by dialysis from a mixture of protein, lipid, and detergent in water. The outer diameter of the lipid vesicle is approximately 90 nm. After addition of ATP to the external medium, only those ATPase molecules are activated that are orientated with their ATP binding site toward the outside.

Reconstituted systems open up the possibility of varying the composition of both aqueous phases as well as the lipid composition of the membrane. In this way, many experiments can be carried out that would be difficult or impossible to perform with whole cells. In particular, the ATP-driven Na^+ and K^+ fluxes may be measured over a wide range of concentrations of ATP, adenosine diphosphate (ADP), P_i, K^+, and Na^+. For the measurement of Na^+ and K^+ fluxes radioactive ions may be used. The time resolution of such isotope experiments, however, is only of the order of seconds since it is limited by the time required to remove the samples. Better time resolution can be achieved using a recently developed optical method.[246] This method consists in monitoring the K^+ concentration inside the vesicle via the Nernst potential. Addition of valinomycin makes the vesicle membrane selectively permeable for K^+; an electrical potential is thus formed across the membrane (the Nernst potential U) which is dependent on the ratio of the K^+ concentration outside to that inside the membrane, c_K^o/c_K^i.

$$U = \frac{RT}{F} \ln \frac{c_K^o}{c_K^i} \tag{5}$$

R is the gas constant, T the absolute temperature, and F Faraday's constant). Since it is impossible to introduce an electrode into a vesicle having a diameter of 100 nm, the potential U has to be measured indirectly. This is achieved by introducing into the vesicle membrane a fluorescent dye whose absorption and emission properties depend on the transmembrane electrical field.[247] After calibration using a known concentration ratio c_K^o/c_K^i, the membrane potential can be determined from the measured fluorescence intensity. In the experiment illustrated in Figure 24, ATP was added to the external medium at time $t=0$. From the time dependence of the membrane potential U, the time course of the K^+ concentration inside the vesicle can be obtained and thus the ATP-driven K^+ flux can be determined for a given c_K^o using Equation (5).[246]

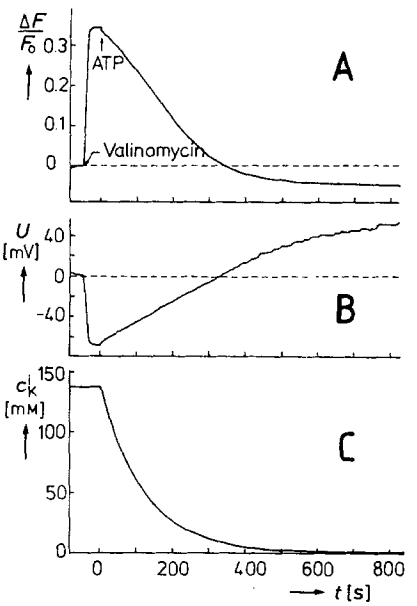


Fig. 24. Optical measurement of ATP-driven transport of K^+ in artificial lipid vesicles [246]. Each vesicle contains on the average three to five ATPase molecules, which are oriented with their ATP binding site facing outward. The initial concentrations inside and outside were: $C_{Na}^i = 10$ mM, $C_K^i = 140$ mM, $C_{Na}^o = 140$ mM, $C_K^o = 10$ mM. At time $t=0$, 250 μM ATP was added to the outside. A: Relative fluorescence change $\Delta F/F_0$ of the dye (1,3,3,1',3',3'-hexamethylindodicarbocyanine); B: Membrane potential U; C: internal K^+-ion concentration c_K^i. T = 16 °C.

8. Theoretical Concepts for the Description of Ion Transport through Channels

For the microscopic description of ion transport through channels, it is useful to introduce the potential profile of an ion along its transport pathway, which consists of a series of potential minima and maxima. Potential minima are located at positions where the ion is surrounded in an energetically favorable manner by ligand atoms. The movement of an ion through the channel may thus be described as a series of thermally excited jumps across energy barriers.[173-175,248] According to the theory of absolute reaction rates,[248] the rate constant k' for jumps across an energy barrier of height E is approximately given by the following relationship:

$$k' = \nu \cdot \exp(-E/kT) \tag{6}$$

where $\nu \simeq 10^{12}$–$10^{13}\ s^{-1}$ is the oscillation frequency of the ion in the potential minimum and k the Boltzmann constant. From the rate constants for the jumps across the individual barriers it is possible to calculate the total rate of transport through the channel.[173]

8.1. Channels with Multiple Conformations. Relationship between Carrier and Channel Mechanisms

The traditional application of reaction-rate theory is based on the (implicit) assumption that the potential profile of a channel is fixed, i.e., independent of both time and the movement of ions inside the channel. This corresponds to a purely static view of channel structure. Recent investi-

gations, however, have shown that proteins can adopt a variety of different conformations and that at physiological temperatures they can rapidly undergo transitions between different states.[249,250] Evidence for the dynamic nature of protein structure comes from X-ray diffraction and Mössbauer studies,[251,252] fluorescence depolarization experiments,[253] and nuclear magnetic resonance measurements.[254] These and other studies have shown that the time scale for the internal motions of proteins covers an extremely wide range, from picoseconds to seconds.

Of special interest is the coupling between conformational transitions of a channel protein and ion movements inside the channel.[255–258] Such coupling may arise, for example, from the electrostatic interactions between the ion and the ligand system. Binding of an ion to a binding site may result in a reorientation of the neighboring ligand dipoles due to the strong coulomb field of the ion. Coupling between conformational changes and movement of ions will occur when the time required for the conformational change is similar to or greater than the mean residence time of the ion at the binding site. In this case, the channel conductivity explicitly depends on the rate constants for the conformational transitions.[256–258]

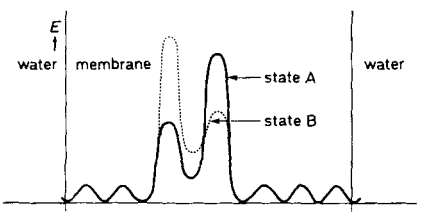


Fig. 25. Potential profile of an ion inside a channel that fluctuates between two states A and B. The channel contains a single (main) binding site which is separated from the aqueous phases by rate-limiting barriers. Further, low-energy barriers (not rate limiting) are located near the channel openings.

The example illustrated in Figure 25 depicts a channel with a single binding site which is separated from the aqueous phases by two rate-determining barriers. The conformation of the channel protein fluctuates between two states A and B having different potential profiles. State A may be the preferred state of the channel when the binding site is unoccupied and state B the preferred polarized state when the binding site is occupied. The dependence of the average conductivity Λ on the ion concentration c is given by the following equation:[256]

$$\Lambda(c) = \frac{z^2 e_0^2}{kT} \cdot \frac{\alpha c + \beta c^2}{\gamma + \delta c + \varepsilon c^2} \tag{7}$$

z is the valency of the ion, e_0 the elementary charge and α, β, γ, δ, and ε concentration independent combinations of the rate constants for transitions between the different states of the channel. Thus, the channel conductivity is a nonlinear function of the ion concentration c containing terms proportional to c^2. For a channel with only one binding site and a fixed potential profile, theory predicts a simple saturation behavior:[173]

$$\Lambda(c) = \frac{z^2 e_0^2}{kT} \cdot \frac{pc}{q + rc} \tag{8}$$

p, q, and r are concentration-independent constants. Deviations in channel behavior from that described by Equation (8) are commonly interpreted by the assumption of ion-ion interactions inside the channel or by the introduction of regulatory ion binding sites. For the case discussed here of a channel with conformational fluctuations, the appearance of the quadratic terms in Equation (7) results from coupling between ion transport and conformational transitions.

A particularly strong coupling occurs if in one conformational state the barrier on the right-hand side is very high (binding site accessible only from the left-hand side) and in the other conformational state the barrier on the left-hand side (Fig. 26). In this case, the channel conductivity is extremely small for either state; however, ion transport is possible by a cyclic sequence of ion jumps and conformational changes, which lead to an alternating exposure of the binding site to the right- and left-hand side.[257,259–261] In this case the channel approaches the kinetic behavior of a carrier. This means that carrier and channel mechanisms cannot be strictly distinguished. Carrier-like behavior and the behavior of channels with a fixed structure should be regarded as limiting cases of a more general transport mechanism represented by a channel with multiple conformational states.

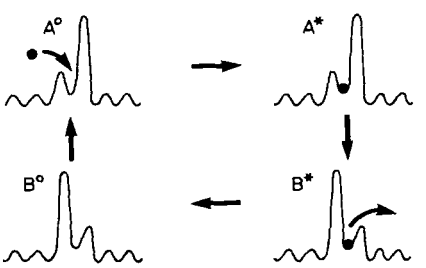


Fig. 26. Carrier-like behavior of an ion channel. In conformation A, the barrier towards the right is high (binding site mainly accessible from the left side), while in conformation B the left-hand barrier is high. During the cycle $A^\circ \rightarrow A^* \rightarrow B^* \rightarrow B^\circ \rightarrow A^\circ$, an ion is transported from the left to the right.

8.2. Energy-Driven Cyclic Conformational Transitions: Ion Pumps

The concept of a channel exhibiting multiple conformational states can also be applied to the description of active ion transport. An ion channel acts as a pump if the potential profile is transiently modified in an appropriate way by an energy-supplying reaction.[259–263] Absorption of a photon or phosphorylation of the channel protein can change the affinity of an ion binding site and simultaneously alter the height of the neighboring energy barriers. In this way an ion can leave the binding site preferentially in one direction; after the protein has returned to the initial state, another ion may enter the binding site from the opposite direction.

Figure 27 illustrates the simplest model of an ATP-driven proton pump. (H^+-transporting ATPases have been found, for example, in plant cell membranes.[264,265]) In the dephosphorylated state (HC) of the pump, the binding site, which is accessible from the left-hand (cytoplasmic) side, is occupied by a proton. Phosphorylation of the protein

leads to the state HE in which the energy barriers are altered in such a way that the proton is released preferentially to the right-hand (extracellular) side. After dissociation of H^+, the protein is dephosphorylated and adopts conformation C, which exhibits a low barrier on the cytoplasmic side. The ground state HC is reached again after binding of H^+ from the cytoplasmic side. During the cycle HC→HE→E→C→HC, a proton is transported from the cytoplasm to the extracellular medium.

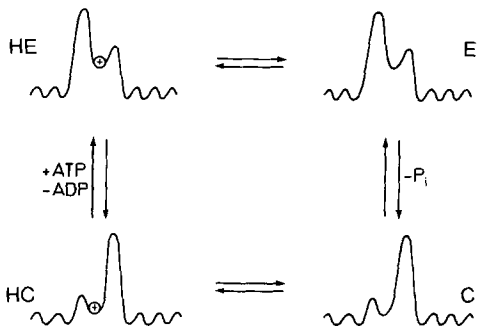


Fig. 27. Minimal model for a proton pump driven by ATP hydrolysis. In the dephosphorylated state (HC/C) of the pump, the proton-binding site is accessible from the left (cytoplasmic) side; in the phosphorylated state (HE/E), from the right (extracellular) side. During the cycle HC→HE→E→C→HC, a proton is transported from the cytoplasm to the extracellular medium (for abbreviations see text).

The ATP-driven ion pump thus represents a thermodynamic "machine" which uses the free energy of the reaction ATP→ADP+P_i to build up a concentration gradient (and/or a potential gradient). For maximum efficiency of energy conversion, two conditions have to be fulfilled. First, the energy barriers on both sides of the binding site have to be very different so that the ion cannot leave the binding site in the "wrong" direction, and, second, a spontaneous dephosphorylation (cleavage of P_i from the phosphorylated protein) is only permitted in the deprotonated state E and not in the protonated state HE. If these conditions are met, the free energy ΔG of ATP hydrolysis can be completely converted into osmotic or electrical energy. Since proton transport is associated with charge transport, the maximum possible concentration ratio $[H^+]_e/[H^+]_c$ is dependent on the membrane potential $U=\psi_c-\psi_e$ (the subscripts c and e refer to the cytoplasmic and the extracellular side, respectively; ψ is the electrical potential). For a proton pump with a stoichiometric ratio of 1 H^+ : 1 ATP, the maximum possible concentration ratio is given by the following equation:

$$\frac{[H^+]_e}{[H^+]_c} = \exp\left(\frac{UF-\Delta G}{RT}\right) \qquad (9)$$

For $\Delta G \simeq -50$ kJ/mol and $U=-0.1$ V, $[H^+]_e/[H^+]_c = 1\times10^7$ is obtained. In practice, the observed values for $[H^+]_e/[H^+]_c$ are considerably lower than this thermodynamic maximum; this results from the existence of parallel passive transport pathways for H^+ through the membrane as well as incomplete coupling between ATP hydrolysis and proton transport.

9. Summary and Outlook

The basic structure of biological membranes consists of a bilayer of oriented lipid molecules, which is almost impermeable to ions. Ion transport across the membrane depends on the presence of specialized transport molecules that are integrated into the lipid layer. Two limiting cases for such transport mechanisms can be distinguished: ion carriers and ion channels. An ion carrier is a transport molecule with an ion binding site that is accessible (due to a conformational change or a movement of the carrier relative to the membrane) from one side or the other in an alternating fashion, but not from both sides simultaneously. An ion channel, on the other hand, is a transmembrane pathway that is simultaneously open at both ends. Ion transport across the channel can be linked to a conformational change of the channel protein; in this way an ion channel may approach the kinetic properties of a carrier. Since the membrane is only about 5 nm thick, the electrical field inside the membrane is extremely large (of the order of 10^7 V/m) at physiological membrane potentials (≈ 0.1 V). In nerve excitation, the permeability of ion channels is modulated by field-induced conformational changes.

Carriers and channels are passive transport pathways; net ion transport occurs only if the electrochemical potential of the ion is different on both sides of the membrane. Active transport systems, on the other hand, have the ability to transport ions against a thermodynamic potential difference at the expense of energy. In the case of primary active transport systems (ion pumps), the energy is supplied by the hydrolysis of ATP or the absorption of light. The mechanism of active transport systems such as the Na^+, K^+ pump is only partly understood at present; a number of experiments indicate that the transport protein undergoes an energy-driven cycle of conformational changes during which an ion is bound in a first step from one side and is released in a later step to the other side.

In the investigation of biological transport systems, artificial lipid membranes have been widely used. Planar lipid bilayers with areas of 10 μm^2 to 10 mm^2 can be formed from chemically homogeneous lipids in aqueous medium. After incorporation of a biological ion transport system into the artificial membrane, the electrical properties of the transport system can be studied under defined conditions. A number of small to medium-sized transport molecules that act as ion carriers or ion channels have been studied in detail. For the K^+-specific carrier valinomycin, transport rates of 10^4–10^5 s^{-1} per single molecule have been found from electrical relaxation experiments. The rate of the individual transport steps depends strongly on the structure of the membrane lipid.

Substantially higher transport rates (10^7–10^8 s^{-1}) are observed for ion channels. A model compound for the study of the mechanism of ion transport through channels is gramicidin A, a hydrophobic pentadecapeptide isolated from *Bacillus subtilis*. Gramicidin A forms helical channels in lipid membranes, which are generated by a head-to-head association of two monomers. Along the helix axis a "tunnel" of 0.4 nm diameter is present which is lined by carbonyl oxygen atoms. The gramicidin channel is permea-

ble to small monovalent cations (alkali metal ions, NH_4^+, H_3O^+). Because of the high rates of ion transport, it is possible to detect the formation and decay of single gramicidin channels by sensitive current measurements. Investigations on gramicidin channels open up the possibility of studying the relationship between chemical structure and transport properties of an ion channel. Gramicidin analogues with modified amino acid sequences show changes in both transport rates and ion specificity. Introduction of charged residues at the channel openings permit the formation of ion channels with rectifying properties.

Methods are now available for the incorporation of large membrane proteins such as ion channels from nerve membranes or ion pumps into artificial lipid membranes. This permits the use of a variety of methods which previously have been applied to small transport molecules. Interesting prospects result from the possibility of incorporating membrane proteins obtained by cell-free protein synthesis directly into an artificial lipid membrane. Gene technology allows the synthesis of transport proteins with specific amino acid substitutions at particular positions in the sequence. The functional characterization of such modified transport proteins is likely to make substantial contributions to the understanding of ion transport mechanisms.

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Phosphorus, Arsenic, Antimony, and Bismuth Multiply Bonded Systems with Low Coordination Number— Their Role as Complex Ligands

By Otto J. Scherer*

Dedicated to Professor Max Schmidt on the occasion of his 60th birthday

Multiply bonded systems with low coordination number (one to three) involving phosphorus and its homologues, whether isolable or generated *in situ* at a metal complex, are versatile ligands that can function as two-, four-, six- or eight-electron donors to transition metal fragments and that may be coordinated in η^1 (terminal), η^2 (side-on), edge- or face-bridging modes. The (p-p)π bonding system of the ligand is thereby rendered capable of addition and intra- or intermolecular cycloaddition reactions. Some of the polycyclic species thus generated represent novel, polydentate ligands.

1. Introduction

The textbook theories explaining the nonexistence of certain groups of compounds[1] (noble gas compounds, N_2-complexes, isolable compounds with multiple bonds between 2p-elements and those lower in the periodic table or between the latter only) disappeared gradually in the early 1960's as these compounds began to be discovered. It is obvious from the new (fourth) edition of the standard text of *Cotton* and *Wilkinson*[2] that the necessary changes of attitude are not easy; nitrogen is ascribed very strong (p-p)π bonds, phosphorus unstable (p-p)π bonds. However, the following multiply bonded systems (Scheme 1) with low coordination number, all stable at room temperature, have been known for many years (phosphorus compounds are presented as representative of these compounds).

:P≡	R–C≡P	trivalent phosphorus, coordination number 1 (σ^1, λ^3–P)
	A	R = CMe_3, adamantyl, $SiMe_3$ etc.
=P:	X=P–R	trivalent phosphorus, coordination number 2 (σ^2, λ^3–P)
	B	X = R'_2C, C=O, C=NR' etc., R'E (E = N, P, As, Sb)
–P=	R–P(=X)–Y	pentavalent phosphorus, coordination number 3 (σ^3, λ^5–P)
	C	X = R'_2C, O, S, Se, R'N etc. Y = R'_2C, S, R'N etc.

Scheme 1. Low-coordination number multiply bonded systems of phosphorus.

The preferred substituents R and R' are often the sterically demanding groups *tert*-butyl, trimethylsilyl, mesityl, tris(*tert*-butyl)phenyl, adamantyl, bis(trimethylsilyl)amino, *tert*-butyl(trimethylsilyl)amino, and bis- or tris(trimethylsilyl)methyl. In contrast to classes **A** and **C**, **B** is represented also by acyclic or cyclic compounds in which the P-atom is replaced by its homologues. There are few current research topics to which so many and so varied review articles[3] have been dedicated in so short a time, but these have been concerned predominantly with the synthesis, reactivity, and structure of such compounds; the associated ligand behavior, intensively studied for about five years, has been poorly covered. It is the purpose of this review to present the chemistry of ligands of the types **A** to **C** and also of derivatives that can only be generated and stabilized at a metal center.

2. Multiply Bonded Systems with Ligand Coordination Number One

2.1. Terminal and Bridging Coordination of PN and E_2 (E = P, As, Sb, Bi)

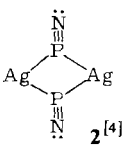
These ligands, characterized in the gas phase or in an inert matrix, can be stabilized in a complex in various ways.

2.1.1. 2e-Donor Ligands

$$P_3N_5 \xrightarrow{\Delta} :P{\equiv}N: \xrightarrow[10\ K,\ krypton]{Cu,\ Ag,\ Au\ atoms}$$

:N≡P: →M← :P≡N:

1, M = Cu, Au[4]



2[4]

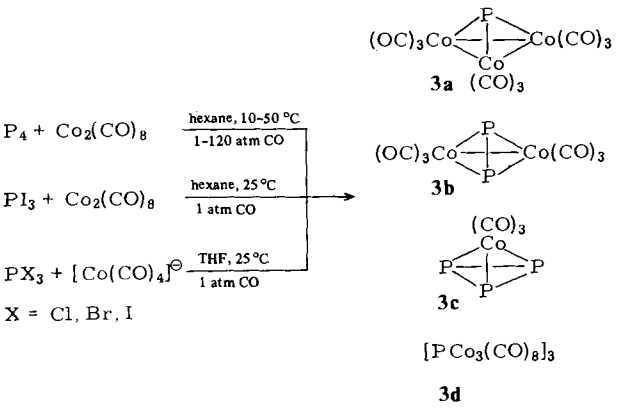
IR-spectroscopic measurements formed the basis for the suggested structures: **1** with terminal, **2** with μ-P coordination.[4]

2.1.2. 4e-Donor Ligands

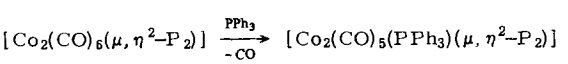
These most intensively studied μ,η^2-coordination types of the P_2 or As_2 molecule can be synthesized by a wide range of reactions.

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The first metal-phosphorus tetrahedranes **3a–d** were synthesized using $Co_2(CO)_8$ or $[Co(CO)_4]^{\ominus}$ and P_4 or PX_3 (X = Cl, Br, I) as the source of $(OC)_3Co$ and P_x respectively[5a,b] (THF = tetrahydrofuran).

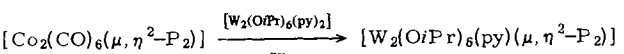


The Co_2P_2 tetrahedrane structure was demonstrated by an X-ray structure analysis (Table 1) of **3e**,[5c] the Ph_3P substitution product of **3b**.



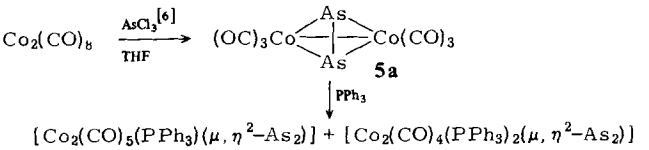
3b **3e**[5a,c]

The reaction of **3b** with $W_2(OiPr)_6(py)_2$ allows the transfer of the P_2 unit to tungsten at room temperature with the elimination of pyridine.[5d]



3b **4**[5d]

The pioneering experiment that stabilized an N_2 homologue at a metal complex goes back to 1969. **5a** was synthesized from $Co_2(CO)_8$ and $AsCl_3$ (excess) and characterized by X-ray methods as the Ph_3P derivatives **5b** and **5c**[6] (Table 1).



5b[6] **5c**[6b]

The transformation of $[(CO)_4Fe]_3(P_4)$ to the polymeric P_2-complex $[(CO)_3Fe(P_2)]_n$ can be brought about thermally or photochemically.[7]

A further 15e metal-ligand fragment suitable for constructing M_2E_2 clusters is $Cp(CO)_2M$ (M = Mo, W). The As_2-compounds **6a, b** are formed by the co-thermolysis of $(AsC_6H_5)_6$ and $[Cp(CO)_3Mo]_2$(*Mo–Mo*) or $CpW(CO)_3H$,[8a] or by the reaction of a trinuclear μ_3-As metal complex with

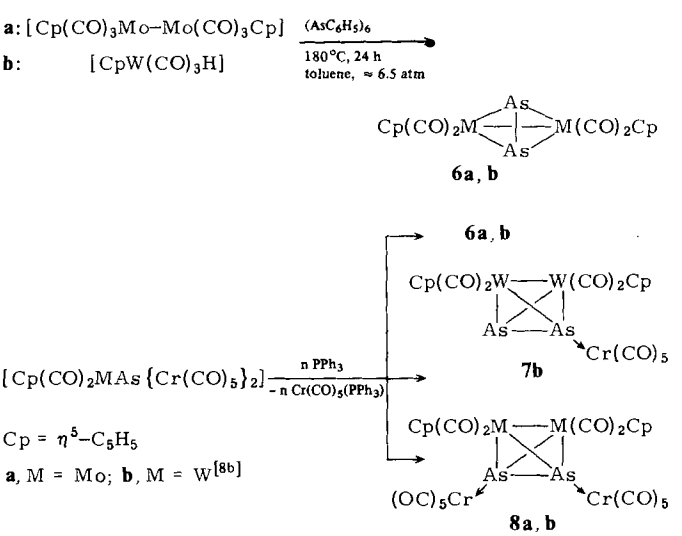


Table 1. $^{31}P\{^1H\}$-NMR data (δ values, J in Hz), metal-metal and E-E bond lengths [Å] in complexes with an M_xE_y framework. Cp = η^5-C_5H_5, Cp* = η^5-C_5Me_5. Gas-phase bond length of P_2 for comparison: 1.875 Å (D. E. C. Corbridge, *The Structural Chemistry of Phosphorus*, Elsevier, New York 1974).

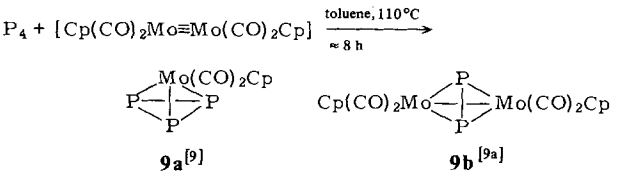
Compound		$^{31}P\{^1H\}$	M–M	E–E	Ref.
3e	$[Co_2(CO)_5(PPh_3)P_2]$		2.574(3)	2.019(9)	[5c]
4	$[W_2(OiPr)_6(py)P_2]$		2.695(1)	2.154(4)	[5d]
9b	$[Cp_2Mo_2(CO)_4P_2]$	− 42.9 (s)	3.022(1)	2.079(2)	[9a]
11a	$[\{(Et_2PCH_2CH_2PEt_2)Ni\}_2P_2]$ [a]	133.0 (q), ^2J(PP) 33.0	2.908(3)	2.121(6)	[11]
17a	$[Co_2(CO)_6P_2\{Cr(CO)_5\}_2]$	146.0 (s)	2.565(3)	2.060(5)	[16]
15	$[Cp_2Mo_2(CO)_4P_2\{Re_2(CO)_6(\mu\text{-}Br)_2\}]$	− 78.5 (s)	3.077(2)	2.093(8)	[15a]
16	$[\{Cp_2Mo_2(CO)_4P_2\}_2\{Re_2(CO)_6Br_2\}]$		3.034(2)	2.071(9)	[15a]
22	$[(Cp^*Mo)_2P_6]$	−315.6 (s)	2.647(1)	2.167(3)–2.175(3)	[18]
24	$[Cp^*Mo(CO)P_2\{Cr(CO)_5\}]_2$	[b]	2.905(1)	2.063(5), 2.071(5)	[19]
5b	$[Co_2(CO)_5(PPh_3)As_2]$		2.594(3)	2.273(3)	[6]
5c	$[Co_2(CO)_4(PPh_3)_2As_2]$		2.576(3)	2.281(3)	[6b]
6a	$[Cp_2Mo_2(CO)_4As_2]$ [a]		3.039(2)	2.311(3)	[8a, b]
6b	$[Cp_2W_2(CO)_4As_2]$ [a]		3.026(2)	2.326(5)	[8a]
10	$[Cp^*_2Mn_2(CO)_4As_2]$		4.02	2.225(1)	[10]
20	$[\{CpMn(CO)_2\}_4As_2]$			2.445(4)	[8b]
13a	$[W_2(CO)_7I(\mu\text{-}I)As_2]$		3.069(7)	2.305(10)	[8b]
12a	$[\{W(CO)_5\}_3As_2]$			2.279(4)	[12a]
8a	$[Cp_2Mo_2(CO)_4As_2\{Cr(CO)_5\}_2]$		3.064(3)	2.310(3)	[8b]
19a	$[Co_2(CO)_4\{P(OCH_3)_3\}_2As_2\{W(CO)_5\}_2]$		2.59(2)	2.28(1)	[17]
25	$[(CpMo)_2As_5]$			2.389(2)–2.762(3)	[20a]
12b	$[\{W(CO)_5\}_3Sb_2]$			2.663(3)	[12b]
12c	$[\{W(CO)_5\}_3Bi_2]$			2.818(3)	[12c]
13b	$[\{\mu\text{-}BiCH_3W(CO)_5\}W_2(CO)_8Bi_2]$		3.142(3)	2.795(3)	[14]

[a] Two independent molecules in the asymmetric unit. [b] AA'XX' spin system.

triphenylphosphane; the latter reaction also permits the isolation of **7** and **8**, products showing further complexing of the As_2 ligand.[8b]

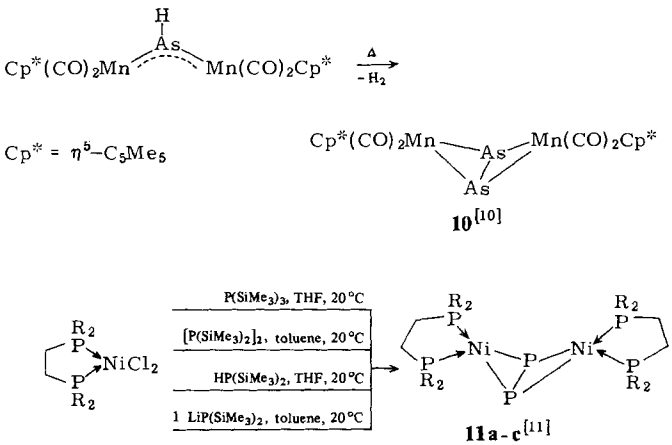
The C_5Me_5 analogue of **6a** is formed by the reaction of $[(C_5Me_5)(CO)_2Mo]_2(Mo{\equiv}Mo)$ with As_4S_4.[8c]

White phosphorus and $[Cp(CO)_2Mo]_2(Mo{\equiv}Mo)$ are suitable reactants for the preparation of molybdenum-phosphorus tetrahedranes **9**.[9a]



9a[9] **9b**[9a]

The butterfly form of the M_2E_2 framework is obtained by employing a 16e- or 14e-fragment M as partner for the As_2 or P_2 ligand, as for **10**[10] and **11**.[11]



10[10] **11a-c**[11]

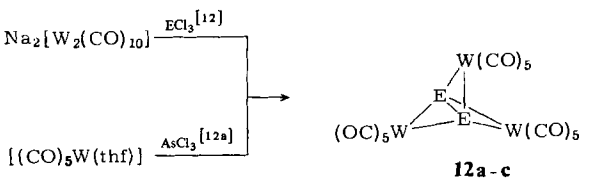
a, R = C_2H_5; **b**, R = C_6H_5; **c**, R = *c*-C_6H_{11}

The X-ray structure analysis (for E-E and M-M bond lengths see Table 1) confirms the butterfly structure for **10** and **11** and the tetrahedrane structure for **3e**,[5a,c] **4**,[5d] **5b**, **c**,[6] **6a**, **b**,[8a,b] and **9b**.[9a]

2.1.3. 6e-Donor Ligands

The most interesting variant of this coordination mode was realized in the chemically and aesthetically striking, star-shaped molecules **12**;[12] the E≡E unit is side-on bonded.

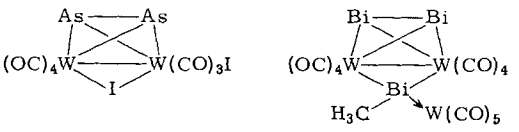
EHT calculations[12a] (cf. the investigations of π-bonded N_2 complexes[13]) on $(L_5W)_3As_2$ model compounds show that a strong π-acceptor interaction of the As_2 molecule



12a-c

a, E = As[12a]; **b**, E = Sb[12b]; **c**, E = Bi[12c]

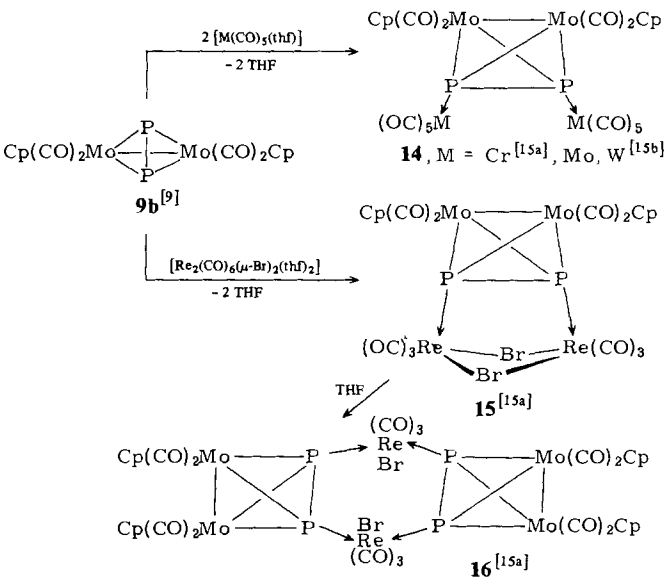
with the ligand fragments of the metal is of importance. In **12** all six bonding electrons of the axial E_2 ligand take part in the coordinative bonding. The E-E bond lengths point to a bond order greater than 1 (Table 1).[12] Reaction of iodine with **12** (E = As)[8b] leads to formation of the E_2M_2 cluster **13a** with an additional bridging iodide; similarly, the bismuth-bridged **13b** and **12** (E = Bi) are formed from $(Me_3Si)_2CHBiCl_2$ and $Na_2[W(CO)_5]$.[14]



13a[8b] **13b**[14]

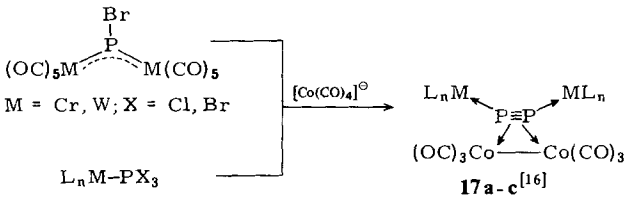
2.1.4. 8e-Donor Ligands

The non-bonding electrons of certain P_2M_2 complexes can be utilized for further terminal (complexes **14**,[15] **17**[16]) or bridging (complexes **15**, **16**[15a]) coordination to transition metal fragments.



9b[9] **14**, M = Cr[15a], Mo, W[15b] **15**[15a] **16**[15a]

The molybdenum clusters **14**–**16**[15] are obtainable directly from the Mo_2P_2 precursor **9b**;[9a] the cobalt clusters **17** are generated in the coordination sphere of the metals.[16]

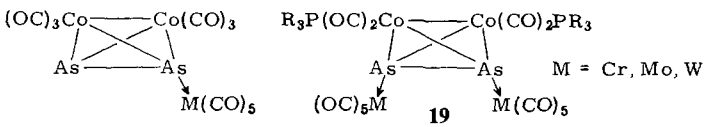


17a-c[16]

17a, L_nM = $Cr(CO)_5$; **17b**, L_nM = $W(CO)_5$; **17c**, L_nM = $CpMn(CO)_2$

The less pronounced donor properties of the $Co_2(CO)_6As_2$ unit are illustrated by the complexes **17** and **18** (cf. **7b** and **8a**, which are also directly obtainable from **6b** or **6a** and $Cr(CO)_5(thf)$[8b]). In contrast to **17**,[16] **18**[17]

shows only the very unstable mono-coordination (6e-donor ligand, as for **7b**) of the As_2 unit. Appreciably more stable complexes **19**[17] are formed if the basicity of the As_2Co_2 tetrahedrane is increased by the introduction of R_3P ligands.

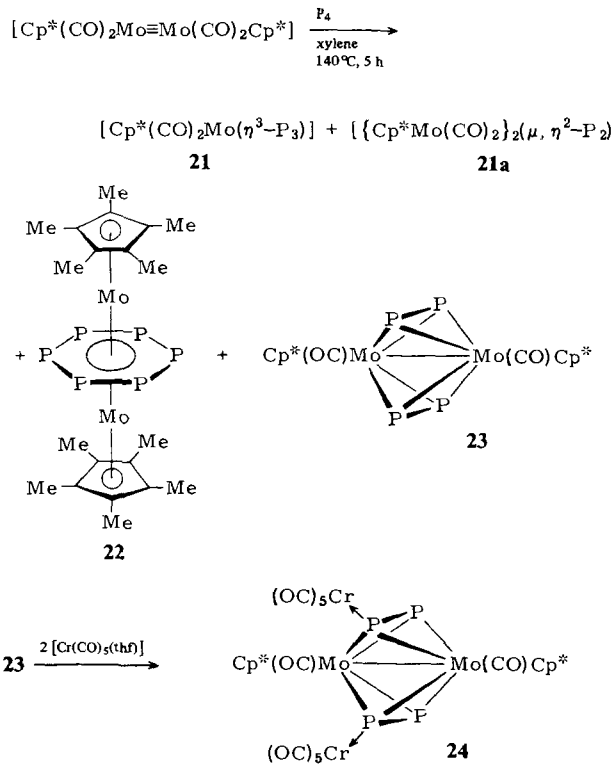


[{Cp(CO)$_2$Mn}$_4$As$_2$] **20**

The As–As single bond length of 2.445 Å and the planar environment of the As atoms in **20**[8b,10] suggest the presence of a diarsinidene (Äs–Äs) 8e-donor ligand.

2.1.5. Complexes with More Than One E_2 Unit

If the η^5-C_5H_5 ligand in $[CpMo(CO)_2]_2$(*Mo≡Mo*) is replaced by η^5-C_5Me_5, the reaction with P_4 not only leads to formation of **21**, **21a**, and the triple-decker sandwich complex **22** but also **23**,[18] which in turn reacts with $Cr(CO)_5$(thf) to give **24**, a complex with two 6e-donor μ,η^2-P_2 units.[19]



The X-ray structure analysis shows **22** to be a centrosymmetric molecule (Fig. 1), in which all the rings are planar and parallel. The average P–P distance is 2.170 Å. In the ^{1}H-NMR spectrum (^{31}P, Table 1) the CH_3 signal is shifted to high field ($\delta = 0.47$, septet, $^4J(PH) = 0.45$ Hz; cf. the usual range $\delta \approx 2$ for C_5Me_5); this is caused by the anisotropic cone of the P_6 ring (ring current effect). **23** can be converted into **22** with P_4;[19] it probably occupies a key position in the formation of the hexaphosphabenzene ligand P_6, which may be formally regarded as being composed of three P_2 units (cf. the isoelectronic pair P_2/C_2H_2 and the benzene synthesis of *Reppe*). X-ray studies have shown that the bond lengths and angles of the M_2E_2 unit are not significantly altered on further complexing (Table 1). If we use Figures 2 and 3 as models for **23**, then it can be seen from the P2···P4 and P1···P3 distances[19] and the orientation of the $Cp^*_{center}MoMoCp^*_{center}$ moiety [Cp^*_{center}

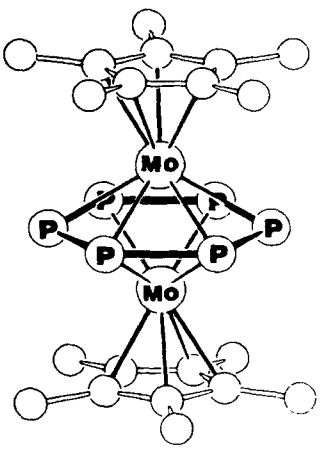


Fig. 1. Molecular structure of **22** in the crystal [18].

MoMo 160.8 and 161.1°, dihedral angle 1.3°] that a similar trapezoid arrangement of the P_4 unit in **23** could lead to formation of the P_6 "middle deck" of **22** by introduction of a further P_2 unit with CO elimination.

The thermolysis of $[CpMo(CO)_3]_2$(*Mo–Mo*) and $(CH_3As)_5$ forms (amongst other products) **25**, in which the great differences in As–As bond lengths (Table 1) suggest

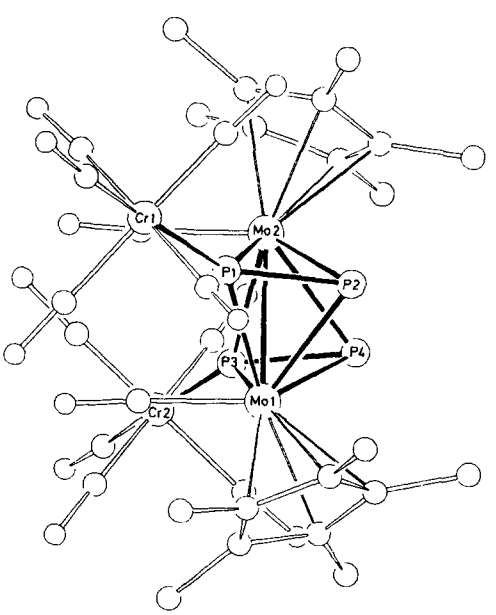


Fig. 2. Molecular structure of **24** in the crystal [19].

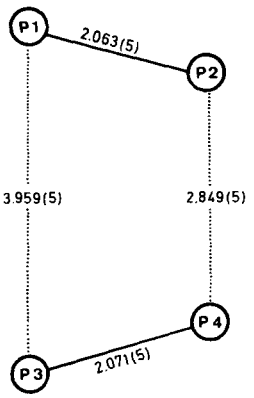
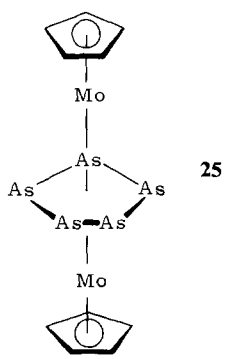


Fig. 3. The planar $(P_2)_2$ unit of **24** with PP distances [Å].

the formulation of the ring as μ,η^2-As_3 and μ,η^2-As_2 ligand fragments[20a] (cf. the μ,η^3-As_3, coordination type in [(triphos)Co(As_3)Co(triphos)]$(BPh_4)_2$,[20b] triphos = $MeC(CH_2PPh_2)_3$).

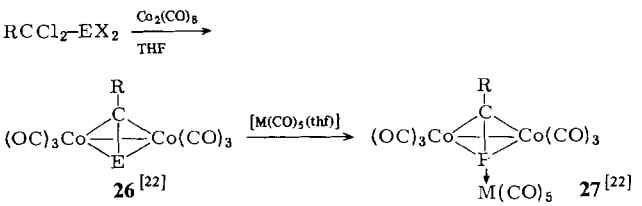


25

$^{31}P\{^1H\}$-NMR data for complexes of the form $M_2P_2[M'(CO)_5]_2$ show a clear shift to higher field on going from M′=Cr to W (**14**, M=Mo, M′=Cr: −36.7; M′=Mo: −64.9; M′=W: −105.1;[15a,b] **17a**, M=Co, M′=Cr: 146; **17b**, M′=W: 44[16]). The transition from the 4e- to the 8e-donor E_2 ligand (e.g. **3e/17a**; **9b/15**, **16**; **5b**, **c/19a**; **6a/8a**) causes only minor changes in the E–E bond lengths. Comparison of the E_2M_2 butterfly complexes **10**[10] and **11a**[11] with the "normal" As_2- and P_2-complexes, respectively, shows a definite shortening of the E–E distance for the As derivative **10**, but a lengthening in the P derivative **11a**. The unusually long P–P distance in **4** is mirrored in the C–C distance of the isoelectronic μ,η^2-C_2H_2 complexes.[5d] The complexing of the P_2 molecule causes its bond to be lengthened by 0.14 (**3e**) to 0.28 Å (**4**) from its original value of 1.875 Å (cf. Table 1).

2.2. Bridging Phospha- and Arsa-alkynes

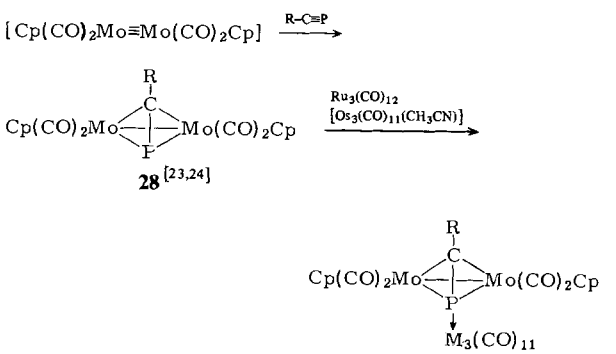
The ligand of choice is (for phosphorus) $Me_3C-C\equiv P$,[21a] which is stable at room temperature (cf. adamantyl-C≡P and other derivatives[21b]). Less sterically demanding R–C≡P ligands can also be generated in the coordination sphere of the transition metal; for R–C≡As ligands this is the only method (as in complexes of the type **26** and **27**[22]).



26[22] **27**[22]

X = Cl, Br; E = P, As; R = H(As), CH_3, C_6H_5, $SiMe_3$; M = Cr, Mo, W

2,2-Dimethylpropylidinephosphane, $Me_3C-C\equiv P$, adds to the Mo≡Mo bond like an acetylene to give complexes of the type **28**, which possess an organometallic tetrahedrane skeleton.[23,24] **28** reacts further with trinuclear carbonylmetal compounds, forming polyhedral metal clusters **29**.[25]

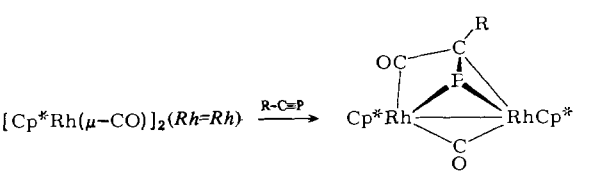


28[23,24]

29a,**b**[25]

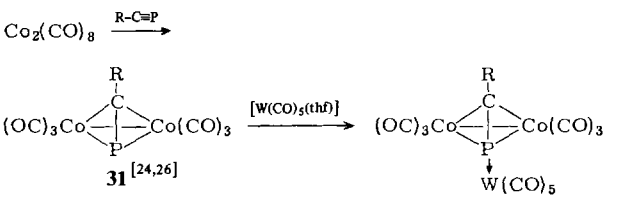
R = CMe_3; **a**, M = Ru; **b**, M = Os

The regiospecific formation of **30** is based on the addition of $Me_3C-C\equiv P$ to the Rh=Rh bond and an insertion into one of the Rh–CO bonds of the starting material.[23]



R = CMe_3 **30**[23]

The ligand properties of the Co cluster **31** (analogous to **28**) are seen in its reaction with $W(CO)_5$(thf) to give **31a** ($Me_3C-C\equiv P$ as 4e-donor ligand).[24]

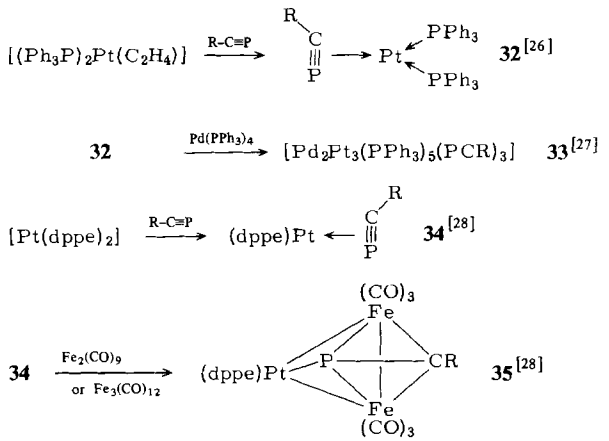


31[24,26] **31a**[24]

R = CMe_3

The reaction of $Me_3C-C\equiv P$ with $(Ph_3P)_2Pt(C_2H_4)$ or $Pt(dppe)_2$ proceeds with elimination of C_2H_4 or dppe to give the Pt complexes **32**[26] and **34**,[28] which show classi-

cal side-on coordination of the phospha-alkyne ligand (2e-donor). Both compounds are suitable for cluster-building reactions.



The framework of **33**[27] is structurally analogous to that of the star-shaped molecules **12**;[12] a Pd_2 axis (instead of E_2) is symmetrically bridged by three metal fragments (Pt). Each metal atom is also coordinated to one PPh_3 ligand. The three RCP ligands then bridge this trigonal bipyramidal Pd_2Pt_3 unit in such a way as to form a hexagonal bipyramid (*closo* cluster) with P_3Pt_3 in the equatorial plane.[27] **35** is the first example of μ_3-P-coordinated R–C≡P.[28]

An extremely high-field shift of the ^{31}P-NMR signal is observed on going from **28** to **29b** (Table 2). **32** and **34** show distinct differences in the chemical shift and the ^1J(PtP) coupling of the R–C≡P ligand (Table 2).

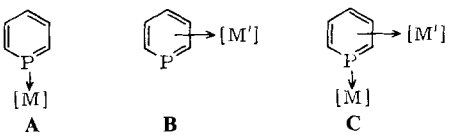
Complex **29b**[25] shows an unusually long P–C bond [1.86(1) Å; cf. 1.536(2) Å in the free ligand and the values for the other complexes (Table 2)]; this is considered to be a typical single-bond length, the other values lying in the double-bond region.

He(I)-photoelectron spectroscopic studies[29] of R–C≡P (R = CMe_3, Ph) show a greater π-n separation than the nitrile analogues; this is a quantitative indicator of reduced overlap for a $2p_\pi$-$3p_\pi$ interaction and it also suggests that side-on coordination of the R–C≡P ligand will usually be preferred. Complexes of the type R–C≡P:→M remain unknown.

3. Multiply Bonded Systems with Ligand Coordination Number Two

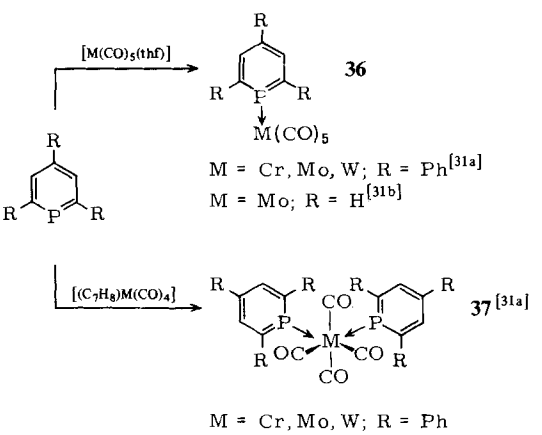
3.1. Phosphinines (λ^3-Phosphorins)

The following coordination types are known for these cyclic representatives of trivalent phosphorus:



3.1.1. 2e-Donor Ligands (σ-Complexes)

Some years after the discovery[30] of 2,4,6-triphenylphosphabenzene (2,4,6-triphenylphosphinine), its terminal P-coordination mode **A** was demonstrated.[31]



Apart from the complexes **36** (some characterized by X-ray structure determination)[31a,b] (Table 3), representatives of the elements Mn,[31g] Ni,[31h] Ag,[31e] and Au[31d] are known and have been characterized by ^{31}P{^{1}H} NMR.

The chemical behavior of the phosphinine σ-complexes has not been studied to any great extent. The complex **38** was shown spectroscopically to be an intermediate in the synthesis of λ^5-phosphinines by oxidative addition of nucleophiles to λ^3-phosphinines.[31e] The reaction of 2,4,6-triphenylphosphinine→AuCl with sodium methoxide in the presence of methanol is said to lead to an Au_3 cluster.[32]

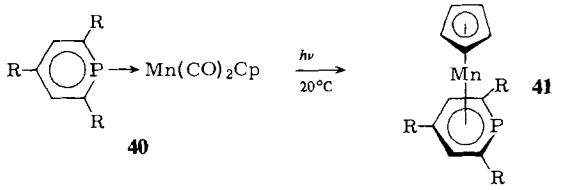
Table 2. ^{31}P{^{1}H}-NMR data (δ values, J in Hz) and M-M and P-C bond lengths [Å] in phospha-alkyne complexes. R = CMe_3. Cp = η^5-C_5H_5. PC bond length (gas phase) in Me_3C–C≡P 1.536(2) Å (H. Oberhammer, G. Becker, G. Gresser, *J. Mol. Struct.* 75 (1981) 283).

Compound		^{31}P{^{1}H}	M–M	P–C	Ref.
28	$[Cp_2Mo_2(CO)_4(PCR)]$	– 42.5 (s)	3.014(0)	1.719(3)	[23]
29b	$[Cp_2Mo_2(CO)_4(PCR)\{Os_3(CO)_{11}\}]$	–287.4 (s)	2.860(1), 2.892(1) (Os–Os)	1.86(1)	[25]
	$[Cp_2Mo_2(CO)_4(PCR)\{W(CO)_5\}]$	[a]	[a]	1.733(12)	[25]
31a	$[Co_2(CO)_6(PCR)\{W(CO)_5\}]$	[a]	[a]	1.695(6)	[24]
32	$[(Ph_3P)_2Pt(PCR)]$	56.9 (dd), ^1J(PtPCR) 62		1.672(17)	[26]
33	$[Pd_2Pt_3(PPh_3)_5(PCR)_3]$	[a]	2.679(2) (Pd–Pd)	1.62(2)	[27]
34	[(dppe)Pt(PCR)]	– 53.3, ^1J(PtP) 166			[28]
35	[(dppe)PtFe$_2$(CO)$_6$(PCR)]	–192.8 (m), ^1J(PtPCR) 128	2.518(1) (Fe–Fe), 2.669(1), 2.671(1) (Pt–Fe)	1.703(6)	[28]

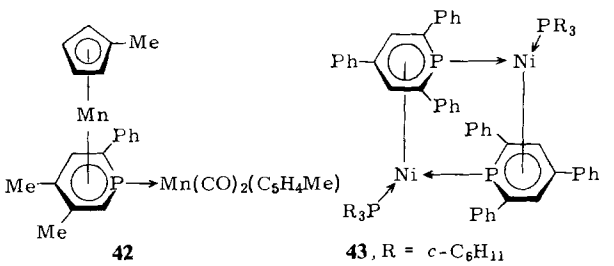
[a] Not given.

$[2,4,6\text{-}(C_6H_5)_3C_5H_2P\{Hg(OOCCF_3)_2\}]$ **38**
$[2\text{-}C_6H_5\text{-}4,5\text{-}(CH_3)_2C_5H_2P\{W(CO)_5\}]$ **39**

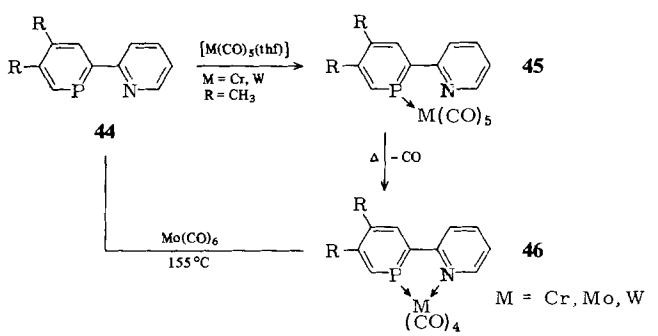
The complex **39** reacts with 2,3-dimethylbutadiene as a dienophile in the 1,6-position, but with *N*-phenylmaleimide, dimethyl acetylenedicarboxylate and cyclopentadiene in the 1,4-position.[31i]



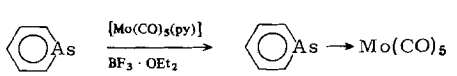
The photochemical CO elimination from the σ-phosphinine complex **40** causes a change of coordination mode from η^1 to η^6, forming a sandwich complex.[31g,39] The transition from **40** to the X-ray structurally characterized **41** (type **B**) is accompanied by a drastic high field shift of the ^{31}P-NMR signal ($\Delta\delta = 293$ ppm). Small changes in the Cp ring and the R groups of **40** lead instead to the formation of the σ,π complex **42** (type **C**), where the phosphinine acts as an 8e-donor.[31g]



A further interesting example of this coordination type is seen in **43** (a 16- or 18-electron configuration, with Ni coordinated by a double bond or a diene fragment of the phosphabenzene ligand, might also be thought feasible).[31h]

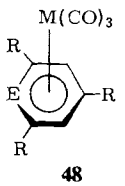


Preliminary studies of **44**, the phosphorus analogue of a 2,2'-bipyridyl derivative, promise to reveal remarkable ligand properties.[33] **47** is so far the only representative of σ-complexes of λ^3-arsinines.[34]



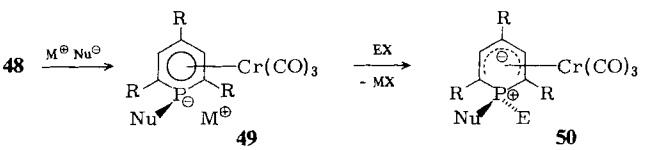
3.1.2. 6e-Donor Ligands (π-Complexes)

The use of $M(CO)_6$ or $L_3M(CO)_3$ ($L = CH_3CN$, py) as transition metal source allows the synthesis of the η^6-coordination type **48** (cf. **B**).



E	M	R	Ref.
P	Cr, Mo	Ph	[35a, b]
P	Cr	CMe_3	[35c]
As	Mo	e.g. H(2), Ph(4), H(6)	[36]
As, Sb	Mo	H	[34]

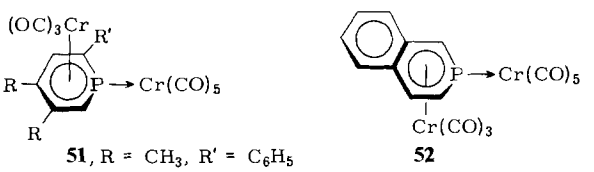
The addition of nucleophiles (Nu) such as alkyl or aryl anions or alkoxide ions to **48**, E = P, leads via the spectroscopically characterizable **49** to isolable tricarbonylchromium λ^5-phosphorus ylide complexes **50** on treatment with electrophiles (e.g. ethyl halides).[35c]



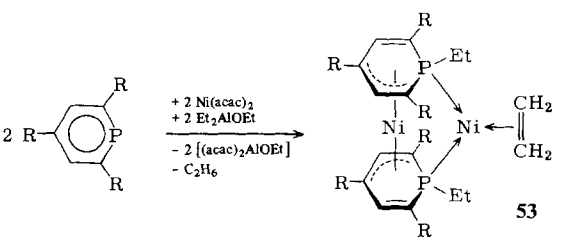
R = C_6H_5, CMe_3

3.1.3. 8e-Donor Ligands (σ,π Complexes)

Simultaneous σ- and π-coordination is possible if sterically suitable λ^3-phosphinines are allowed to react with e.g. $Cr(CO)_6$, forming **51** and **52** (see also **42**, **43** and Ref.



[31f]).[37] Phosphinines can be converted into phosphininyl ligands[38a] according to the method of *Lehmkuhl* et al.[38a]



To comply with the 18e rule at nickel in **53** (each phosphininyl ligand is both a 2e- and 3e-donor), the Ni–Ni bond (2.498(1) Å) can be ascribed double bond character (Table 3).[38a] In the iron complexes **54**, which possess structures related to **53**,[38] the double bond of the phosphininyl ligand is probably also bonded to the iron atom. **54b** is a structurally dynamic system.

$[\{(C_6H_5)_3C_5H_2PR\}_2Fe]$ **54a**, $R = CH_3$[38b]; **54b**, $R = C_2H_5$[38a]

The change from a σ- to a π-complex (**36a** → **48a**) causes an upfield shift of 193.5 ppm in the $^{31}P\{^1H\}$-NMR spectrum (Table 3). The P-C bond length (Table 3) of phosphinine(yl) complexes lies in the range 1.695–1.816 Å.

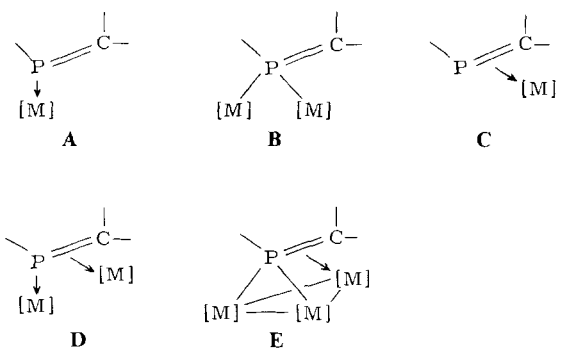
Table 3. $^{31}P\{^1H\}$-NMR data and P-C bond lengths [Å] in complexes with phosphinine ligands. Cp = η^5-C_5H_5.

Compound	$^{31}P\{^1H\}$ δ	$^{31}P\{^1H\}$ Δδ [a]	P–C	Ref.
2e-Donor ligand				
36a [2,4,6-$(C_6H_5)_3C_5H_2P$[Cr(CO)$_5$]]	+197.8 (s)	+ 19.6	1.73(1), 1.73(1)	[31a]
36b [C_5H_5[Mo(CO)$_5$]]			1.717(8), 1.695(8)	[31b]
46a [4,5-$(CH_3)_2$-2-(2-pyridyl)-C_5H_2P[Cr(CO)$_4$]]	+247.7 (s)	+ 62.8	1.707(5), 1.709(4)	[33]
5e-Donor ligand				
53 [[2,4,6-$(C_6H_5)_3C_5H_2P$(Et)]$_2$Ni$_2$(C_2H_4)] [b]	+ 0.7 (s)		1.805(3)–1.816(3)	[38a]
6e-Donor ligand				
48a [2,4,6-$(C_6H_5)_3C_5H_2P$[Cr(CO)$_5$]]	+ 4.3 (s)	−173.9	1.762(12), 1.742(12)	[35a, b]
41 [2,4,6-$(C_6H_5)_3C_5H_2P$(MnCp)]	− 50.0 (s)	−228.0		[39]

[a] Shift on coordination: + = low field, − = high field with reference to free ligand. [b] Ni–Ni: 2.498(1) Å.

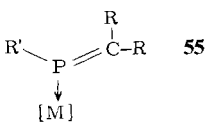
3.2. Phospha-alkenes

Of the many possible coordination types, **A**–**E** have so far been realized.



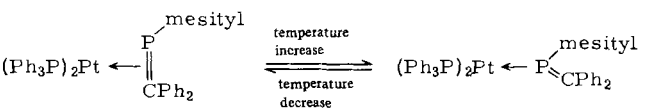
3.2.1. *Terminal P-Coordination*

This preferred coordination mode (type **A**, 2e-donor ligand) allows in **55** a great variety of R, R′ groups and of metal fragments [M] (see also Table 4).[40]



To prepare the complexes **55**, readily available transition metal compounds can be used, for example $M(CO)_6$, [$M(CO)_5$(thf)], M = Cr, Mo, W, R = C_6H_5, R′ = mesityl,[40a, b] R, R′ = diazaphosphole derivative[40c, d] (M = Cr, Mo); $CpMn(CO)_3$, $Fe(CO)_5$, $Fe_2(CO)_9$, R, R′ = diazaphosphole derivative[40c] (M = Mn, Fe); R = $SiMe_3$, R′ = $(Me_3C)_3C_6H_2$[40e] (M = Fe); R = $SiMe_3$, C_6H_5, R′ = $(Me_3C)_3C_6H_2$[40f] (M = Fe); R = $SiMe_3$, R′ = $N(SiMe_3)_2$[40g] (M = Fe); R = H, R′ = $(Me_3C)_3C_6H_2$[48b] (M = Fe); $RhCl(PPh_3)_3$;[40b] $Ni(CO)_4$, R = C_6H_5, R′ = mesityl;[40h] R = H, R′ = $(Me_3C)_3C_6H_2$[48b] (M = Ni); PtL_x (L = R_3P, x = 3, 4), $PtL_2(C_2H_4)$, $Pt(cod)_2$, $Pt_2Cl_4(PR_3)_2$, R, R′ = diazaphosphole derivative;[40i] R = C_6H_5, R′ = mesityl;[40j, 41] ClAu(CO), $[Me_2AuCl]_2$, R, R′ = diazaphosphole derivative[40k] (cod = 1,5-cyclooctadiene).

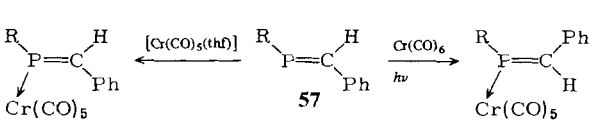
56 exhibits a temperature-dependent equilibrium between side-on and end-on coordination.[41]



56a **56b**

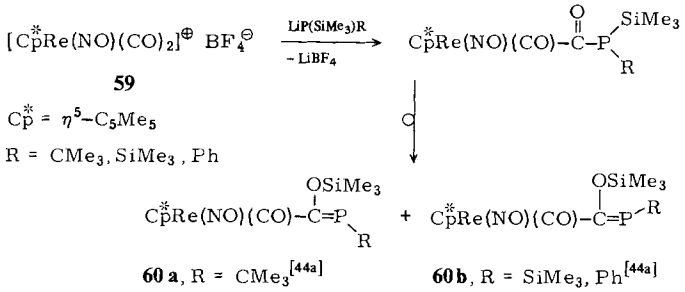
DNMR studies[41a, b] show that, in solution at −40 °C, 75% **56a** and 25% **56b** are present. Solid state ^{31}P-NMR data[41b, c] and a crystal structure analysis[41a] confirm the η^1-coordination (**56b**) in the solid state. Hartree-Fock-Slater (LCAO-X_α) calculations[41b] on the model system $(H_3P)_2Pt(HP{=}CH_2)$ provide qualitative agreement with these experimental results. Theoretical[42] and photoelectron spectroscopic[42h, k, l] investigations on the parent substances H–P=CH_2,[41b, 42a–d] H–P=N–H,[42b, c, e, l] H–P=P–H,[42f–l, 62a] H–P=O,[42b] and derivatives[42a, c, m] furnish the first satisfactory explanation for its reaction behavior.

57 is converted thermally into **58a** with retention of configuration, but photochemically into the *Z*-isomer **58b**.[43]



58a R = 2,4,6-$(Me_3C)_3C_6H_2$ **58b**

Phospha-alkenyl complexes (compounds in which a transition metal fragment is a C- or P-substituent) can be generated directly in a complex.[44] Thus, the reaction of the cationic complex **59** and monosilylated lithium phosphides at low temperature forms at first phosphinocarbonyl complexes (demonstrated by ^{31}P NMR), which then isomerize in a 1,3 migration of the Me_3Si group to the phospha-alkenyl complexes **60**.[44a]



59

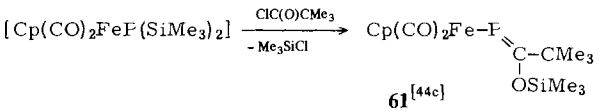
$Cp^* = \eta^5\text{-}C_5Me_5$

R = CMe_3, $SiMe_3$, Ph

60a, R = CMe_3[44a] **60b**, R = $SiMe_3$, Ph[44a]

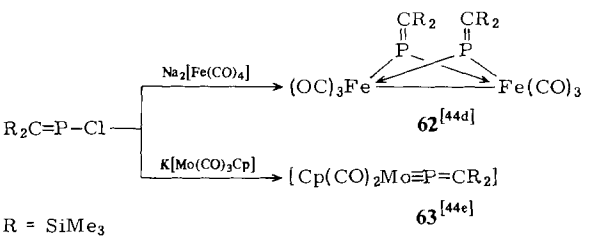
60a (*Z* form) is formed instead as **60a'** (*E* form) (Table 4) if η^5-C_5H_5 is employed instead of η^5-C_5Me_5.[44b]

The phospha-alkenyl complex **61** (Table 4), with an Fe–P single bond and *Z*-configuration, is formed directly in the reaction of a disilylphosphido-iron complex with pivaloyl chloride.[44c]



61[44c]

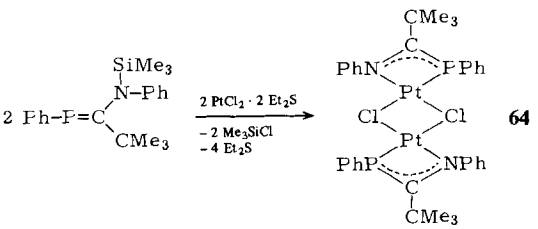
A further route to this class of compound ($L_nMP{=}CR_2$) is the reaction of $(Me_3Si)_2C{=}PCl$ with $Na_2[Fe(CO)_4]$[44d] or $K[Mo(CO)_3Cp]$.[44e]



62[44d] **63**[44e]

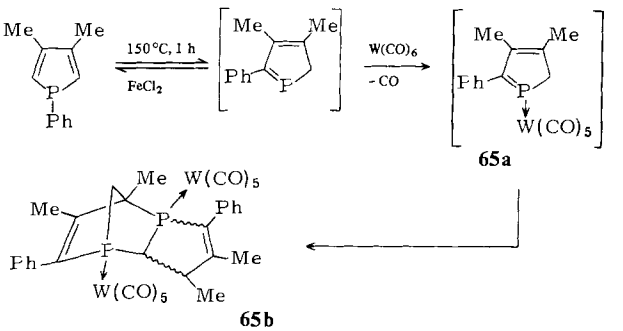
R = $SiMe_3$

The 18-electron rule requires a le-donor ligand for **61**,[44c] and a 3e-donor ligand for the linear phosphavinylidene complex **63**,[44e] the bridging variant of which is seen in **62**[44d] (Table 4). Allyl-type coordination has been suggested for the ambidentate phosphaamidine anion in complex **64**.[45]



64

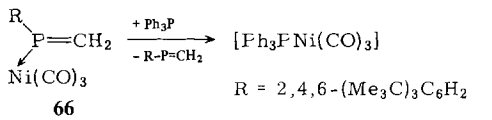
The chemistry of phospha-alkene or -alkenyl complexes with terminal P-coordination has hardly been investigated. Isomerization, formation of the complex **65a** and [4+2] cycloaddition have been discussed for the reaction of 3,4-dimethyl-1-phenylphosphole with $W(CO)_6$ to give the isomer mixture **65b**.[46]



65a

65b

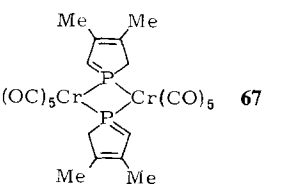
Triphenylphosphane displaces the phospha-alkene ligand from **66**.[48b]



66

3.2.2. *Bridging P-Coordination*

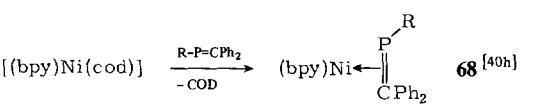
This rare coordination mode (cf. **B**) has been postulated for the isomer mixture **67** ($^{31}P\{^1H\}$-NMR: $\delta = 45.7$, 45.9)[47] (cf. also the complex **62**[44d]).



67

3.2.3 η^2-*Coordination (Side-on Coordination)*

The η^2-coordination of the P=C-π-bond (cf. **C**) can be verified both by the reaction of an isolated phospha-alkene with a suitable transition metal fragment and also by formation at a complex.

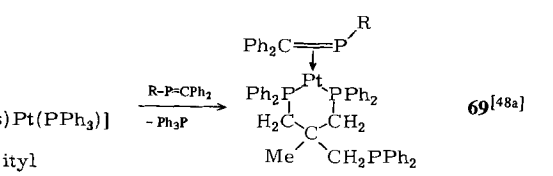


68[40h]

R = 2,6-$(CH_3)_2C_6H_3$

The starting material of choice is (bpy)Ni(cod) for the nickel complex **68** (Table 4),[40h] (triphos)Pt(PPh_3) for the platinum compound **69**[48a] (see also compound **56**[41]). The reaction of (triphos)Pt(PPh_3) with $Me_3C{-}C{\equiv}P$ leads to the phospha-alkyne complex analogous to **69**.[48a] $^{195}Pt\{^1H\}$-NMR studies show **69** to be a mixture of isomers.[48a]

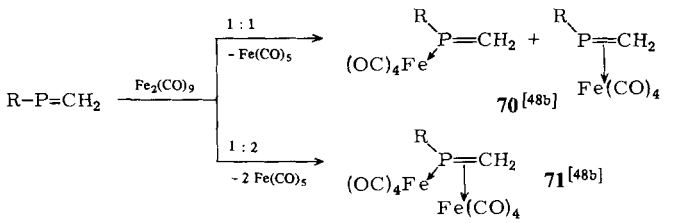
According to the stoichiometry employed, the reaction of $Fe_2(CO)_9$ with the stable methylene(2,4,6-tri-*tert*-butyl-



69[48a]

R = mesityl

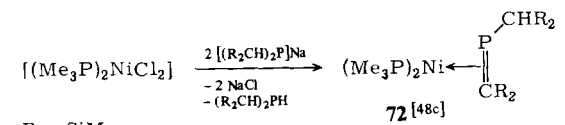
phenyl)phosphane leads to either the non-separable isomer mixture **70** (demonstrated by $^{31}P\{^1H\}$ NMR) or the crystallographically characterized product **71** (Table 4) with η^1,η^2-coordination (type **D**).[48b]



R = 2,4,6-$(Me_3C)_3C_6H_2$

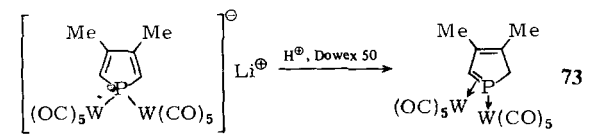
In **71** the η^1-P moiety occupies the axial site and the η^2-P=C moiety the equatorial site of the respective trigonal bipyramids.

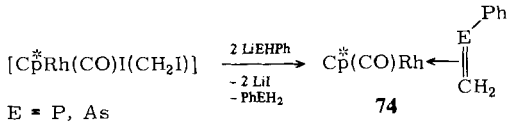
The reaction of $(Me_3P)_2NiCl_2$ with a highly substituted phosphide ion provided unexpected access to the chemistry of η^2-coordinated phospha-alkenes by leading, inter alia, to the nickel complex **72** (Table 4).[48c]



R = $SiMe_3$

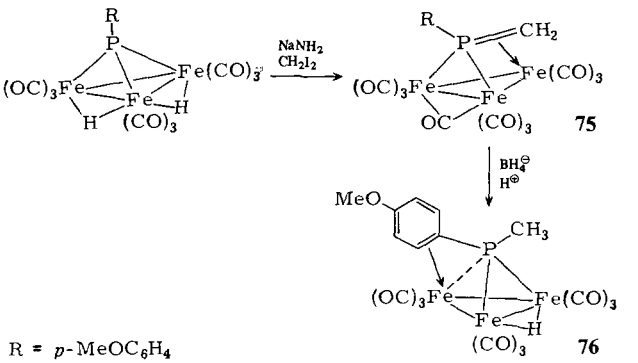
The 4e-donor type (as in **71**) was discovered in **73** (Table 4).[47]





The ligands Ph–E=CH_2 (E = P, As), unknown in the free state, were generated in the coordination sphere of rhodium and stabilized by η^2-coordination.[48d]

Cluster-stabilized R–P=CH_2 caps the Fe_3 triangle of **75** (Table 4) as a μ_3,η^2-ligand; it can be reduced to the μ_3,η^2-phosphino ligand $RPCH_3$ in **76**.[49] **75** is an example of a *type* **E** *complex*.



R = p-$MeOC_6H_4$

The coupling of a phosphanediyl and a carbene ligand to form μ-PhP=C(OEt)Ph is observed in the generation of **78** from **77** (Table 4), a complicated series of reactions.[50]

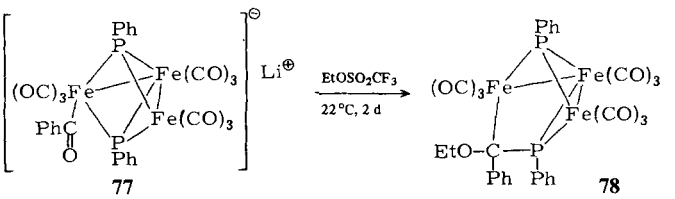
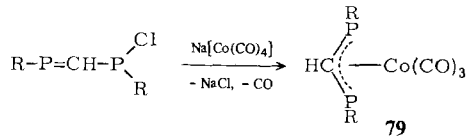


Table 4. $^{31}P\{^1H\}$-NMR data (δ values, J in Hz) and some molecular dimensions (from X-ray studies) of complexes with acyclic and cyclic phospha-alkene or -alkenyl ligands. Cp = η^5-C_5H_5. Cp* = η^5-C_5Me_5. Comparative PC distance in mesitylP=CPh_2 1.692(3) Å [42d].

Compound	$^{31}P\{^1H\}$	CPC [°]	P=C [Å]	Ref.
Terminal P-coordination				
55a [Ph_2C=P(mesityl)$\{Cr(CO)_5\}$]	237.3 (s)	109.8(2)	1.679(4)	[40a]
55b *cis*-[$\{Ph_2C$=P(mesityl)$\}\{PtCl_2(PEt_3)\}$]	149.0 (s), ^1J(PtP=C) 4294	112.5(5)	1.660(9)	[40j]
56 [Ph_2C=P(mesityl)$\{Pt(PPh_3)_2\}$]	[41]	108.5(5)	1.65(1)	[41a]
55c [$(Me_3Si)(Ph)C$=P$\{C_6H_2(CMe_3)_3\}\{Fe(CO)_4\}$]	285.5 (s)	[a]	1.670(4)	[40e, f]
55d [$(Me_3Si)_2C$=P$\{N(SiMe_3)_2\}\{Fe(CO)_4\}$]	311.4 (s)	(115.2(8) (CPN))	1.657(5)	[40g]
Metal-C-substitution				
60a [Cp*Re(NO)(CO)$(Me_3SiO)C$=$PCMe_3$]	271.7 (s)	[a]	1.662(12)	[44a]
60a' [CpRe(NO)(CO)$(Me_3SiO)C$=$PCMe_3$]	250.1 (s)	109.1(2)	1.689(4)	[44b]
Metal-P-substitution				
61 [$CpFe(CO)_2$P=$C(OSiMe_3)(CMe_3)$]	215.2 (s)	(113.8(2) (FePC))	1.701(4)	[44c]
62 [$(OC)_6Fe_2(\mu$-P=$CR_2)_2$] R = $SiMe_3$ [b]	452.6 (s)	(142.5(1) (FePC))	1.650(4)	[44d]
63 [$CpMo(CO)_2$≡P=$C(SiMe_3)_2$] [c]	497.0 (s)	(178.3(2) (MoPC))	1.649(4)	[44e]
η^2-coordination				
68 [(2,6-dimethylphenyl)P=$CPh_2\{Ni(bpy)\}$]	−16.1 (s)	102.6 (3)	1.832(6)	[40h]
71 [2,4,6-$(Me_3C)_3C_6H_2$P=$CH_2\{Fe(CO)_4\}_2$]	6.5 (s)	102.5 (3)	1.737(6)	[48b]
72 [$\{(Me_3Si)_2CHP$=$C(SiMe_3)_2\}\{Ni(PMe_3)_2\}$]	23.4 [d]	110.3(4)	1.773(8)	[48c]
73 [$\{H_2C(Me)C$=$(Me)C(H)C$=P$\}\{W(CO)_5\}_2$]	−31.9 (s)	93.2(8)	1.78(1)	[47]
75 [p-$MeOC_6H_4$P=$CH_2\{Fe_3(CO)_{10}\}$]	[a]	[a]	1.76(1)	[49]
78 [$\{$PhP=CPh(OEt)$(\mu_3$-PPh)$\}\{Fe_3(CO)_9\}$]	163.7 (d), 142.7 (d), ^2J(PP) 28/23 [e]	[a]	1.800(6)	[50]
79 [(RPCHPR)$\{Co(CO)_3\}$] R = 2,4,6-$(Me_3C)_3C_6H_2$	34.4 (d), ^2J(PH) 7.0	(101.8(4) (PCP))	1.769(7), 1.791(7)	[51]

[a] Not given. [b] Fe–Fe: 2.666(1) Å. [c] Mo–P: 2.174(1) Å. [d] X part of an ABX spectrum. [e] Diastereomers in solution; μ(P=C).

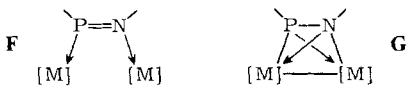


79

R = 2,4,6-$(Me_3C)_3C_6H_2$

The first phosphorus analogue of an (η^3-allyl)tricarbonylcobalt complex, **79** (Table 4), is formed as described in Ref. [51] from a chlorophosphino-substituted methylenephosphane.

A particularly marked downfield shift of the $^{31}P\{^1H\}$-NMR signal of phospha-alkenes is observed in those cases where the P atom bonded to the transition metal fragment can be ascribed 3e-donor character (**62** and **63**, Table 4); the η^2-coordination mode, in contrast, causes a large upfield shift (cf. Ref. [41]). The P=C bond length for terminal coordination or metal-C- or metal-P-substitution falls in the range 1.649(4) (**63**) to 1.701(4) Å (**61**); in **55a,b** and **56** this bond length is slightly shorter than in the free ligand (Table 4). For η^2-coordination, longer bonds are observed (up to 1.832(6) Å in **68** (Table 4)).



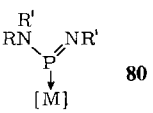
F G

3.3. Iminophosphanes

In addition to the coordination types **A**–**E** discussed above for phospha-alkenes (Section 3.2), iminophosphanes display the N,P 4e- and 6e-donor types **F** and **G**.

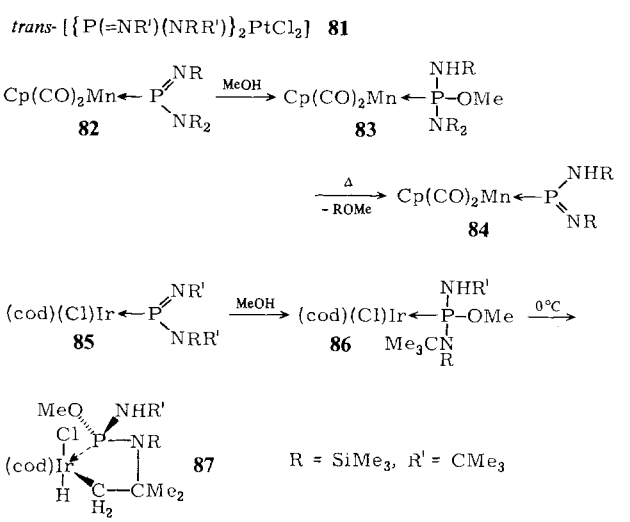
3.3.1. 2e-Donor Ligands

η^1-P Coordination: The terminal coordination **80** is preferred; for acyclic ligands it has been observed for the metals Cr,[52a,54] Mn,[52b] Ir,[52c] Ni,[56] and Pt.[52d-g] Compounds characterized by X-ray structure determination are shown in Table 5. N- and/or P-coordination is found in di- and triazaphosphole complexes of Au,[40k] Pd,[53] Pt,[40i,53] and Cr, W.[40c]



80

The reactivity of the P=N unit bound to the metal is of particular interest. Water and methanol addition were discovered in the case of **81**[52d] and successfully extended to **82** and **85**.



trans-[{P(=NR')(NRR')}$_2$PtCl$_2$] **81**

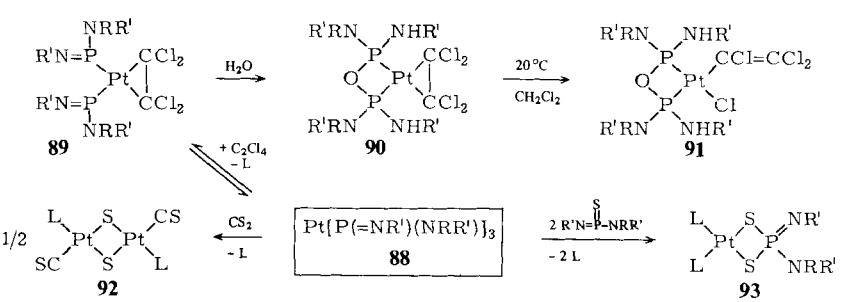
82 83 84 85 86 87

R = $SiMe_3$, R' = CMe_3

While **83** eliminates Me_3SiOMe at 60 °C to give **84** (containing $Me_3SiNH-P=NSiMe_3$, unstable in the free state)[52b] (cf. Ref. [52a] and **80b**, Table 5), **86** undergoes diastereoselective intramolecular oxidative addition of C–H (CMe_3 group) at 0 °C, forming the crystallographically characterized iridium(III) heterocycle **87**.[52c]

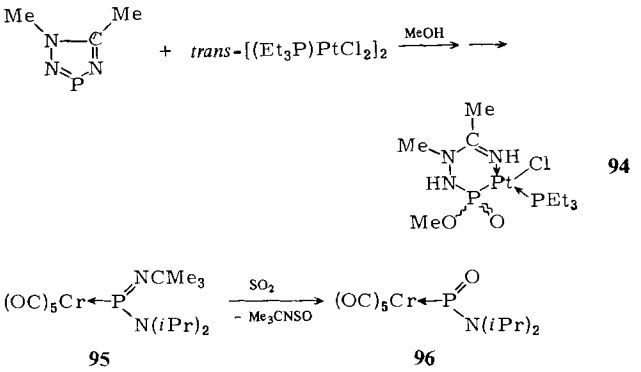
The reactions of $Pt(PPh_3)_3$ with alkenes and alkynes are very well known; some interesting reactions of the ligand were found to occur with the analogous phosphazene complex **88**.[52g] If (as in **89**) the phosphazene ligands are adjacent to each other, then the addition of a water molecule forms the platinum four-membered ring complex **90**, containing a P-O-P chelate ligand. **90** isomerizes quantitatively in CH_2Cl_2 in a few hours to the vinyl complex **91**, characterized by X-ray structure analysis.[52g] The reaction of **88** with CS_2 splits the latter into CS and S fragments, forming **92**.[52g] The synthesis of **93** from **88** may formally be regarded as the oxidation of platinum(0) to platinum(II) coupled with reduction of one molecule of the double ylide (by sulfur transfer) from phosphorus(V) to phosphorus(III) (σ^2-phosphazene).[52g] The formation of **94** in a multi-step reaction has also been described[53]

The stabilization of an aminooxophosphane as metal complex is achieved by the reaction of **95** with SO_2, forming **96**.[54]

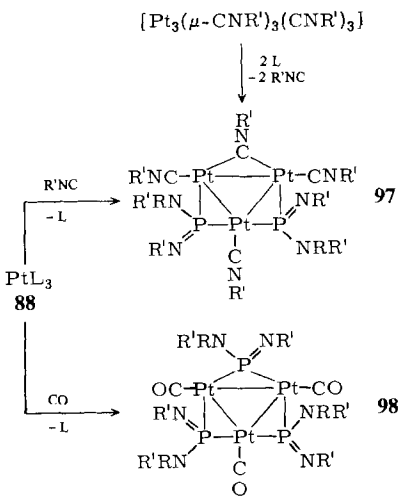


89 90 91 92 88 93

L = R'N=P–NRR'; R = $SiMe_3$, R' = CMe_3



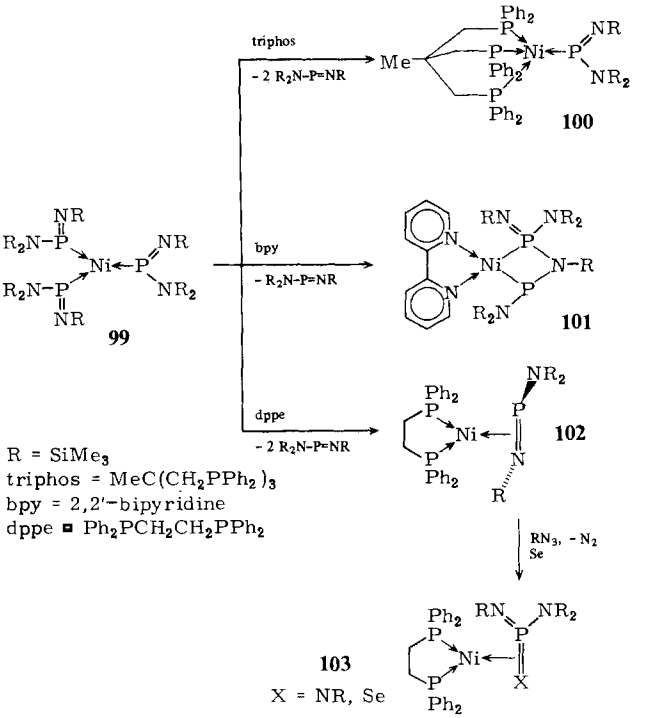
μ-P Coordination: Edge-bridging μ-P coordination of the phosphazene ligand is realized in the trinuclear platinum clusters **97** and **98**.[52f,55] The Me_3Si groups of these clusters undergo intramolecular 1,3-exchange. The constitution of **97** and **98** is established from ^{1}H-, ^{13}C{^{1}H}-, ^{31}P{^{1}H}- and ^{195}Pt{^{1}H}-NMR studies and X-ray structure analyses (Table 5).[52f,55]



L = R'N=P–NRR'; R = $SiMe_3$, R' = CMe_3 etc.

η^2-Coordination: Complex **99**, prepared from $Ni(cod)_2$ and $R_2N-P=NR$ (R = $SiMe_3$), is a versatile synthetic reagent.[56]

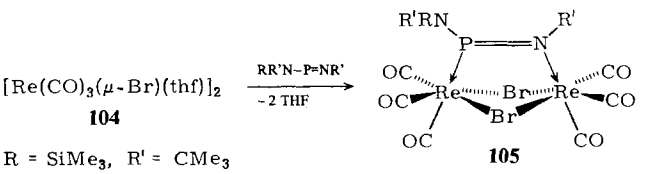
Its reaction with a tripod ligand to form **100** leaves the η^1-P coordination intact, but with bpy, transformation to the nickelaazadiphosphetidine **101** takes place (formally by formation of a P–N bond from two P=N units). The chelating ligand dppe causes a change of coordination mode from η^1 to η^2 (**102**). The classical side-on coordination in **102** has been proven by NMR studies and X-ray structure analysis (Table 5). Its oxidation by, e.g., Me_3SiN_3 or selenium leads to **103**, X = $NSiMe_3$ and Se, respectively, with side-on coordination of the P=X moiety of a σ^3,λ^5-phosphazene.[56]



R = $SiMe_3$
triphos = $MeC(CH_2PPh_2)_3$
bpy = 2,2'-bipyridine
dppe = $Ph_2PCH_2CH_2PPh_2$

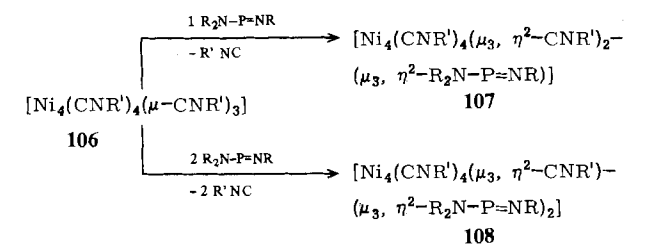
3.3.2. 4e-Donor Ligands

μ,η¹,η¹-N=P Coordination: This coordination type (cf. **F**) is represented by the dinuclear rhenium complex **105**.[57] The short P=N bond (1.56 Å, Table 5) means that the two distorted, edge-sharing octahedra in **105** tend towards face-sharing. The introduction of the P=N ligand changes the *trans*-**104** to the *cis*-**105**.[57]



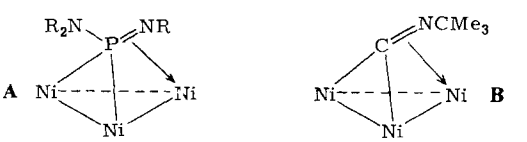
R = $SiMe_3$, R' = CMe_3

μ_3,η^2-N=P Coordination: The Ni_4-clusters **107** and **108** are formed by the displacement of the bridging isocyanide ligands of **106** by amino(imino)phosphane ligands.[58]

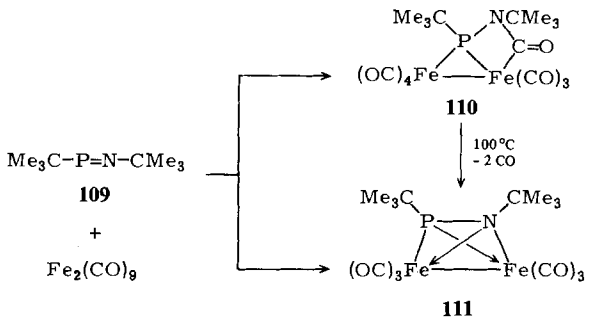


R = $SiMe_3$, R' = CMe_3

The crystal structure analysis (Table 5) shows that, in the flattened trigonal Ni_4-pyramid of **108**, two triangular faces are capped by μ_3,η^2-$R_2N-P=NR$ units and one by a μ_3,η^2-$C\equiv N-CMe_3$ ligand (see **A** and **B**; R = $SiMe_3$).



3.3.3. 6e-Donor Ligands



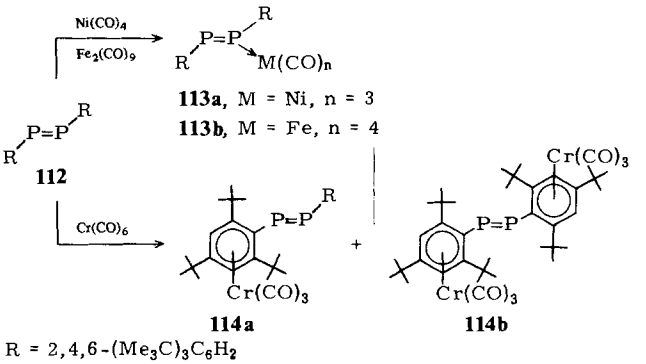
The reaction of **109** with $Fe_2(CO)_9$ leads to **110** and **111**.[59] It is possible that **110** arises from $[(OC)_8Fe_2\{\mu\text{-}P(=NCMe_3)CMe_3\}]$ by intramolecular nucleophilic attack of the imino nitrogen on a CO ligand. According to a crystal structure analysis (Table 5) the P-N bond length in **111** (cf. G) corresponds to the PN single bond length required for this coordination type[59] (see, in contrast, P-P in the isoelectronic **125**, Table 6[67a]).

$^{31}P\{^1H\}$-NMR data are also a useful indication of coordination type for the iminophosphane ligands; thus a significant upfield shift is observed on going from the terminal P- or NP- to the P=N side-on coordination. Associated with this is the expected increase of the P=N bond length (cf. also the acyclic complexes **80** with **102** and **108** and with the free ligand, Table 5).

3.4. –E=E- and –P=E-Ligands (E = P, As, Sb)

3.4.1. Diphosphenes (R–P=P–R)

The isolation and X-ray structural characterization of the first diphosphene **112**[60] showed how to stabilize these ligands in the free state by using sterically demanding groups (see summary of the literature in Refs. [3o, p]). The reaction of **112** with carbonylmetal compounds leads with nickel and iron to terminal P-coordination (**113**)[61a,63], but with chromium (reflux, dioxane) to η^6-coordination (**114**).[61b]



If one tri(*tert*-butyl)phenyl group of **112** is replaced by the sterically less demanding mesityl group, the E→Z photoisomerization **115** → **115a** can be carried out at the metal complex.[62a]

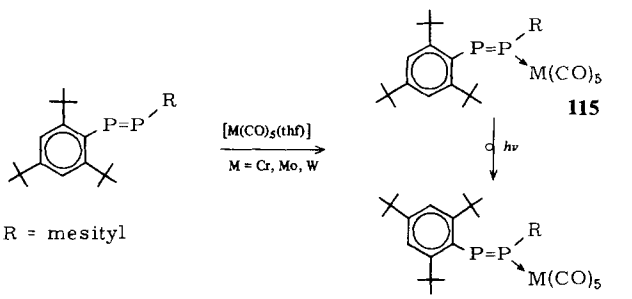


Table 5. $^{31}P\{^1H\}$-NMR data (δ values, J in Hz) and selected molecular dimensions (from X-ray studies) of complexes with acyclic and cyclic iminophosphane ligands. $(Me_3Si)_2N-P=NSiMe_3$: NPN 108.4(1)°, P–N 1.674(1), P=N 1.545(2) Å; $(Me_3Si)(Me_3C)N-P=NCMe_3$; NPN 104.9(2)°, P–N 1.658(4), P=N 1.544(4) Å (S. Pohl, *Chem. Ber. 112* (1979) 3159).

Compound		$^{31}P\{^1H\}$	NPN [°]	P–N [Å]	P=N	Ref.
η^1-P coordination						
80a	$[\{(Me_3Si)_2N(Me_3CN=)P\}\{Cr(CO)_5\}]$	[a]	119.6(2)	1.671(4)	1.519(4)	[52a]
80b	$[\{(Me_3C)HN(Me_3SiN=)P\}\{Cr(CO)_5\}]$	[a]	112.3(2)	1.640(4)	1.505(4)	[52a]
80c	$[\overline{NN(Me)C(Me)C(H)}PCr(CO)_5]$ [b]	237.8 (s)			1.637(7)	[40c]
80d/88	$[\{(Me_3Si)(Me_3C)N(Me_3CN=)P\}_3Pt]$ [c]	276.8 (s), ^1J(PtP) 5379	103.7	1.68	1.556	[52e]
80e	$[\overline{NN(Me)C(Me)NP}Pt(PPh_3)_3]$	234.4 (q), ^1J(PtP) 3580	96.5(7)	1.63(1)	1.64(1)	[40i]
μ-P coordination						
97	$[Pt_3\{\mu\text{-}P(=NCMe_3)N(CMe_3)(SiMe_3)\}_2(\mu\text{-}CNCMe_3)(CNCMe_3)_3]$ [c]	286.7, ^1J(PtP) 1417, 1752	96.6	1.678	1.545	[52f, 55]
98	$[Pt_3\{\mu\text{-}P(=NCMe_3)N(CMe_3)(SiMe_3)\}_3(CO)_3]$ [c]	237.3, ^1J(PtP) ±1345	101.9	1.674	1.555	[55]
μ,η^1,η^1-N=P coordination						
105	$[\{Re_2(CO)_6(\mu\text{-}Br)_2\}P(=NCMe_3)N(CMe_3)(SiMe_3)]$	303.4 (s)	122.6(9)	1.66(2)	1.56(2)	[57]
η^2-coordination						
102	$[(dppe)NiP(=NSiMe_3)N(SiMe_3)_2]$	65.8 [d]	109.1(1)	1.737(2)	1.646(2)	[56]
μ_3,η^2-N=P coordination						
108	$[Ni_4(CNCMe_3)_4(\mu_3,\eta^2\text{-}CNCMe_3)(\mu_3,\eta^2\text{-}R_2N-P=NR)_2]$ R = $SiMe_3$ [c]	170.6 (d), 173.8 (d), ^2J(PP) 40.6	106.0	1.720	1.603	[58]
μ,η^2-N=P coordination						
111	$[(OC)_6Fe_2PN(CMe_3)_2]$ [e]	81.0 (s)			1.687(7)	[59]

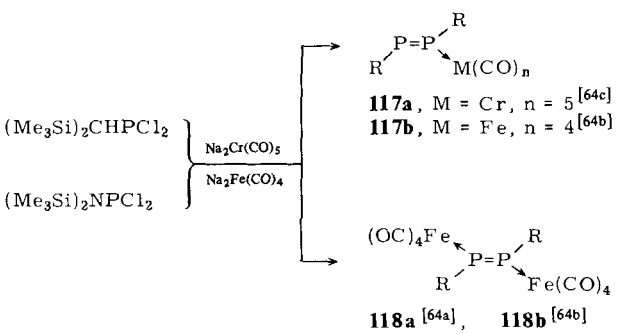
[a] Not given. [b] NPC: 95.2(4)°; PC: 1.729(10) Å. [c] Angles and bond lengths: mean values. [d] ABC spin system. [e] NPC: 130.4(4)°.

The rate of isomerization decreases in the order Cr ≫ Mo > W. Ab initio calculations suggest that the activation energy for the isomerization of HP=PH is very high (whereby rotation is preferred to inversion in the formation of the transition state). The energy barrier is lowered, sterically and electronically, by the formation of a complex[62a] (cf. Refs. [42f–l]).

Fenske-Hall MO calculations[62b] on $H_2P_2[Cr(CO)_5]$ (coordination type **113**, **115**, **117**) show that the end-on coordination cannot be described as a pure σ-donor bond, but that delocalized σ- and π-interactions play an important role.

η^1-P coordination of the less sterically shielded phosphorus atom has also been suggested for the complex **116**.[61a,63] The 2e-donor coordination type **113** can, as with **117**, be synthesized at a metal complex; this is the only known method for the 4e-donor type.

$[\{2,4,6\text{-}(Me_3C)_3C_6H_2P{=}PCH(SiMe_3)_2\}\{Fe(CO)_4\}]$ **116**



a, R = $CH(SiMe_3)_2$; **b**, R = $N(SiMe_3)_2$

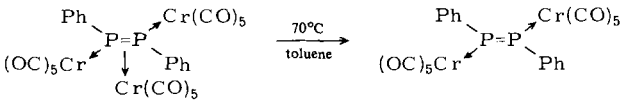
Reaction of $(Me_3Si)_2CHPCl_2$ with $Na_2[M_2(CO)_{10}]$ (M = Cr, W) leads, after initial formation of deep-colored phosphanediyl complexes, to isolable compounds of the type **118a** in which $Fe(CO)_4$ is replaced by $Cr(CO)_5$ or $W(CO)_5$. Upon heating to 60 °C (toluene), these compounds yield **117a** or its tungsten analogue **117a''**.[65b] The molybdenum analogue **117a'** has been characterized X-ray crystallographically (Table 6).[65b]

Dichloro(mesityl)phosphane reacts with $Na_2[M_2(CO)_{10}]$, M = Cr, Mo, W, in such way that the compounds **119a–c** are formed alongside the isolable phosphanediyl complexes $[RP\{M(CO)_5\}_2]$, M = Cr, W. The structure of compounds of the type **119a–c** (cf. also complex **115a**) is confirmed by an X-ray structure analysis of the molybdenum derivative **119b** (Table 6).[65b]

cis-$[\{(mesityl)P\}_2\{M(CO)_5\}_2]$
119a, M = Cr; **119b**, M = Mo; **119c**, M = W

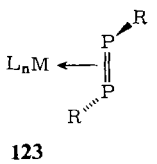
The stabilization of *trans*-Ph–P=P–Ph in a metal complex can be achieved using the method described by *Huttner* et al.[65] (X-ray data of **120**, **121**, Table 6).

Compound **120** is prepared from $Na_2[Cr_2(CO)_{10}]$ and $(OC)_5Cr(PPhCl_2)$;[65] the comparable Pd complex **122** can be prepared directly from the η^2-precursor and $W(CO)_5(thf)$.[66d] The classical side-on coordination **123**, the longest-known coordination mode of diphosphenes, has been achieved exclusively in the coordination sphere of a transition metal; compounds **123a–e** have been characterized by X-ray structure determination (Table 6).



120 **121**

$[(dppe)Pd(\eta^2\text{-}PhP{=}PPh)\{W(CO)_5\}_2]$ **122**



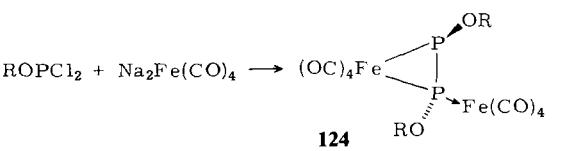
123

123	M	L_n	R	Ref.
a	Mo	$(\eta^5\text{-}C_5H_5)_2$	H	[66a]
b	Pt	$(PPh_3)_2$	C_6F_5	[66b]
c	Ni	$(PEt_3)_2$	$SiMe_3$	[66c]
d	Pd	dppe	C_6H_5	[66d]
e	Ni	[a]	C_6H_5	[66e]

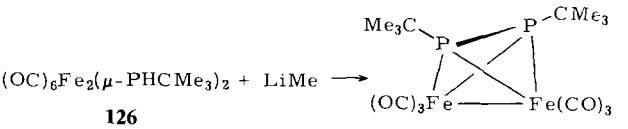
[a] 3,4-Bis(diphenylphosphino)-1-methyl-2,5-bis(trimethylsiloxy)pyrrole.

The thermolysis of $(\eta^5\text{-}C_5H_5)_2MoH_2$ and P_4[66a] or $M(PPh_3)_3$ and $(EC_6F_5)_4$ (M = Pd, Pt, E = P, As)[66b] gives **123a**, **b**. $[PdCl_2(dppe)]$ reacts with $Li_2(PhP{-}PPh)$ to give **123d**; the compounds with M = Pt, L_n = dppe, $(PPh_3)_2$, are also known.[66d] $[(Et_3P)_2NiCl_2]$ reacts with $LiP(SiMe_3)_2$ to give (amongst other products) **123c**; the Me_3P- and nBu_3P-compounds have been prepared analogously[66c] (cf. also Ref. [11]). **123e** and its arsenic analogue **134d** can be obtained from the 2,3-bis(diphenylphosphino)-*N*-methylmaleimide complex of $NiCl_2$ and $PhE(SiMe_3)_2$, E = P, As.[66e]

The 4e- and 6e-donor coordination modes of a diphosphene ligand (**124**[64c] and **125**[67a]) can be attained by the reactions of $2,4,6\text{-}(Me_3C)_3C_6H_2OPCl_2$ with $Na_2[Fe(CO)_4]$ or of $(OC)_6Fe_2(\mu\text{-}PHCMe_3)_2$ (**126**) with LiMe, respectively.



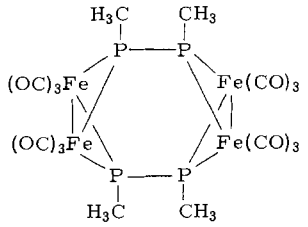
124



126 **125**

R = $2,4,6\text{-}(Me_3C)_3C_6H_2$

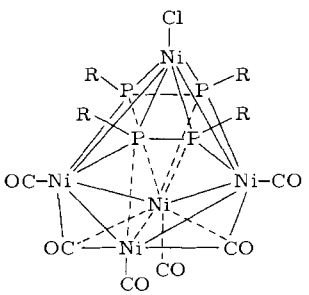
If the CMe_3 group of **126** is replaced by a methyl group, **127** (an organometallic analogue of octabisvalene) is formed rather than the methyl derivative of **125**. The P–P



127

bond length of **127** (2.226(4) Å) suggests that the ligands should not be described as diphosphene units.[67b]

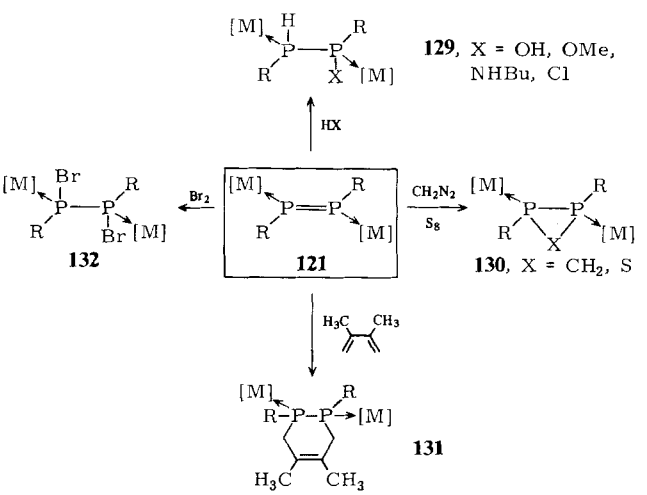
RPPR ligands are part of a Ni_5 cluster in **128**, prepared from $(Me_3Si)_2CHPCl_2$ and $Na_2[Ni_6(CO)_{12}]$[68] (Table 6).



128, R = $(Me_3Si)_2CH$

Temperature-dependent $^{31}P\{^1H\}$-NMR studies of the systems RP=PR/$Ag(SO_3CF_3)$ and RP=PR/$[Et_3PAu][PF_6]$ provide evidence for the formation of the cationic complexes $[R(Ag)P=P(Ag)R]^{2\oplus}$, $[RP=P(Ag)R]^{\oplus}$, and $[RP=P(AuPEt_3)R]^{\oplus}$, where R = 2,4,6-$(Me_3C)_3C_6H_2$.[69]

The addition and cycloaddition reactions carried out on complex **121**[70] show in striking fashion the versatile reactivity of diphosphene ligands.

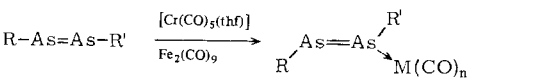


[M] = $Cr(CO)_5$, R = Ph

129 and **130** are formed stereoselectively, while **132** is a mixture of racemate and *meso*-form. The [4+2]-cycloaddition of **121** with cyclopentadiene is analogous to the formation of **131** (one isomer, in each case). **129** (X = OH, NHBu), **130** (X = CH_2), and **131** were additionally characterized by X-ray structure analysis.[70]

3.4.2. *Diarsenes (R–As=As–R), Distibenes (R–Sb=Sb–R)*

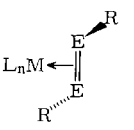
For the few diarsene derivatives R–As=As–R′ (R, R′ bulky groups) that are isolable in the free state, only the 2e-donor coordination type is known (**133**).[63,71]



R = 2,4,6-$(Me_3C)_3C_6H_2$ **133a**, M = Cr, n = 5[63,71]

R′ = $(Me_3Si)_2CH$ **133b**, M = Fe, n = 4[71]

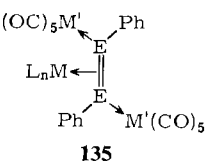
η^2-Coordination (**134**, **135**) can be generated in the coordination sphere of a transition metal.



134

134	M	E	L_n	R	Ref.
a	Pt	As	$(PPh_3)_2$	C_6F_4	[66b]
b	Fe	As	$(CO)_4$	C_6F_5	[66b]
c	Fe	As	$(CO)_4$	C_6H_5	[72]
d	Ni	As	[a]	C_6H_5	[66e]
e	Fe	Sb	$(CO)_4$	$CH(SiMe_3)_2$	[73]

[a] See **123e**.



135

135	M	M′	E	L_n	Ref.
a	Cr	Cr	As	$(CO)_5$	[74a]
b	Cr	Cr	As	$(CO)_4[P(OMe)_3]$	[74b]
c	Pd	Cr	As	$[P(OMe)_3]_2$	[74b]
d	Pd	Cr	As	bpy	[74b]
e	W	W	Sb	$(CO)_5$	[75a]
f	Cr	Cr	[a]	$(CO)_5$	[75b]

[a] $Me_3CSb{=}SbCMe_3$ instead of PhE=EPh.

134a, **b** and **134d** are prepared analogously to the diphosphene complexes **123b** and **123e**. The metathetic reaction of $Na_2[Fe(CO)_4]$ with $C_6H_5AsCl_2$[72] or $(Me_3Si)_2CHSbCl_2$[73] leads to **134c** and **134e**; **135a** is formed from $C_6H_5AsCl_2$ and $Na_2[Cr_2(CO)_{10}]$, or $(OC)_5Cr(AsPhLi_2)$ and $(Cl_2PhAs)Cr(CO)_5$;[74a] **135e** from $C_6H_5SbCl_2$ and $Na_2[W_2(CO)_{10}]$.[75] **135e** reacts with phosphanes with formation of adducts of the stibanediyl complex $PhSb[W(CO)_5]_2$.[75b] When Me_3CSbCl_2 is allowed to react with $Na_2[Cr_2(CO)_{10}]$ in $CHCl_2$, not only the stibanediyl complex $[Me_3CSb\{Cr(CO)_5\}_2]$ is obtained but also the distibene complex **135f**,[75b] the structure of which has been confirmed by an X-ray structure analysis (Table 6). Starting material for the synthesis of **135b–d** is $[(OC)_5CrAs(Ph)(H)]_2$; this is allowed to react with Pd/C/2L or Pt/C/L, when the required products are formed by H_2 elimination, probably via the intermediate **136**.[74b]

The transition from terminal to η^2-coordination is in most cases accompanied by the expected change in PP or AsAs bond length in the direction of a single bond (e.g. **113b/124**, **133a/135a**; Table 6). An exception is furnished by **125**,[67a] the short P–P bond of which can be contrasted with the long P–N bond of the isoelectronic **111**[59] (Table 5). The η^1-P- or η^1-As-coordination in **113b** and **133a** has the effect of lengthening the P=P or As=As bond by ca. 0.02 Å compared with the free ligands (Table 6), which also have the *trans* configuration.

Table 6. $^{31}P\{^1H\}$-NMR data (δ values, J in Hz) and E-E bond lengths [Å] for complexes with R–E=E–R(R') ligands. Comparative distance of the free ligand in **113b**: P=P 2.034(2) Å [60]; in **133a**: As=As: 2.224(2) Å (A. H. Cowley, J. G. Lasch, N. C. Norman, M. Pakulski, *J. Am. Chem. Soc. 105* (1983) 5506).

Compound		$^{31}P\{^1H\}$	E–E	Ref.
η^1-P coordination				
113b	[{2,4,6-$(Me_3C)_3C_6H_2P$}$_2${$Fe(CO)_4$}]	423.6, 396.4 [a], ^1J(PP) 578	2.050(1)	[61a, 63]
115a	[{2,4,6-$(Me_3C)_3C_6H_2PP$(mesityl)}{$Cr(CO)_5$}]	393.9, 384.9 [a], ^1J(PP) 603	2.039(3)	[62a]
117a	[{$(Me_3Si)_2CHP$}$_2${$Cr(CO)_5$}]	477.3, 446.2 [a], ^1J(PP) 510	2.027(3)	[64c]
117a'	[{$(Me_3Si)_2CHP$}$_2${$Mo(CO)_5$}]	465.4, 433.0 [a], ^1J(PP) 515	2.006(3)	[65b]
118a	[{$(Me_3Si)_2CHP$}$_2${$Fe(CO)_4$}$_2$]	384.6 (s)	2.039(1)	[64a]
118b	[{$(Me_3Si)_2NP$}$_2${$Fe(CO)_4$}$_2$]	403.9 (s)	2.053 (1)	[64b]
119b	[(mesitylP)$_2${$Mo(CO)_5$}$_2$]	367.7 (s)	2.026(2)	[65b]
121	[$(PhP)_2${$Cr(CO)_5$}$_2$]	369 (s, br.)	2.021(2)	[65]
η^2-coordination				
120	[$(PhP)_2${$Cr(CO)_5$}$_3$]	97 (s)	2.125(6)	[65a]
122	[(dppe)Pd$(PhP)_2${$W(CO)_5$}$_2$]	17.0, ^1J(PP) 344	2.186(6)	[66d]
123a	[$(HP)_2Mo(\eta^5$-$C_5H_5)_2$]	203	2.146(3)	[66a]
123b	[$(C_6F_5P)_2Pt(PPh_3)_2$]	−22 [66d]	2.156(7)	[66b]
123c	[$(Me_3SiP)_2Ni(PEt_3)_2$]	−62	2.148(2)	[66c]
123d	[$(PhP)_2$Pd(dppe)]	34.3, ^1J(PP) 348	2.121(4)	[66d]
123e	[$(PhP)_2$Ni{$[Ph_2PCC(OSiMe_3)]_2$NMe}]	− 4.9	2.140(1)	[66e]
124	[{2,4,6-$(Me_3C)_3C_6H_2OP$}$_2${$Fe(CO)_4$}$_2$]	233.8, 193.4 [a], ^1J(PP) 532	2.184(2)	[64c]
125	[$(Me_3CP)_2{Fe_2(CO)_6}$]		2.059(3)	[67a]
128	[{$(RP)_2$}$_2${$Ni_5(CO)_6Cl$}], R=$(Me_3Si)_2CH$	353 (s)	2.085(4), 2.098(4)	[68]
η^1-As coordination				
133a	[{2,4,6-$(Me_3C)_3C_6H_2$AsAsCH$(SiMe_3)_2$}{$Cr(CO)_5$}]		2.246(1)	[63, 71]
η^2-coordination				
134b	[$(C_6F_5As)_2${$Fe(CO)_4$}]		2.388(7)	[66b]
134c	[$(PhAs)_2${$Fe(CO)_4$}]		2.365(2)	[72]
134d	[$(PhAs)_2$Ni{$[Ph_2PCC(OSiMe_3)]_2$NMe}]		2.372(1)	[66e]
134e	[{$(Me_3Si)_2CHSb$}$_2${$Fe(CO)_4$}]		2.774(1)	[73]
135a	[$(PhAs)_2${$Cr(CO)_5$}$_3$]		2.371(−)	[74a]
135b	[$(PhAs)_2${$Cr(CO)_5$}$_2${$Cr(CO)_4$[P(OMe)$_3$]}]		2.34(1)	[74b]
135c	[$(PhAs)_2${$Cr(CO)_5$}$_2${$(MeO)_3P$}$_2$Pd]]		2.366(2)	[74b]
135d	[$(PhAs)_2${$Cr(CO)_5$}$_2$(bpy)Pd]]		2.360(6)	[74b]
135e	[$(PhSb)_2${$W(CO)_5$}$_3$]		2.706(4)	[75a]
135f	[$(Me_3CSb)_2${$Cr(CO)_5$}$_3$]		2.720(3)	[75b]

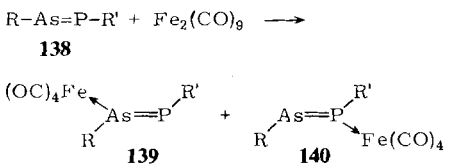
[a] AB spin system.

[{$(OC)_5Cr$}(Ph)As=As(Ph){$Cr(CO)_5$}] **136** $Te_2[W(CO)_5]_3$ **137**

An interesting structural analogy is seen in $(PhSb)_2[W(CO)_5]_3$ (**135e**) and $Te_2[W(CO)_5]_3$ (**137**).[76] The Te–Te bond length of 2.686(4) Å and also the Te–W bond lengths correspond almost exactly with their counterparts in the "isoelectronic" **135e**[75a] (Table 6).

3.4.3. *Phosphaarsaethenes (R–P=As–R')*

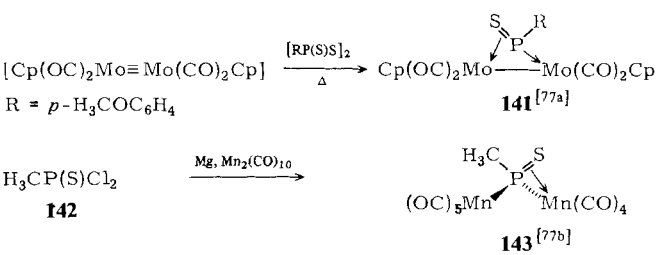
The isomers **139** and **140** are formed on reaction of $Fe_2(CO)_9$ with **138**; their separation proved impossible, but $^{31}P\{^1H\}$-NMR data suggested the structures shown.[63]



R = 2,4,6-$(Me_3C)_3C_6H_2$, R' = $(Me_3Si)_2CH$

3.4.4. *Thioxophosphanes (R–P=S)*

Compounds of this type (with a σ^2,λ^3-phosphorus atom) have not yet been isolated in the free state at room temperature, but have been stabilized in complexes.



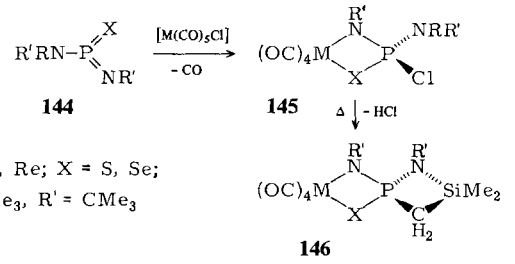
In both cases (**141** and **143**) the R–P=S ligand is coordinated side-on to the metal atom; the PS bond lengths are very similar [2.022(1) Å in **141**,[77a] 2.033(2) Å in **143**[77b]]. The non-bonding electron pair of the phosphorus of RPS is formally a 2e-donor to Mo in **141**, but a 1e-donor to both Mn atoms of **143**. If, instead of $Mn_2(CO)_{10}$, $[Mn(CO)_5]^{\ominus}$ is allowed to react with **142**, then **143** is formed only in trace amounts; this has been interpreted as evidence for the role of H_3C–P=S as an intermediate of **142** leading to **143**.[77b] The terminal P-coordination of an amino(oxo)phosphane is revealed by the crystal structure of **96**.[54]

4. Multiply Bonded Systems with Ligand Coordination Number Three

4.1. Aminoiminothioxophosphoranes and Aminoiminoselenoxophosphoranes

The isolable ligand **144**, a pentavalent phosphorus compound with coordination number 3 (σ^3,λ^5-P), adds, e.g., to

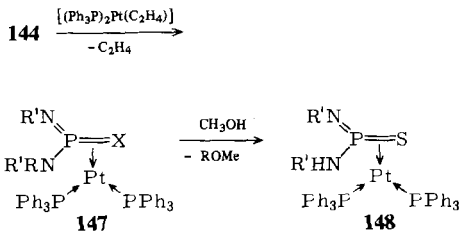
$M(CO)_5Cl$ to form the four-membered ring chelate complexes **145**, thermolysis of which leads to the spiro systems **146**.[78] **146** is also formed directly from, e.g., $Mn(CO)_5Br$ and **144**.[78]



144 **145** **146**

M = Mn, Re; X = S, Se;
R = $SiMe_3$, R' = CMe_3

The η^2-coordination of the P=S or P=Se unit of **144** is achieved in the platinum complexes **147**.[79] Methanolysis of the Si–N bond of **147** furnishes an aminoiminothiophosphorane $Me_3CNH-P(S)=NCMe_3$, unknown in the free state but stabilized at the metal center.[79] The X-ray structure analysis of **147** (X = S) reveals the side-on coordination (P–S 2.073(3) Å) and also a weak N→Si donor-acceptor interaction of 2.629(6) Å.[79]



147 **148**

X = S, Se; R = $SiMe_3$, R' = CMe_3

Coordination type **147** for nickel (see compound **103**) can be achieved by oxidation of an η^2-$R_2N-P=NR$ ligand.[56]

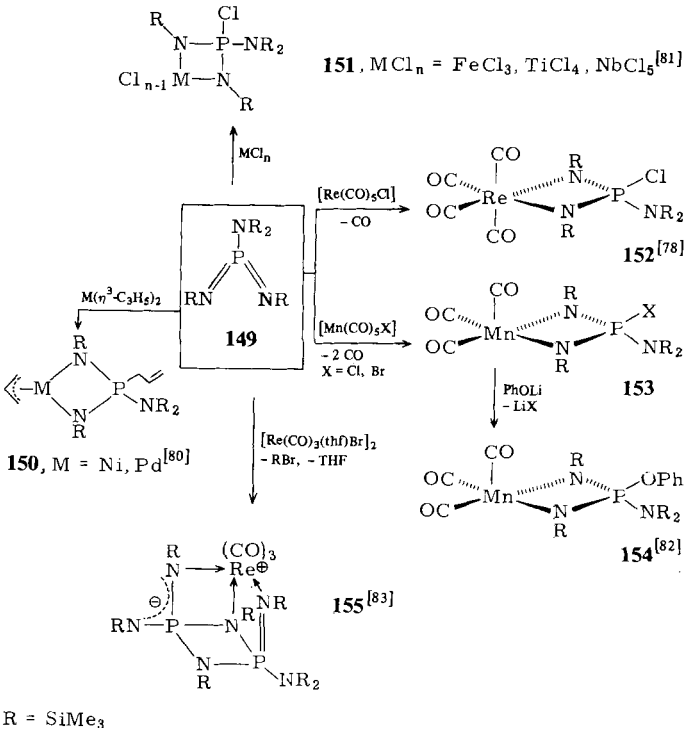
4.2. Aminobis(imino)phosphoranes

The persilylated compound **149** surpasses **144** in its versatility as a ligand.

149 reacts with bis(η^3-allyl)nickel and bis(η^3-allyl)palladium to form the four-membered ring framework **150** by allyl migration.[80] With transition metal halides[81] or carbonyl halides,[78,82] the chelate complexes **151**–**153** are formed; the formation of the five-coordinate Mn^I complex **153** is particularly notable, and the square pyramidal coordination at Mn was proved by an X-ray structure analysis of the derivative **154**.[82]

The removal of an R group from the amino nitrogen of **149** would formally produce **156**, a derivative of the monomeric metaphosphate ion; **156** could react with itself or with **149** by [2+2] cycloaddition to form the polydentate ligands **157** and **158**, which in turn (as **155** and the following examples show) can be synthetic units for mono- and dinuclear rhenium complexes.

The tricyclic **155** contains the anion **158** acting as a 6e-donor, whereas in **159** and **160**, the dianion **157** is an 8e- and 12e-donor, respectively, to Re^I. Starting material for



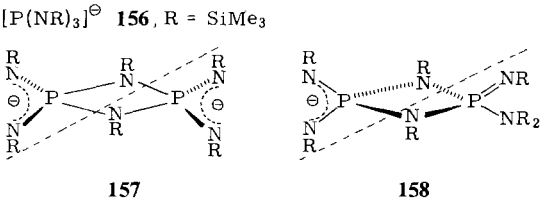
151, MCl_n = $FeCl_3$, $TiCl_4$, $NbCl_5$[81]

152[78] **153** **154**[82] **155**[83]

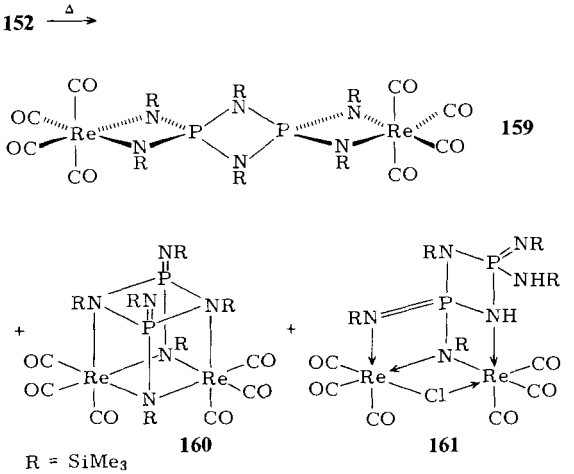
150, M = Ni, Pd[80]

R = $SiMe_3$

the synthesis of the polydentate ligand system **157** is the chelate complex **152**, thermolysis of which leads to the polycyclic phosphorus-nitrogen-rhenium compounds **159**–**161**.[84]



157 **158**



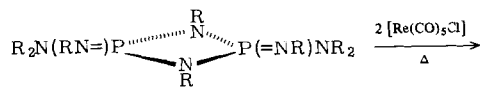
159 **160** **161**

R = $SiMe_3$

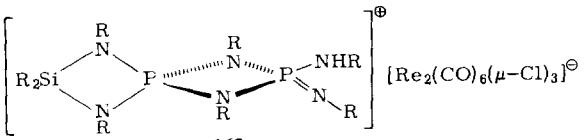
The centrosymmetric dispiro compound **159** (a derivative of a dimeric metaphosphate, stabilized at a metal complex) contains PN_2Re four-membered rings slightly bent about the N···N axis.[84] **161** (identified by crystal structure analysis) is probably formed from the "cubane" **160**

($M_2A_4B_2$ structure type) and the HCl formed by the thermolysis (cf. the formation of **146**), with simultaneous elimination of Me_3SiCl.[84]

Attempts to synthesize **159** ($^{31}P\{^1H\}$-NMR control) by reaction of **162** (dimeric **149**[85]) with $Re(CO)_5Cl$ lead instead to the ionic **163**.[84]



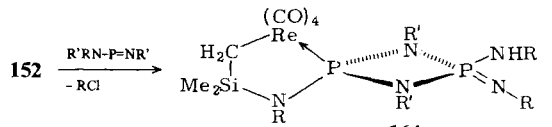
162



163

R = $SiMe_3$

A no less surprising reaction is the co-thermolysis of **152** with amino(imino)phosphanes.



164

R = R' = $SiMe_3$; R = $SiMe_3$, R' = CMe_3

The spirocycle **164** formed in this way is of structural interest for the novel linkage of the P–N–Re units and also for the formation of a Re–C bond, probably by oxidative addition of a $SiMe_3$ methyl group (cf. the iridium complex **87**[52c]). An approximately linear P=N–R unit has been established for **163** (173°) and **164** (168°) by X-ray structure determination.[84] Me_3SiN_3 oxidizes (dppe)Ni(η^2-R_2N–P=NR) **102** to **103**, X = $NSiMe_3$, which contains the aminobis(imino)phosphorane **149** side-on bonded to the metal via one of its phosphorus-nitrogen double bonds.[56]

5. Concluding Remarks and Outlook

The chemistry of complexes of multiply bonded systems of phosphorus, arsenic, antimony and bismuth with low coordination number has so developed, especially in the last few years, as to be a connecting link between main group and transition metal chemistry; notwithstanding its diversity, there are clearly many more important discoveries to be made. Ligands with triple or double bonds, analogous to alkyne, alkene, benzene, and diazene derivatives, can also display novel coordination modes and variants. The coordination sphere of transition metals allows the generation and stabilization of ligands such as PN, E_2 (E = P, As, Sb, Bi), P_6, As_5, HP=PH (the simplest diphosphene), PhAs=AsPh, RSb=SbR, RPCHPR (the diphosphorus analogue of the allyl group), insufficiently sterically protected trivalent phosphorus and arsenic compounds with coordination number 1 (E≡) and 2 (–E=) and pentavalent phosphorus of coordination number 3 (=P–); transition metal-phosphorus units of the type L_nM–P= and L_nM⇆P= can similarly be synthesized in stable form.

It is to be expected that new ligand systems and coordination types (cluster units) will be discovered and that our knowledge of the reactivity of the coordinated ligands will be extended. Studies of catalytic activity will certainly be worthwhile. Further valuable help for our understanding of the bonding involved in these compounds will be provided by the theoreticians.

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2,3-Dihydro-1,3-diborole-Metal Complexes with Activated C–H Bonds: Building Blocks for Multilayered Sandwich Compounds

By Walter Siebert*

Dedicated to Professor Max Schmidt on the occasion of his 60th birthday

Derivatives of 2,3-dihydro-1,3-diborole acting as four-electron ligands form various metal complexes in which the ring-methylene carbon atom is pentacoordinated. The resultant activation of the C–H bond can be used to prepare triple-decker to hexadecker sandwich complexes. Bis(2,3-dihydro-1,3-diborole)nickel complexes undergo a spontaneous stacking and formation of tricarbahexaboranyl oligodecker complexes with stacks of 2,3-dihydro-1,3-diborolylnickel. These findings finally led to the synthesis of the first polydecker sandwich complex which was obtained by vacuum thermolysis of a tris(allyl)(μ-2,3-dihydro-1,3-diborolyl)dinickel complex. The black polymer possesses remarkable semiconductor properties.

1. Introduction

In the last few years various papers dealing with the interaction between the C–H bonds of saturated (sp^3) and unsaturated (sp^2) carbon atoms and the metal atoms in complexes have appeared.[1] *Brookhart* and *Green* have suggested the term *agostic* to describe the three-center, two-electron bond (3c/2e) between a carbon, hydrogen, and metal atom (C–H→M). Such systems are characterized by longer C–H and M–H bonds, ^{1}H-NMR shifts to higher fields, and smaller ^{13}C-^{1}H coupling constants. For the formation of an agostic 3c/2e-bond it is necessary to create a complex with two valence electrons (VE) less, which can then electronically stabilize itself by an intramolecular C–H→M bond. As a result of an oxidative addition of the C–H bond to the metal atom, these interactions often lead to organometallic hydrides (C–M–H), which is usually observed in an intermolecular reaction.

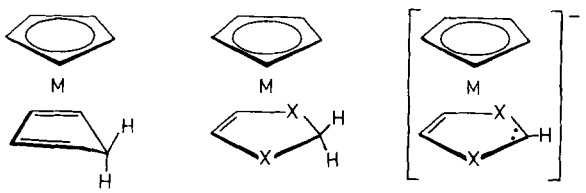
Recently, *Saillard* and *Hoffmann*[2] have analyzed the activation of the C–H bond of methane by transition metal complexes and metal surfaces in detail. This field of research has attracted broad interest regarding catalytic processes.[1,2] Not only spectroscopic and structural data

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but especially stoichiometric reactions involving the activated C–H bonds yield important information. Hence, we are interested in new kinds of sandwich complexes,[3] which contain a pentacoordinated carbon atom with at least one C–H bond in a terminal cyclic ligand and which are also expected to exhibit an enhanced reactivity.

Cobalt compounds of type **I** containing carbacyclic ligands are known to easily lose a hydrogen from the methylene moiety.[4] The axial C–H group exhibits a strong peak at $\approx 2750\ cm^{-1}$ in the IR-spectrum. However, no C–H→Co bond is involved, since the cobalt atom already possesses an 18 VE shell. In the analogous manganese compound (**I**) a C–H→Mn interaction is to be expected at lower temperatures.

Substituting the CH-groups adjacent to the methylene carbon atom in **I** by electron-deficient X atoms (see **II**) could (with M = cobalt) lead to a C–H→Co bond. Such postulated complexes based on the 18-VE rule should exhibit an increased CH-acidity and should be easily deprotonated to **III**.

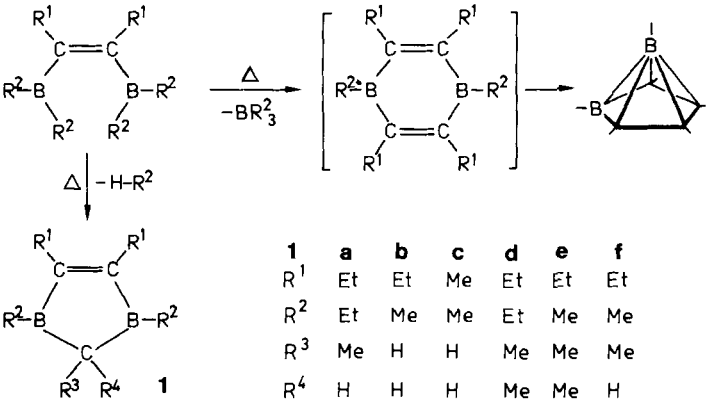


The first example of such a complex was obtained in the reaction of $(C_5H_5)Co(CO)_2$ with the 2,3-dihydro-1,3-diboroles **1**. In this report, iron, cobalt, nickel, rhodium, and platinum complexes will be described, which exhibit a preparatively widely used reactivity of the methylene bridge of the monofacially coordinated ligand **1**. However, instead of the expected 3c/2e interaction C–H→M,[5a] a new type of bonding system which will be introduced in Section 4, is observed.

This C–H-acidity as well as the donor/acceptor properties of complex-bonded **1** open the door to new compounds which in turn can serve as educts for the construction of many-layered sandwich complexes with stacked structures. One-dimensional polydecker complexes should possess anisotropic properties. Especially the electrical conductivity along the stacking axis is of theoretical[6] and practical interest. The preparative possibilities of the 2,3-dihydro-1,3-diborole-metal complexes become apparent when the isolobal principle[7] is applied. In the 18-VE complexes of **1** the heterocycle is isolobal with cyclopentadiene; thus, a new dimension of organometallic and complex chemistry can be developed.

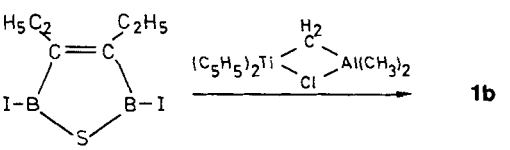
2. Synthesis of 2,3-Dihydro-1,3-diboroles

The heterocycle **1** was first prepared by *Binger*[8] in the thermal ring closure of hexaalkyl-*cis*-diborylethene with simultaneous elimination of alkane (Scheme 1). From the hexaethyl derivative, **1a** is obtained in 35–40% yield, while hexamethyldiborylethene yields, instead of **1c**, the permethylated 2,3,4,5-tetracarbahexaborane(6) practically quantitatively via the 1,4-diboracyclohexadiene. These and other rearrangements of organoboranes into carbaboranes have been studied by *Lipscomb* et al.[9] using PRDDO calculations.



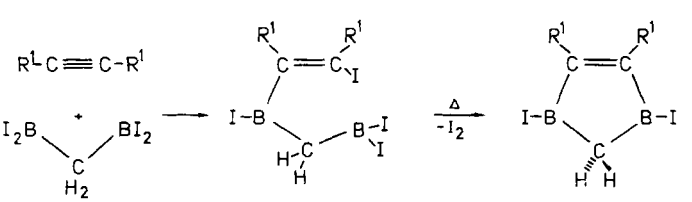
Scheme 1. Thermal ring closure of 3,4-bis(diethylboryl)-3-hexene to the heterocycle **1a** [8]. 2,3-Bis(dimethylboryl)-2-butene yields only the C_4B_2-carbaborane. The synthesis of **1b** and **1c** takes place according to Schemes 2 and 3, respectively, while **1d–f** can be prepared by methylating the complexed ligands **1a** or **1b** [3, 20].

The reaction of 3,4-diethyl-2,5-diiodo-2,5-dihydro-1,2,5-thiadiborole[10] with $(C_5H_5)_2Ti(Cl)CH_2Al(CH_3)_2$,[11] in which methylation and S/CH_2-exchange took place, led to a direct synthesis of **1b** (Scheme 2).[12] The disadvantage of this dihydro-diborole synthesis, besides the meager yield, is that it is limited to the 3,4-diethyl-2,5-diiodo-2,5-dihydro-1,2,5-thiadiborole, since the corresponding 3,4-dimethyl compound is difficult to synthesize.



Scheme 2. Synthesis of the heterocycle **1b** from 3,4-diethyl-2,5-diiodo-2,5-dihydro-1,2,5-thiadiborole and $(C_5H_5)_2Ti(Cl)CH_2Al(CH_3)_2$ [12].

The redox reaction between dialkylacetylenes and bis(diiodoboryl)methane[13] (Scheme 3) offers a new reaction pathway to the heterocycle **1**. Elimination of iodine and ring closure leads to formation of the corresponding diiodine derivative ($R^2 = I$) in 80% yield. Subsequent alky-



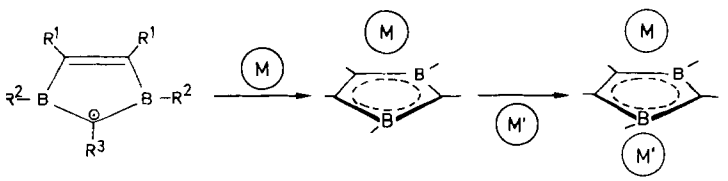
Scheme 3. Synthesis of 4,5-dialkyl-1,3-diiodo-2,3-dihydro-1,3-diborole derivatives using the redox reactions between dialkylalkynes and bis(diiodoboryl)methane [13]; **1c** and other derivatives by alkylation of the diiodine compounds with AlR_3.

lation using trialkylaluminum yields the air-sensitive organoboranes.

Attempts to synthesize penta- und hexaalkyl derivatives are presently being carried out. **1d** (**1f**) can be prepared in poor yields upon allowing the brown solution obtained from **1a** (**1b**) and potassium to react with methyl iodide.[14]

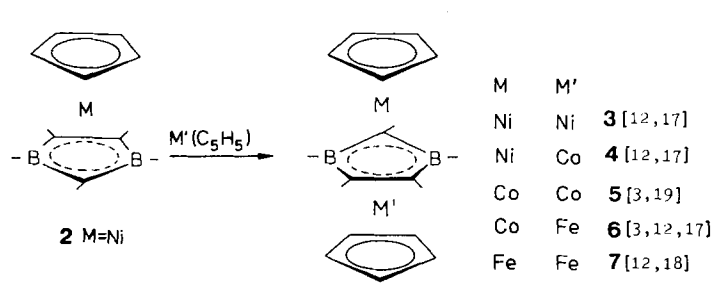
3. Donor/Acceptor Properties of 1

2,3-Dihydro-1,3-diboroles can act as three- or four-electron donors. Cleavage of a hydrogen atom from the methylene bridge leads to an intermediate 2,3-dihydro-1,3-diborolyl radical $(1-H)^{\odot}$, which can react with metal complex fragments mono- or bifacially as a 3e ligand to form mono- or dinuclear complexes[5] (Scheme 4).



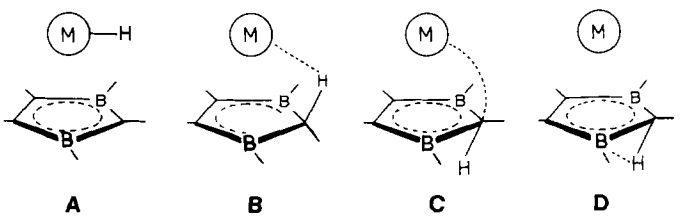
Scheme 4. Mono- and bifacial coordination of the 3e ligand 2,3-dihydro-1,3-diborolyl$(1-H)^{\odot}$ with metal-complex fragments.

The 15e fragments $Ni(C_5H_5)$ and $Co(CO)_3$ yield the 18 VE complexes **2**[15] and $(CO)_3Co(\mathbf{1a}-H)^{\odot}$,[16] in which the heterocycle acts as a 3e donor. The electron deficiency of the ligand is mainly compensated by the π-back bonding between occupied d-orbitals of the metal and acceptor orbitals of the C_2B_2C ligand. However, the remaining acceptor properties are often strong enough for a bifacial coordination of the ligand. With the complex fragments $Ni(C_5H_5)$ and $Co(C_5H_5)$ the Lewis-acidic nickel sandwich **2** (M = Ni) undergoes an almost quantitative stacking to the triple-decker sandwich complexes **3** and **4**, respectively (Scheme 5). The three-component reaction between **1a**, $[(C_5H_5)Fe(CO)_2]_2$ and $(C_5H_5)Co(CO)_2$ led to the triple-decker sandwich complex **6a** in poor yields, whereas **5a** is formed from $(C_5H_5)Co(CO)_2$ and **1a**.[17] It can thus be assumed that the mononuclear complex $(C_5H_5)Co(\mathbf{1a})$ is the primary product in the synthesis of **5a** and **6a**. Since $Co(C_5H_5)$ is a 14 VE fragment, **1a** should act as a 4e ligand in the complex if a C–H bond is involved in the bonding. For the latter, several possible structures (**B**–**D**) have been discussed.[3] In **A** a hydrogen atom has migrated to the metal, so that the ligand acts as a 3e donor as in the complexes **2** to **7**. Until now we have had no concrete evidence of the existence of hydride complexes;[3] however, recent results have identified a complex of type **A** as a labile primary product.[20] In the intact heterocycle **1**, the 3c/2e bonds could be present in **B**, M←H–C, in **C**, M←C–H, or in **D**, B←H–C. Type **B** represents an agostic interaction, while **C** represents a M←C–H bond between the axial C–H group and the metal; **D** represents a part of the 4c/4e bond made up of the 3c/2e bonds B←H–C and B–M–C (similar to the bridging bond in diborane). Each of these electronic interactions between the intact 2,3-dihydro-1,3-diborole **1** and the metal in **B**, **C**, and **D** is expected to activate the C–H bond.



M	M'	
Ni	Ni	**3** [12,17]
Ni	Co	**4** [12,17]
Co	Co	**5** [3,19]
Co	Fe	**6** [3,12,17]
Fe	Fe	**7** [12,18]

Scheme 5. Stacking of sandwich complexes (M = Ni, **2**; M = Co, Fe) with $M'(C_5H_5)$ complex fragments to give the triple-decker sandwich complexes **3**–**7** [3, 12].



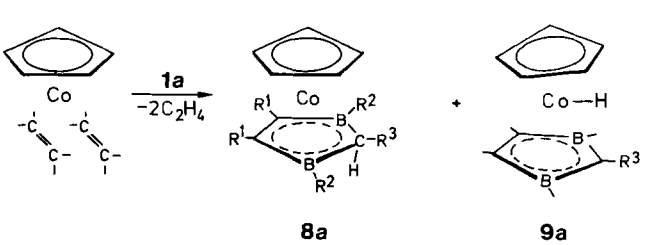
Scheme 6. Possible interactions between the ligand **1** and a metal-complex fragment with the formation of **A** (M–H bond), **B** (C–H→M bond), **C** (H–C→M bond), and **D** (C–H→B bond) [3].

4. Synthesis of 2,3-Dihydro-1,3-diborole-Metal Complexes

4.1. Cyclopentadienylcobalt Complexes

The photolytic reaction between $(C_5H_5)Co(CO)_2$ and **1a** leads to traces of the red, diamagnetic complex **8a**.[17b] The poor yield is related to the reactivity of the released carbon monoxide, which can insert itself into the B–C bond of **1a** (see Scheme 11). Rearrangement results in the formation of compounds with boron-oxygen bonds, which are no longer capable of bonding to the $Co(C_5H_5)$ fragment. The crystalline complexes **8** containing the ligands **1a**–**1c** and **1f** are obtained in up to 80% yields[3,22] using the *Jonas*-reagent[21] $(C_5H_5)Co(C_2H_4)_2$ (Scheme 7).

The side of the C=C double bond of **1a** that attacks the $Co(C_5H_5)$ fragment plays an important role in the synthesis of **8a**. If the methyl group of the methylene bridge faces the cobalt atom, **8a** is obtained. Otherwise, the yellow complex **9a** containing a Co-hydride bond [^{1}HNMR: $\delta = -10.6$ (Co–H)] is formed via a C–H→Co interaction. **9a** can only be isolated if the reaction mixture (20°C/1 h)

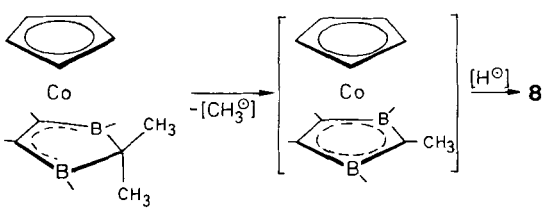


Scheme 7. Replacement of ethylene in $(C_5H_5)Co(C_2H_4)_2$ by **1a** with formation of the red complex **8a** [3, 22] and the yellow complex **9a** [20].

is quickly worked up (yields of **8a** : **9a** ≈ 4 : 1). At room temperature **9a** is transformed into **8a** by migration of the hydrogen atom from the cobalt to the axial position of the methylene carbon atom.[20]

The triple-decker **5b** and the tetradecker **41b** are formed as by-products in the preparation of **8b**.[3] This increased reactivity of **8b** with respect to stacking can be ascribed to the decreased shielding in the ligand **1b** compared to **1a**. A characteristic property of the cobalt sandwich complexes is the upfield ^{1}H-NMR shift of the axial proton at $\delta = -8.3$. The ^{11}B-NMR shifts ($\delta = 25$–30) indicate that the boron atoms are well shielded by the metal atom, which is not consistent with an agostic arrangement. A decrease in the ^{13}C-^{1}H coupling constant for the methylene carbon atom from 115 Hz in the free ligand **1a** to 81 Hz in the complex **8a** is observed in the ^{13}C-NMR spectrum. An unequivocal decision as to which of the possibilities **B**, **C** or **D** correctly describes the bonding situation cannot be made on the basis of these NMR data.

Reaction of the hexaalkyl derivatives **1d**,**e** with $(C_5H_5)Co(C_2H_4)_2$ yields the violet, wax-like complexes **10d**, **e**, which decompose to **8a**, **f** above 60 °C (Scheme 8). The blue 1,3-diphenyl-1,3-diborole complex is thermally more stable.[20] **9a** reacts with methyl iodide at 20 °C with formation of **10d**. Complex **10** probably contains a 16 VE configuration which does not involve a $H_2C{-}H \rightarrow Co$ bond. The much lower ^{11}B-NMR upfield shift ($\delta = 42$) strongly suggests that the interaction between metal and ligand must be weaker (see Section 6.1).

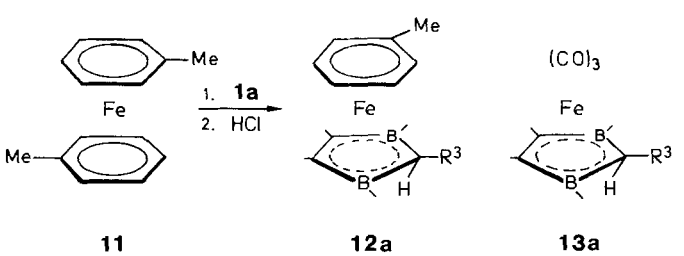


Scheme 8. Thermal conversion of the violet complex **10** into red **8** [3, 20].

4.2. Areneiron and Tricarbonyliron Complexes

To prepare arene(2,3-dihydro-1,3-diborole)iron complexes the reaction of bis(toluene)iron **11** with **1a** was investigated.[23] At first, a brown, impure product containing finely divided iron was obtained, which after treatment with hydrogen chloride yielded the red, crystalline sandwich complex **12a** (Scheme 9).

The ^{1}H-NMR spectrum of **12a**, like that of **8a**, exhibits a high-field quartet at $\delta = -8.6$ due to coupling between



Scheme 9. Synthesis of the iron sandwich complex **12a** from bis(toluene)iron **11** and **1a** [23].

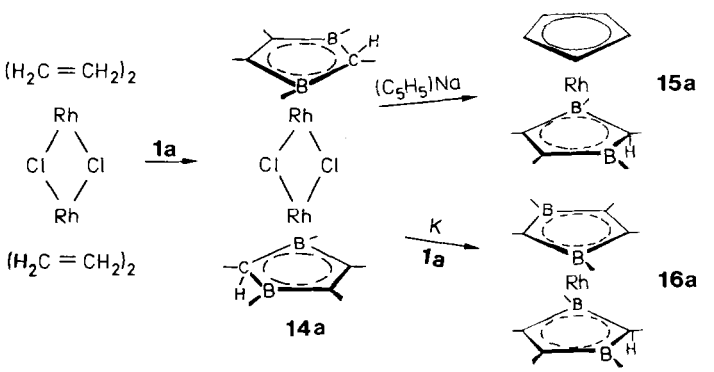
the proton of the pentacoordinated carbon atom and the methyl group.

The ^{11}B-NMR shift of $\delta = 24$ also suggests that the bonding relationships in **12a** and **8a** are similar. The corresponding toluene-iron complexes with the ligands **1b**, **c** could not be obtained, probably because of their increased reactivity.

The tricarbonyliron fragment, isolobal with arene-iron, reacts with **1a** to yield the yellow complex **13a**.[23] Due to CO-insertion into **1a** the reaction is not successful with $Fe(CO)_5$ or $Fe_2(CO)_9$ but with tricarbonylbis(π^2-cis-cyclooctene)iron.[24] The MS and NMR data provide strong proof for the structure of **13a**: the high-field quartet for the acidic proton appears at $\delta = -6.52$, the ^{11}B-NMR signal at $\delta = 26.6$. The compound decomposes above 60 °C; the corresponding complexes **13b**, **c** are no longer stable at 20 °C.

4.3. 2,3-Dihydro-1,3-diborole-Rhodium Complexes

The reactions of $(C_5H_5)Co(C_2H_4)_2$, $Ni(C_2H_4)_3$, and $Pt(C_2H_4)_3$ (see Section 4.4) with the ligands **1** have clearly demonstrated the advantage these reagents have over the carbonyl complexes. Thus, the analogous reactions with $[(C_2H_4)_2RhCl]_2$ were carried out to determine, among other things, whether diborolerhodium complexes with 16 VE are stable. The reaction with **1a** in THF results in the formation of the chloro-bridged dinuclear complex **14a** in 70% yield (Scheme 10). **14a** reacts with C_5H_5Na to yield the sandwich complex **15a**, which exhibits a high-field ^{1}H-NMR signal ($\delta = -6.9$) with a ^{103}Rh-^{1}H coupling constant of 7 Hz.[25] The new sandwich complex **16a**, in which for the first time both the 2,3-dihydro-1,3-diborole **1a** and the 2,3-dihydro-1,3-diborolyl $(\mathbf{1a} - H)^{\odot}$ are complexed, is formed in the reaction of **14a** with potassium in the presence of **1a**. In this 16 VE complex the high-field ^{1}H-NMR signal appears at −3.7 ppm with $^2J_{Rh-H} = 5$ Hz.

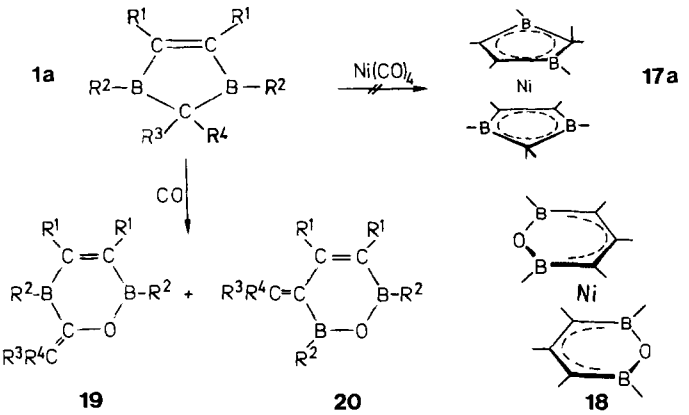


Scheme 10. Replacement of ethylene in $[(C_2H_4)_2RhCl]_2$ by **1a** with formation of the dinuclear complex **14a**, and its reaction with $(C_5H_5)Na$ or with potassium and **1a** to yield the sandwich complexes **15a** and **16a**, respectively [25].

4.4. 2,3-Dihydro-1,3-diborole-Nickel and -Platinum Complexes

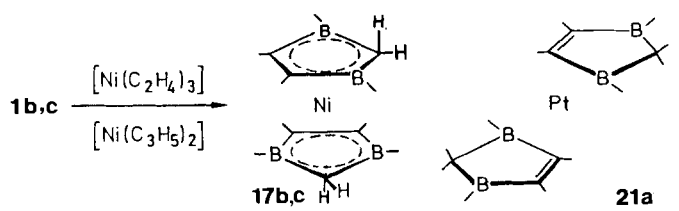
Reaction of **1a** with $Ni(CO)_4$ did not yield bis(diborole)nickel **17a**; instead the unusual bis(allyl)nickel com-

plex **18** (15% yield) was obtained, the constitution of which was proven by an X-ray structure analysis.[26] Carbon monoxide insertion into **1a**, rearrangement of the primary products to **19** and **20**, and the complexation of **20** to $Ni(CO)_4$ leads to the reddish-orange complex **18** (Scheme 11).



Scheme 11. Reaction of the heterocycle **1a** with CO to give **19** and **20**. Reaction of **20** with $Ni(CO)_4$ leads to formation of the bis(allyl)nickel complex **18** [26].

The reduction of $NiBr_2$ with $NaHBEt_3$ in the presence of **1a** led to the isolation of the yellowish-brown compound **17a**, whose ^{1}H-NMR spectrum showed that it is indeed a bis(diborole)nickel complex.[27] This synthetic route cannot be used to prepare **17b**, **c**. The latter, yellowish orange crystalline compounds can be obtained, however, by allowing the ligands **1b**, **c** to react with $Ni(C_2H_4)_3$ or $Ni(C_3H_5)_2$[27-29] (Scheme 12). The ^{1}H-NMR spectrum of **17c** exhibits a doublet for the axial proton ($\delta = -2.3$) and the equatorial C–H group. A *gauche*-arrangement of the rings is consistent with the ^{11}B-NMR chemical shifts of $\delta = 45.1$ and 39.4. The interaction between boron and nickel is weaker than that observed in the cobalt complexes **8**.



Scheme 12. Formation of the nickel sandwich complexes **17b**, **c** from **1b**, **c** and $Ni(C_2H_4)_3$ or $Ni(C_3H_5)_2$, resp. [28, 63].

The analogous platinum compounds **21** can only be prepared with **1a** and $Pt(C_2H_4)_3$.[19] **21a** exhibits a temperature-dependent ^{1}H-NMR spectrum; an increase in the ^{195}Pt-^{1}H coupling constants and upfield shift are observed with decreasing temperatures. These findings are in agreement with a dynamical sandwich arrangement.

5. Structure and Bonding

X-ray structure analyses were carried out in order to elucidate the bonding relationships in the Co-, Fe- and Ni-complexes **8a**, **12a** and **17c**. Figure 1 shows the result for the cobalt sandwich **8a**. Based on the position of the CH_3-group on C4, an agostic hydrogen atom in a C–H→Co bond can be ruled out. The hydrogen atom on C4 is located on the side of the ligand that faces away from the cobalt atom. A crystallographic mirror plane passes through the atoms Co, C4, C7, and C1. From the data available, it is not possible to decide whether the hydrogen atom H4 lies in the mirror plane and is involved in a H–C→Co bond or whether it is disordered and forms C–H→B bridging bonds. Several factors suggest that the latter possibility is more likely to be the correct one. As is to be expected the geometry about C4 of the 2,3-dihydro-1,3-diborole ring in the cobalt complex differs from that of the 2,3-dihydro-1,3-diborolyl ring in the nickel sandwich complex **2a**: C4–B5 (1.63 Å) is significantly longer than the corresponding bond in **2a** (1.55 Å).

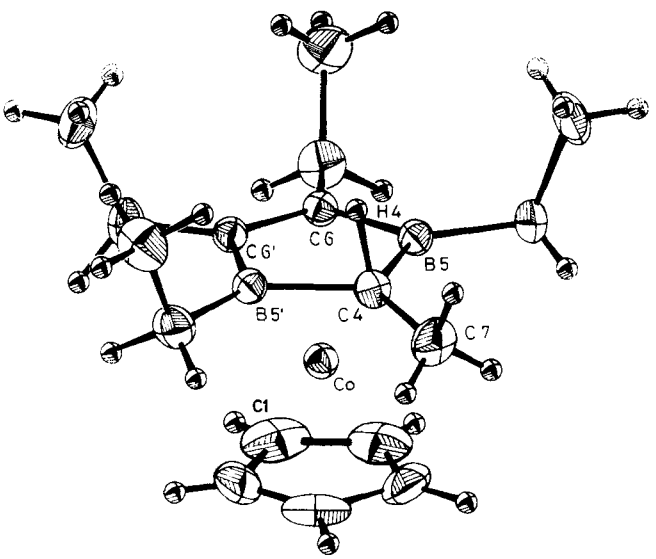


Fig. 1. Crystal structure of the cobalt sandwich complex **8a** [3, 22].

The iron sandwich complex **12a** exhibits a structure similar to that of **8a**, but without the uncertainty with respect to the position of the hydrogen atom caused by the mirror plane. As shown in Figure 2 the hydrogen atom H6 is dis-

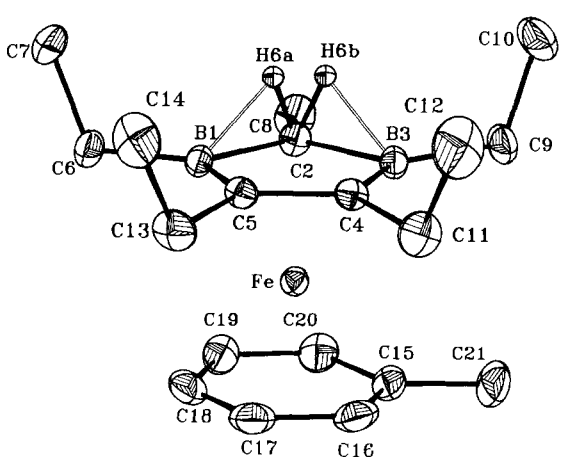


Fig. 2. Crystal structure of the iron sandwich complex **12a** [23, 30]. The axial hydrogen atom H6 at C2 is disordered (H6a, H6b) and forms asymmetric C–H→B bridging bonds (see Fig. 3).

ordered and occupies two independent positions above the plane of the ring, each of which allows an interaction with one of the two boron atoms. Assuming a disorder for H4 in the cobalt sandwich **8a**, both structures exhibit 3c/2e bonds (C–H→B).

The C–H and B–H bond lengths are 0.93 and 1.36 Å, respectively for **8a** and 1.13, 1.14 and 1.53, 1.51 Å, respectively, for **12a**. In order to locate H6 exactly, a neutron structure analysis was carried out for **12a**;[30] the data, however, did not allow a complete refinement of the structure. A combined structure refinement using the X-ray and neutron intensity data confirmed the result of the X-ray structure analysis. The positions of all of the hydrogen atoms were more reliable. The hydrogen atom is disordered and forms asymmetric C–H→B bridges to both boron atoms (Fig. 3).

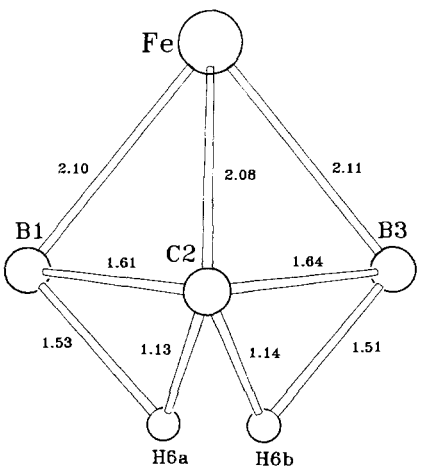


Fig. 3. Section of the structure of the iron sandwich complex **12a** (see Fig. 2). Bond lengths [Å].

The positions of the equatorial (H4) but not of the axial hydrogen atoms were located in an X-ray structure analysis of the nickel sandwich complex **17c** (Fig. 4). The *gauche*-confirmation of both rings as well as the NMR and MS spectra indicate that compounds **17** are nickel(0) complexes containing two 2,3-dihydro-1,3-diborole rings. It is assumed that complexes **17** also contain C–H→B bridges with 3c/2e bonds.

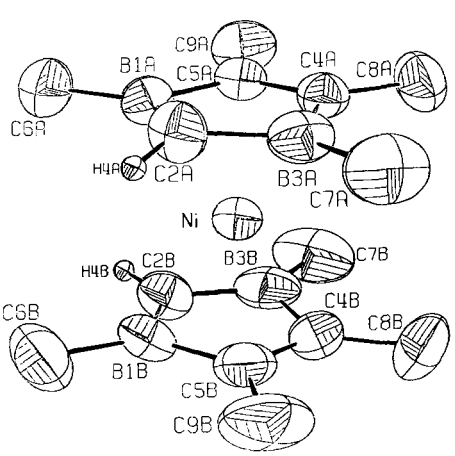


Fig. 4. Crystal structure of the nickel sandwich complex **17c**. The axial hydrogen atoms at C2A and C2B could not be located [29, 62].

Summarizing, one can say that the exact position of the methylene hydrogen atom in the above complexes, except for the iron sandwich complex **12a**, is uncertain. Based on the present data it is assumed that the axial hydrogen atom is involved in C–H→B bonding in each of the complexes.

Hoffmann and *Böhm*[3] have carried out MO-studies (EH and INDO) in order to find out more about the electronic source for the deformation of the ligand **1** in the sandwich complex **8**. Both methods predict a frontier orbital strongly localized at Co–C4–H4 (3c-bond) in the equilibrium geometry. This coupling between Co and C4 results in a weakening of the C4–H4 bond. The nature of the Co←C–H interaction is only slightly changed by the formation of a C–H→B bridge. The LCAO-amplitude is reduced at the carbon atom, while it is increased at the boron atom. The frontier orbital is the result of a linear combination of the $3d_{xz}/3d_{yz}$ of the metal and contributions from C, B and H. Both oligo-center interactions are closely related topologically, since Co and H4 are coupled with one another through fragment orbitals of the ligand.

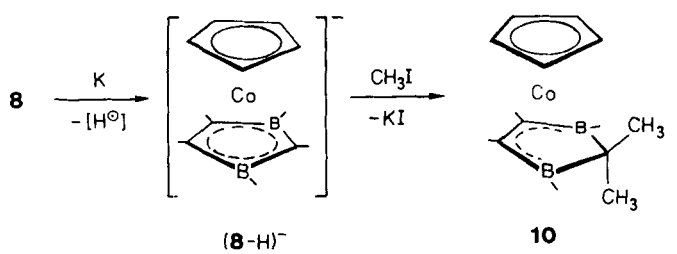
6. Reactivity of the Complexes

The pentacoordination of the methylene carbon atom and the C–H→B three-center bond in the complexes increase the acidity of the C–H bond, which can be taken advantage of preparatively. One can differentiate between two basic types of reactions: 1) formation of sandwich anions and their reaction with MX_2 or RX, and 2) direct reaction between metal complexes and different reagents. In the following sections, characteristic reactions of the cobalt, nickel, and platinum sandwich compounds shall be discussed.

6.1. Deprotonation

Deprotonation of **8** with potassium in THF yields a yellow, extremely air-sensitive anion,[3] in which the boron atoms are more strongly shielded ($\delta(^{11}B) = 19$). With methyl iodide, the violet complex **10d** is formed. Its ^{11}B-NMR signal is shifted 15 ppm downfield relative to **8a**. Hence, a non-parallel arrangement of both rings due to the steric influence of the second methyl group is assumed. Deuteration of the methyl groups confirmed the non-existance of a C–H→Co bond. Two CH_2D groups can be successively introduced into the deprotonated complex **8b**.[20] Due to D–H coupling, one of them appears as a triplet in the ^1H-NMR ($J = 1.8$ Hz, $\delta = 0.35$). The other gives an unresolved signal ($\delta = -0.14$) and can be assigned to the *exo*-position. An isotope effect cannot be observed in the chemical shifts of the bis(CH_2D)-complex. This finding is incompatible with an agostic hydrogen atom (Co←H–CHD). In contrast to the 18 VE complexes **8a**, **b**, the dimethyl derivatives **10d**, **e** can be reversibly reduced electrochemically at 1.38 V[31] (Scheme 13).

Reaction of the anion of **8c** with methyl iodide yields the yellow cobalt hydride **9f**, which can rearrange through a hydrogen shift to **8f**. The formation of **9f** affords evidence of an electrophilic attack at the methylene carbon

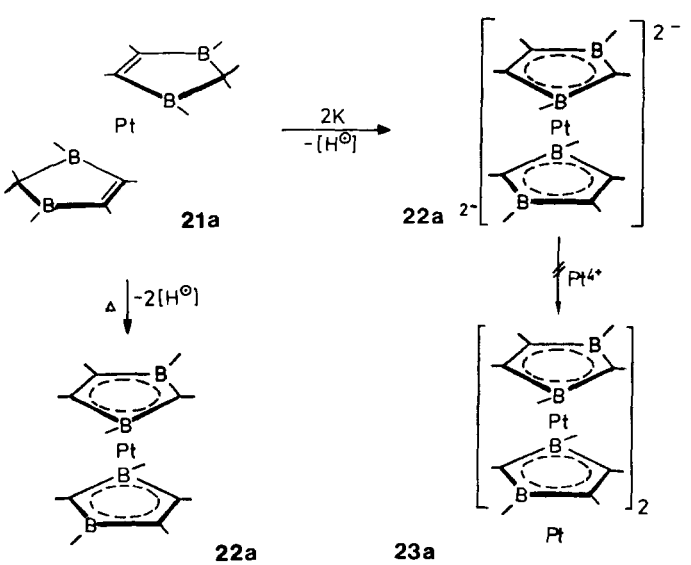


Scheme 13. Deprotonation of the sandwich complex **8** to give the anion $(8-H)^-$ and reaction of the latter with CH_3I to yield **10** [3, 20].

atom by CH_3I from the *exo*-position, since only an *exo*-attack yields **9f**.[20] The reactions of the potassium salts of **8a**, **b** with Me_3SiCl, designed to introduce the silyl group, were unsuccessful, although the formation of potassium chloride was always observed.[3] Since the starting materials **8** could always be recovered, it is most likely that the desired Me_3Si-derivatives of **8** decompose to the 17 VE sandwich radicals, which take up hydrogen atoms from the solvent to form the diamagnetic complexes **8**. An analogous reaction mechanism is assumed to explain the formation of **8a** from **10d**.[20]

The nickel sandwich complexes **17** react like **8** with potassium; however, definite salts or products from the subsequent reactions with methyl iodide could not be isolated. Attempts to eliminate hydrogen from the 18 VE complex **17a** did not yield a 16 VE sandwich complex. However, the postulated 16 VE complexes formed from **17b**, **c** react with the starting material with methylboranediyl abstraction to yield new carbaboranyl nickel complexes (see Section 6.6).[28]

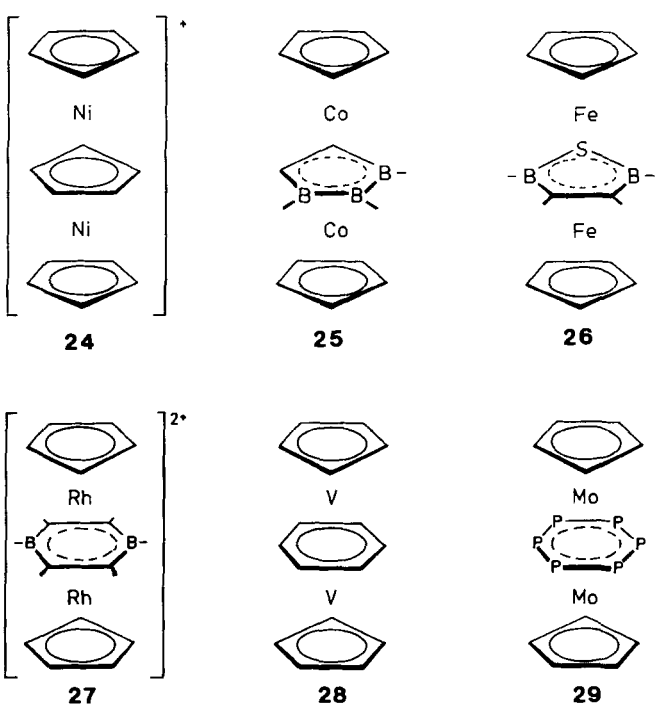
The platinum complex **21a**, the analogue to **17**, can be deprotonated with potassium to the dianion $\mathbf{22a}^{2-}$, whose ^{11}B-NMR signal is shifted 34 ppm upfield relative to **21a** ($\delta = 58$). However, the reaction of $\mathbf{22a}^{2-}$ with Pt^{4+} yields the sandwich complex **22a** instead of the tetradecker **23a**. This sandwich complex can also be directly obtained from **21a** through an elimination of hydrogen in refluxing benzene.[32] The transition from $\mathbf{22}^{2-}$ to **22** takes place via the radical anion $\mathbf{22}^{\odot -}$, which can be observed ESR spectroscopically (Scheme 14).



Scheme 14. Deprotonation of the platinum complex **21a** to the dianion $\mathbf{22a}^{2-}$ and the dehydrogenation of **21a** to the sandwich complex **22a** [19, 32].

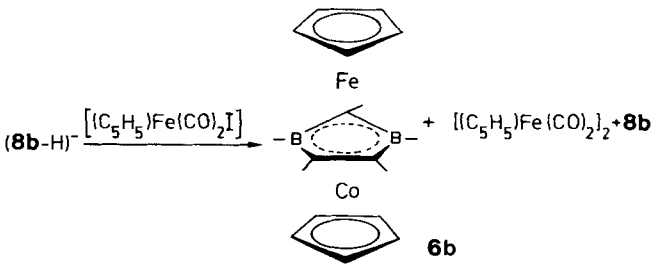
6.2. Formation of Dinuclear Complexes

1 always acts as a 3e donor when it is complexed bifacially. The triple-decker sandwich complexes **3**–**7** are obtained from **1** and the complex fragments $M(C_5H_5)$ (M = Fe, Co, Ni) possessing 13–15 VE. This first complete series with 33 to 29 VE exhibits the magnetic properties and structural changes predicted by the MO-scheme[33] in going from the diamagnetic complex **6** (30 VE) to the paramagnetic, dinickel complex **3** (33 VE). Reduction of the green complex **3** with potassium yields the red, diamagnetic anion $\mathbf{3}^-$, which is isoelectronic with the first triple-decker sandwich complex **24** obtained by *Werner* and *Salzer*.[34,35] The maximum number of valence electrons for triple-deckers is 34, while the optimal number corresponding to the 18 VE of mononuclear complexes is 30. Examples of this rule are **6**, the 1,2,3-triboracyclopentene complex **25** and its 1,2,4-isomer prepared by *Grimes* et al.,[36] the 2,5-dihydro-1,2,5-thiadiborole complex **26**,[37] and the μ-1,4-diboracyclohexadiene complex **27** described by *Herberich, Huttner* et al.[38] *Jonas, Krüger* et al.[39] have reported the first triple-decker containing C_6H_6 as a bridging ligand. According to the EH-MO calculations and PE-data this 26 VE dinuclear complex possesses four unpaired electrons.[40] Recently *Scherer* et al.[41] were successful in synthesizing the unusual 28 VE triple-decker sandwich complex **29**, in which the (in the free state nonexistent) hexaphosphabenzene P_6 acts as a π^6-arene (see p. 924ff).



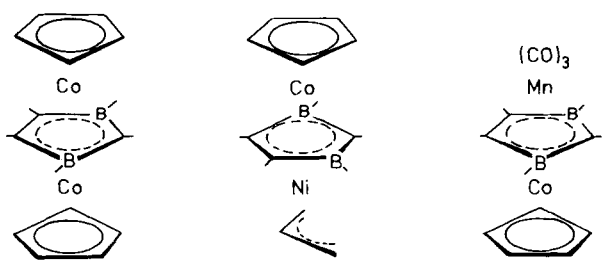
In order to synthesize triple-decker complexes one can use the cobalt sandwich **8** as well as its anion. In the reaction of the anion with $(C_5H_5)Fe(CO)_2I$ a redox reaction

takes place, in which very little **6b** besides **8b** (50%) is formed,[12] presumably because of steric hindrance of the $(C_5H_5)Fe(CO)_2$-group. The redox reaction mainly leads to the formation of $[(C_5H_5)Fe(CO)_2]_2$ (Scheme 15). In contrast, the reaction of $(\mathbf{8b}-H)^-$ with $FeCl_2$ in the presence of $C_5H_5^-$ affords **6b** in 68% yield.



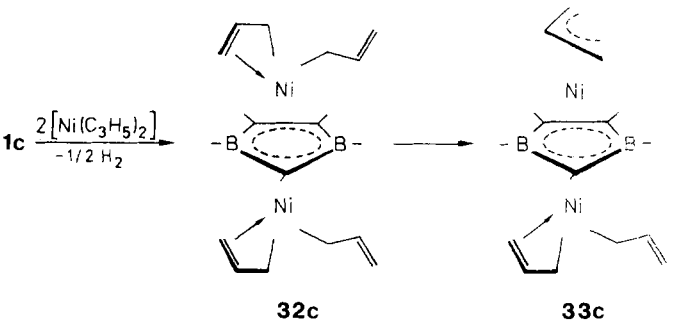
Scheme 15. Reaction of the anion $(\mathbf{8b}-H)^-$ with $(C_5H_5)Fe(CO)_2I$ to give the triple-decker sandwich complex **6b** [3].

Instead of using ions one can synthesize triple-deckers by letting **8** react directly with various complexes. At higher temperatures, however, the starting material **8** can react with itself to form the triple-decker **5** as well as the tetradecker sandwich complex **41** (cf. Scheme 18). **6b** (28%), the tetradecker **40b**, and ferrocene are obtained in the reaction of **8b** with $(C_5H_5)Fe(C_8H_{12})$[42]. The stacking of **8b** with $(C_5H_5)Co(C_2H_4)_2$, $Ni(C_3H_5)_2$, and $Mn_2(CO)_{10}$ to give the dinuclear complexes **5b**,[12] **30b**,[29,43] and **31b**[3] in yields of 54, 96, and 80%, respectively, takes place much more readily. Hence, the substitution of the axial hydrogen atom in **8** by the 13 VE complex fragments $Fe(C_5H_5)$, $Ni(C_3H_5)$, and $Mn(CO)_3$ leads to the diamagnetic 30 VE triple-deckers **6**, **30**, and **31**, respectively. The paramagnetic complexes **5** can be prepared using the 14 VE fragment $Co(C_5H_5)$. This proves that the sandwich **8a** is an intermediate in the reaction of $(C_5H_5)Co(CO)_2$ with **1a** to form **5a**.[12]



5 **30** **31**

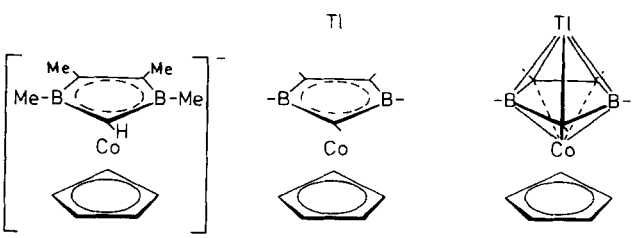
The ease of formation and the high reactivity of **30b** make this allyl triple-decker a valuable starting material[43] for oligodecker complexes. Another allyl complex with triple-decker structure is obtained in the low-temperature reaction of $Ni(C_3H_5)_2$ and **1b**, **c** in the ratio 2:1.[29] It is assumed that the initial product is the tetraallyl triple-decker **32b**, **c** (31 VE), which then eliminates an allyl group to yield the diamagnetic complex **33c** (Scheme 16). Its ^{1}H-NMR spectrum exhibits only two different types of allyl groups due to the rapid interconversion between η^1 and η^3 coordination. **33c** dissociates relatively easily. The liberated $Ni(C_3H_5)_2$ may be removed by vacuum and the remaining $(C_3H_5)Ni$(1,3-diborolyl) complex polymerizes by eliminating hexadiene (see Section 6.7).



Scheme 16. Synthesis of the tris(allyl)(μ-2,3-dihydro-1,3-diborolyl)dinickel complex **33c** from **1c** and bis(allyl)nickel [29].

Another class of dinuclear compounds is obtained in the stacking of a bifunctional acceptor sandwich with a $M(C_5H_5)$ fragment (see Section 6.3).

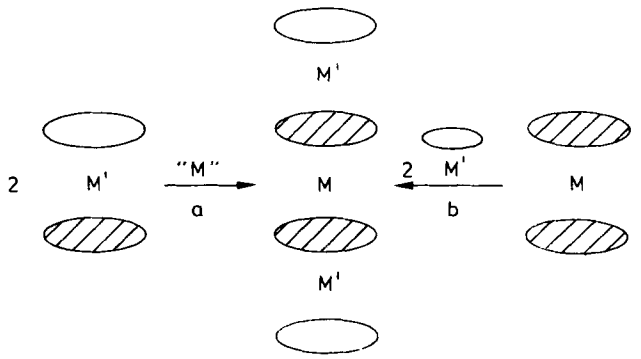
Since the potassium salts of **8** could not be characterized, the more stable Tl^I-compounds were investigated. **8c** reacts with $Tl(C_5H_5)$ to yield the dinuclear complex **34c**, which consists of a molecular unit both in solution and in the crystal.[44] Although $C_5H_5^-$ and the side of the heterocyclic ring of the anion $\mathbf{8c}^-$ are isolobal, **34c** does not exhibit the polymeric zig-zag structure of $Tl(C_5H_5)$.[45] Instead, it possesses a head-to-tail arrangement of the individual molecules without intermolecular contacts. The bonding in this complex with a capping Tl-atom is described by a seven membered *closo*-cluster according to *Wades'* rules.[46] The required $2n+2=16$ electrons for the framework are supplied by the carbon ($3\times3e$), boron ($2\times2e$), cobalt (2e) and thallium (1e) atoms.



6.3. Synthesis of Trinuclear Complexes

Sandwich complexes with acidic C–H bonds are suitable for the synthesis of tetradecker complexes.[47] In Scheme 17 route a describes the coupling of two sandwich units by a central metal and route b the stacking of a sandwich with two $M'(C_5H_5)$ complex fragments.

Within the series of triple-decker complexes, examples containing 26 and 28–34 VE are known; the family of tetradeckers should involve complexes with 36–46 VE. The maximum number is attained by combining two 18 VE sandwich complexes with a d^{10}-metal according to route a;

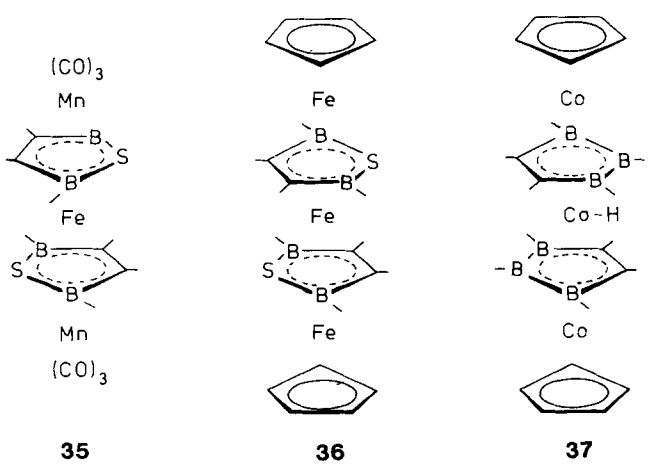


Scheme 17. Formation of tetradecker sandwich complexes by a) the reaction of two acceptor sandwich complexes with a metal and b) the stacking on both sides of an acceptor sandwich complex with M'(C_5H_5)-complex fragments [19, 58].

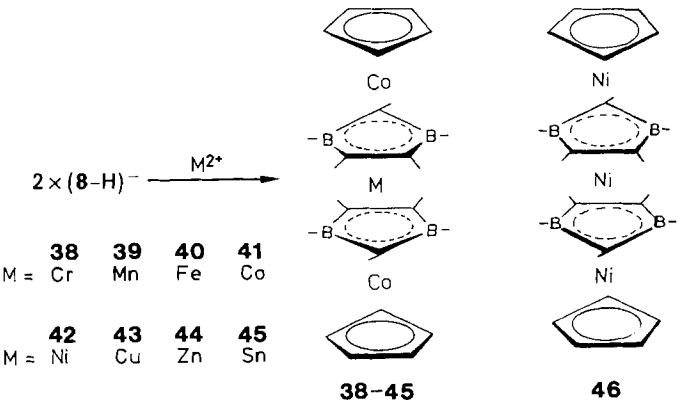
the optimum number of 42 is reached by formally inserting two 12 VE fragments (bridging ligand and metal) into the 18 VE complex ferrocene. Trinuclear complexes having 36 VE should contain beryllium or magnesium as the central metal.

Another way of determining the number of valence electrons is indicated in route b. A 16 VE sandwich with two potential acceptor ligands can be stacked on both sides with the 15 VE fragment Ni(C_5H_5) to yield a 46 VE complex. The analogous reaction with the 18 VE complex bis(2,5-dihydro-1,2,5-thiadiborole)nickel did not yield the 48 VE tetradecker [(C_5H_5)Ni(C_2B_2S)]$_2$Ni. Instead the 19 VE complex (C_5H_5)Ni(C_2B_2S) was obtained as a result of ligand exchange.[51]

The first two trinuclear complexes **35**[52a] and **36**[52b] whose structures have been determined, contain two 2,5-dihydro-1,2,5-thiadiborole ligands which act as 4e donors. While the tetradecker complex **35** is only obtained in poor yields, the tetradecker sandwich complex **36** can be prepared in several steps from [(C_5H_5)Fe(C_8H_{12})]$_2$Zn[42] in good yields. *Grimes*[48] reported a trinuclear complex **37**, in which the central cobalt atom carries a hydrogen atom. The complexes **35**-**37** all possess 42 VE.



As shown in Sections 6.1 and 6.2 the reactions of the anions of **8** with Me_3SiCl and (C_5H_5)Fe($CO)_2$I lead, if at all, to only poor yields of the desired products. The anions of **8** do, however, react with metal salts in high yields to give the corresponding tetradecker sandwich complexes **38**-**44**[3, 19, 53] (Scheme 18).



Scheme 18. Synthesis of the tetradecker sandwich complexes **38**-**45** by reaction of the deprotonated cobalt sandwich complex **8** with metal ions [19, 53].

In this manner, with the exception of the zinc complex **44**, paramagnetic complexes are obtained. The magnetic data of **38**-**41** are in agreement with high-spin configurations. The X-ray structure analyses of **38b**-**44b** have shown that the geometry of the Co-sandwich units is the same in all of the complexes and that the 2,3-dihydro-1,3-diborolyl rings are antiperiplanar.[3, 19, 53] The distances between metal and (C_2B_2C) correlate well with the *Shannon-Prewitt* ionic radii for octahedrally coordinated M^{2+} ions.[54] Two maxima as well as a minimum are observed for the central metals M = Mn, Zn and M = Ni, respectively. Each metal atom M is shifted (slip Δ) from a position above the centroid of the heterocyclic ring. This slip (Δ) takes place along the vector ring-centroid-C2 towards C2. Figure 5 shows the molecular structure of the CoCuCo te-

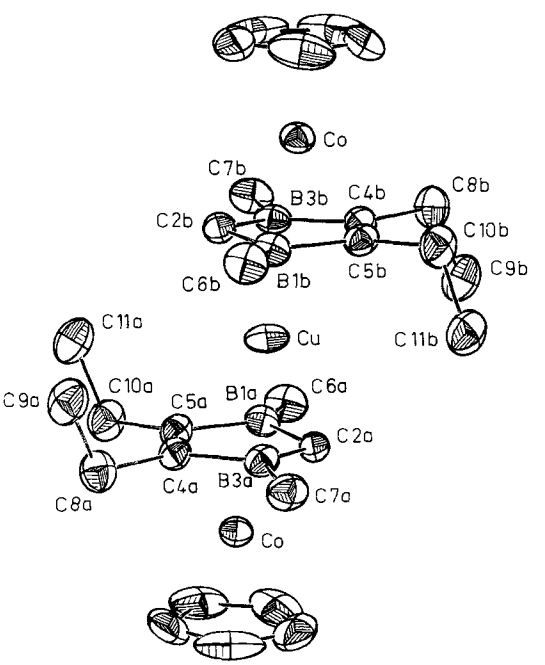


Fig. 5. Crystal structure of the tetradecker sandwich complex **43b** [19].

tradecker sandwich **43b**. The change in the structural parameters d, r and Δ for the complexes **38b**–**44b** as well as the ionic radii of the hexacoordinated metals Cr^{2+}–Zn^{2+} are shown in Figure 6. Electronic factors are primarily responsible for the slip.

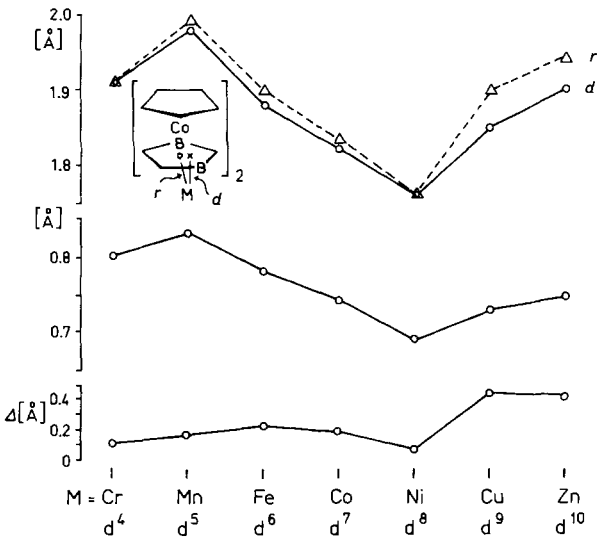


Fig. 6. Top: Distances (r,d) between central metal atom (M) and bridging ligand $(\mathbf{1b}-H)^-$ in the tetradecker sandwich complexes **38b**–**44b**. Middle: Ionic radii of high-spin M^{2+} ions. Bottom: Slip Δ as a function of the central metal in **38b**–**44b** [19].

The CoNiCo tetradecker **42a** was first obtained as a product of the reduction of the NiCo triple-decker **4a** with potassium.[53] It reacts further with potassium via the diamagnetic dianion (46 VE) to yield elemental nickel and the sandwich anion $(\mathbf{8a}-H)^-$. Reaction of $(\mathbf{8b}-H)^-$ with $SnCl_2$ leads to a stannocene analogue **45b** (Fig. 7), the first "bent" tetradecker sandwich complex with bending angles of 112 and 114°, respectively.[55] **45b** is also formed in the reaction of **8b** and stannocene with elimination of cyclopentadiene. This is again proof of the acidity of the axial hydrogen in **8b**.

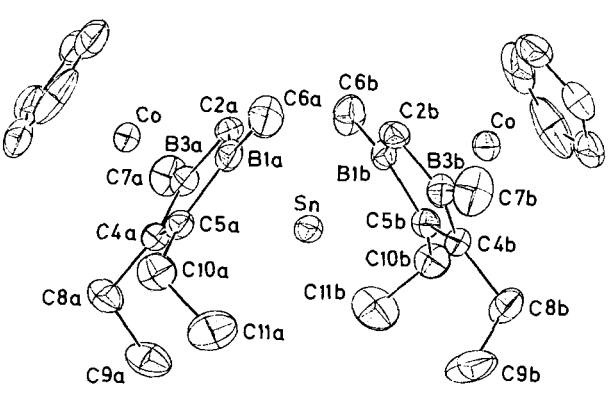
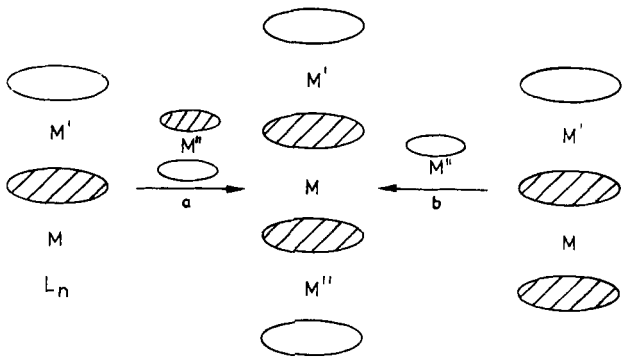


Fig. 7. Crystal structure of the bent tetradecker sandwich complex **45b** [55].

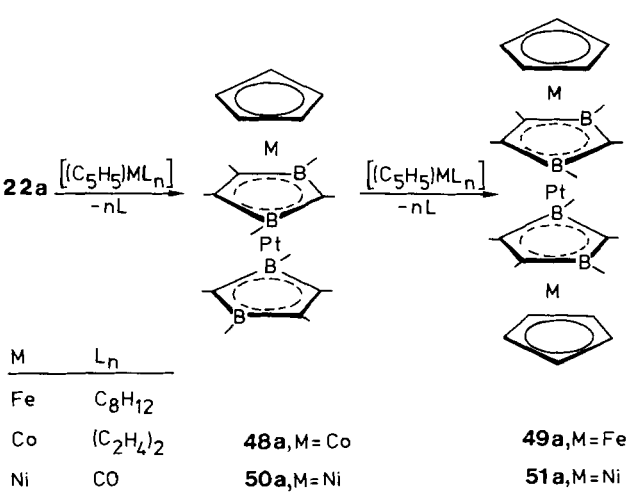
Diamagnetic 46 VE tetradecker complexes **46** containing three nickel atoms are obtained in the reaction of $NiBr_2$ with the anions of the nickel sandwich complexes **2a**,**b**, and in the reaction of **2b** with $[H_2AlOCMe_3]$.[56,57] The attempted preparation of a CoNiNi-tetradecker (**47**) from **53** met without success.[59]

The alternative synthetic route b (Scheme 17, 19) involves complexes with two acceptor ligands. With $M(C_5H_5)$ fragments these complexes can be stacked to give unsymmetric triple-deckers in the first step and then react further to give tetradeckers.



Scheme 19. Formation of tetradecker sandwich complexes by a) the reaction of a triple-decker with a sandwich complex and b) the stacking of a triple-decker sandwich complex with a cyclopentadienylmetal-complex fragment [19].

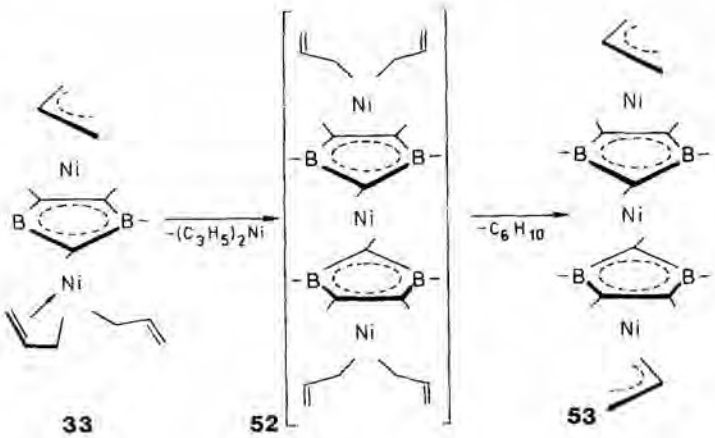
The platinum sandwich complex **22a**, formed upon elimination of hydrogen from the dihydro-complex **21a** and $(C_5H_5)Fe(C_8H_{12})$ yields the FePtFe tetradecker **49a**; the reaction with $(C_5H_5)Co(C_2H_4)_2$, however, stops at the unsymmetrical triple-decker stage (**48a**).[58] On the other hand, the triple-decker **50a** (31 VE) as well as the tetradecker **51a** can be isolated from the stacking reaction with $[(C_5H_5)Ni(CO)]_2$ (Scheme 20). The NMR spectra of the diamagnetic complexes **48a** (30 VE), **49a** (42 VE), and **51a** (46 VE) are indicative of highly symmetrical conformations or a free rotation of the ligands. The X-ray structure



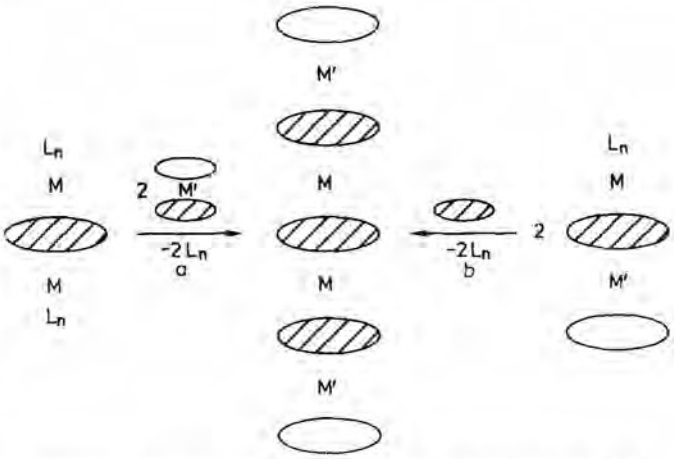
Scheme 20. Stacking of the platinum sandwich complex **22a**, obtained in the elimination of hydrogen from **21a**, with $M(C_5H_5)$-complex fragments to give the triple-decker sandwich complexes **48a** and **50a** and the tetradecker sandwich complexes **49a** and **51a** [58].

analyses of **48a** and **50a** show an antiperiplanar arrangement of the heterocycles, while the tetradeckers **49a** and **51a** are the first of their kind to exhibit synclinal conformations.[58]

Reaction of the allyl triple-decker **30** with the Co-sandwich complex **8** according to Scheme 19a represents another approach to the synthesis of trinuclear complexes. Elimination of propene leads to formation of the CoNiCo-tetradecker **42**.[59] The above-mentioned tetradecker sandwich complexes **38**–**44** with 40–46 VE each possess terminal C_5H_5 ligands, which do not allow a further stacking with complex fragments. The formal replacement of a cyclopentadienyl by an allyl ligand yields reactive complexes, which allow the synthesis of oligodecker complexes. Deeply colored products are obtained upon reaction of bis(allyl)nickel with **1** in refluxing toluene. The red tetradecker complex **53** can be isolated in 4–15% yield.[60] However, the main products are higher oligodeckers, which, although not yet separated, have been observed in the mass spectra.[29] They are probably formed via the tris(allyl) triple-decker **33** and the tetrakis(allyl) trinuclear complex **52**, which upon elimination of hexadiene leads to **53** (Scheme 21).

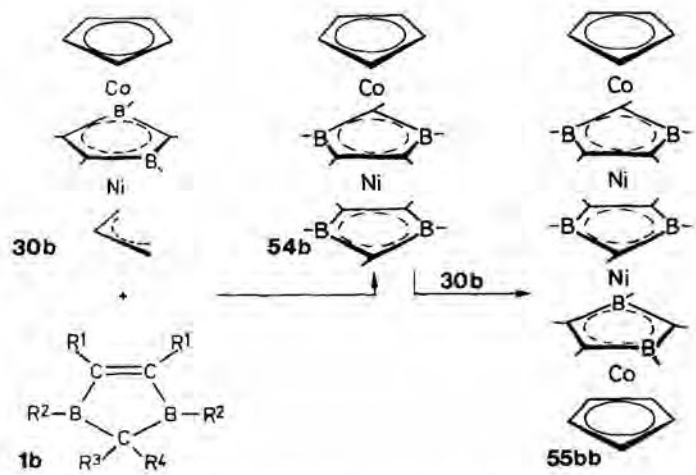


Scheme 21. Conversion of the dinickel complex **33** into the tetradecker complex **53** [29].



Scheme 22. Formation of pentadecker complexes by a) the reaction of a triple-decker with two sandwich complexes and b) the reaction of two triple-deckers with a heterocycle [29].

(Scheme 23). The main product of this reaction is the tetradecker **42b**.[29]



Scheme 23. Reaction of the heterocycle **1b** with the triple-decker **30b** to give the triple-decker sandwich complex **54b**, and the stacking of the latter with **30b** to the pentadecker complex **55bb** [29].

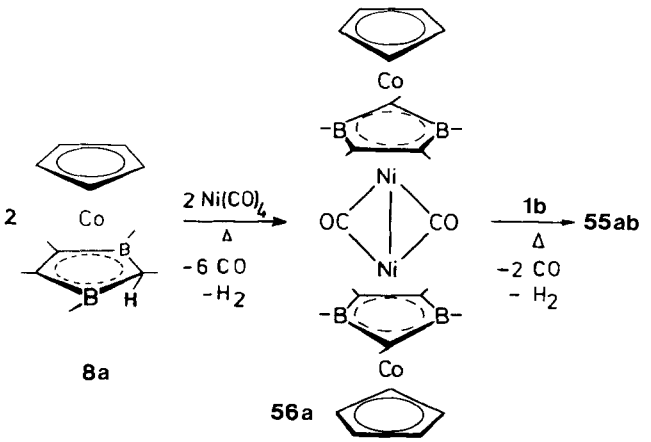
6.4. Synthesis of Tetranuclear Complexes

The above-mentioned reactions of the C–H-acidic sandwich complexes clearly demonstrate their synthetic potential. One of our goals is to use these compounds to prepare polydecker sandwich complexes, which are expected to exhibit interesting anisotropic properties. The pentadecker complexes (Scheme 22) are the first complexes in which a stack $M(C_2B_2C)$ has two analogous units as neighbors. The construction of such systems can take place via reactive triple-deckers according to route a or b (Scheme 22).

In the first step the unsymmetrical triple-decker **30b** reacts with the ligand **1b** to form triple-decker sandwich **54b**, which, in contrast to the analogous PtCo-compound **48a**, is still reactive and can further react with the starting material to yield the pentadecker sandwich complex **55bb**

The pentadecker **55ab** was first obtained in 45% yield upon reaction of the tetranuclear complex **56a** with the ligand **1b**.[61] At first, a cleavage of the carbonyl complex **56a** and formation of the unsymmetrical triple-decker **54ab**, which can be isolated in 7% yield, takes place. Stacking of **54ab** with the $(C_5H_5)Co(C_2B_2C)Ni$-fragment, formed in the elimination of CO from **56a**, then yields the pentadecker sandwich complex **55ab** containing the bridging ligand **1b** (Scheme 24).

The red-violet 57 VE complexes **55** are paramagnetic. They can be reduced with potassium to the diamagnetic anion **55**$^-$. The ^{1}H-NMR spectra of **55**$^-$ and the mixture **55/55**$^-$ behave almost completely analogous to those of the triple-decker pair **3/3**$^-$ (33/34 VE). However, the outer ligands (C_5H_5) of **55** remain almost unaffected by the paramagnetism. Proof of a pentadecker sandwich arrangement is given by the X-ray structure analysis of **55ab**, in which two neighboring C_2B_2C-ligands are *trans* to each



Scheme 24. Reaction of the sandwich complex **8a** with $Ni(CO)_4$ to give the tetranuclear complex **56a** and the reaction of the latter with **1b** to give the pentadecker sandwich complex **55ab** [61].

other while the third is rotated through approximately 70° (Scheme 23).[61]

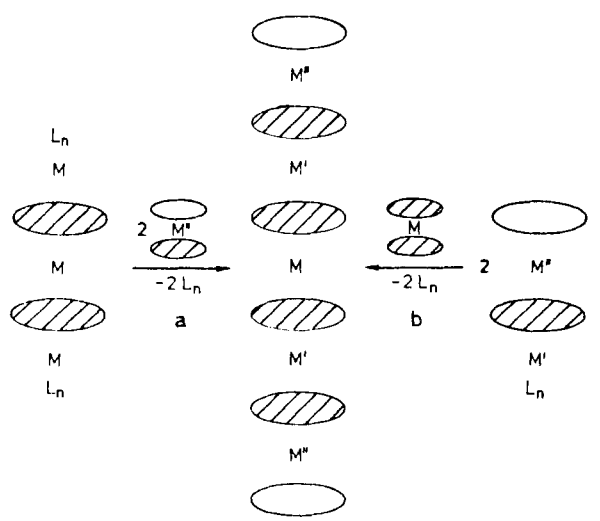
The formation of the carbonyl complex **56a** ($\nu_{CO} = 1852$ cm^{-1}) from **8a** and $Ni(CO)_4$ is another example of the isolobal analogy and chemical similarity between **8a** and cyclopentadiene. Formally, **56a** is the result of the insertion of the 12VE stack $Co(C_2B_2C)$ into the (C_5H_5)-Ni bond of $[(C_5H_5)Ni(CO)]_2$.

The steric influence of the ligand **1** plays an important role in the formation of **56**. With **1a** the synthesis of **56** is possible, while **1b** yields the CoNiCo-tetradecker **42b**.

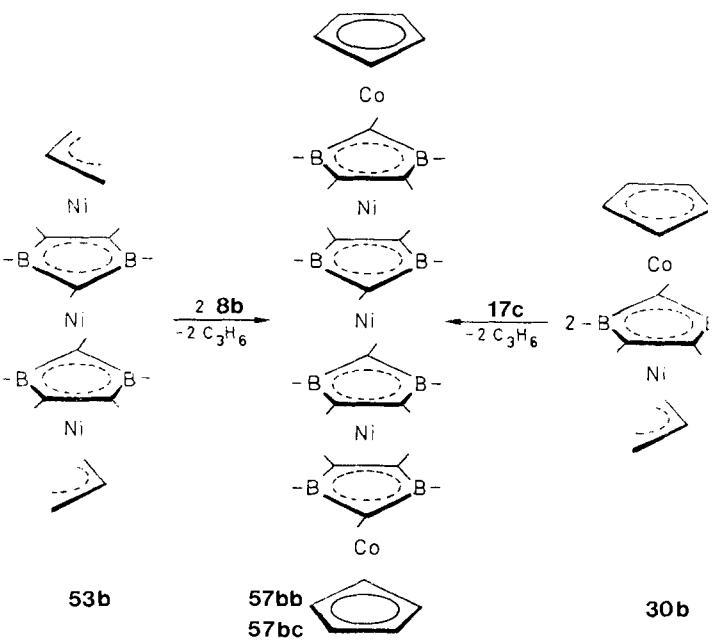
6.5. Synthesis of the First Hexadecker Complexes

With increasing stacking, not only do the number of synthetic routes that lead to oligodecker complexes increase (through the combination of mono-, di- and trinuclear complexes) but also the formation of side products. So far the two reaction pathways shown in Scheme 25 have been studied. The addition of a sandwich unit to both ends of a reactive tetradecker according to route a should be possible. Route b describes the synthesis of a pentanuclear complex in which a triple-decker fragment is added to both sides of a central sandwich unit. The combination of allyl complex building blocks with the C–H-acidic sandwich complexes **8** or **17** should take place with elimination of propene.

Reaction of the allyl tetradecker **53b** with the cobalt sandwich **8b** in refluxing mesitylene yields a mixture from which the red-violet hexadecker sandwich **57bb** can be isolated in 7% yield by column chromatography at −20°C (Scheme 26).[43] The paramagnetic triple- and tetradeckers **5b** and **41b** are by-products formed from **8b** at high temperatures. Furthermore, **42b** is the result of a coupling of **8b** with nickel. The diamagnetic 70 VE complex **57bb** sublimes at 200°C/10^{-5} torr. Its constitution was determined from MS and NMR data.



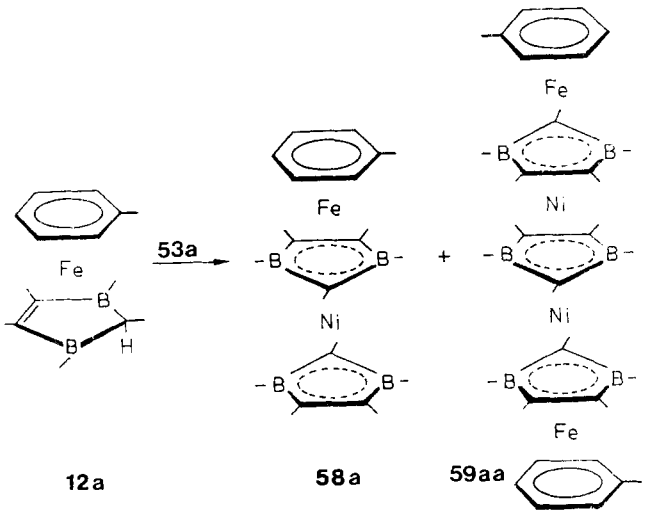
Scheme 25. Formation of hexadecker sandwich complexes by a) the reaction of a tetradecker with two sandwich complexes and b) the stacking of a sandwich complex with two triple-decker complexes [43].



Scheme 26. Synthesis of the hexadecker sandwich complexes **57bb** from the tetradecker **53b** and the sandwich complex **8b** as well as **57bc** from the triple-decker **30b** and the sandwich complex **17c** [43].

If the above reaction is carried out with **53a** and **8a**, the pentadecker **55aa** is obtained instead of the hexadecker. Similarly, reaction between the toluene-iron sandwich complex **12a** and **53a** stops at the triple-decker **58a** and pentadecker **59aa** stage[29] (Scheme 27). This indicates that the steric hindrance of the four ethyl groups in each ligand does not allow a fourfold stacking of **1a** with metal atoms.

A second route leading to a hexadecker involves twofold stacking of the bis(2,3-dihydro-1,3-diborole)nickel sandwich **17c** with the allyl triple-decker **30b** at 160°C. The main product (67%) is the green tetradecker **42b** formed by reaction of **30b** with itself. The hexadecker **57bc** containing two different ligands is obtained in 21% yield. Crystals

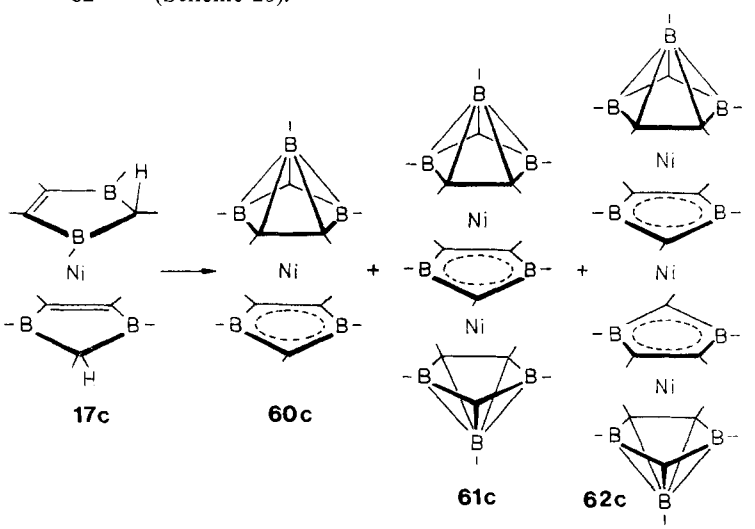


Scheme 27. Formation of the pentadecker sandwich complex **59aa** from the sandwich complex **12a** and the tetradecker **53a** [29].

of **57bb** and **57bc** that are suitable for X-ray structure analyses have not yet been grown[62].

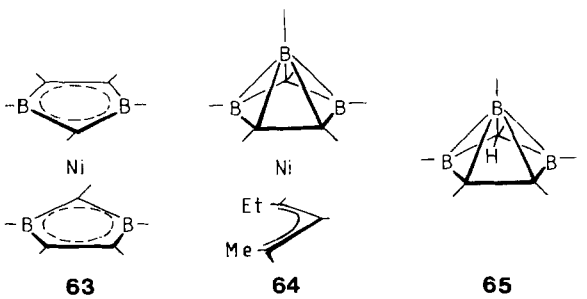
6.6. Carbaboranyl Sandwich Complexes

The bis(2,3-dihydro-1,3-diborole)nickel sandwich complexes **17b, c** already described in Section 4.4 are characterized by a remarkable reactivity. At room temperature they are slowly transformed into a series of carbaboranylnickel complexes, whose first three members are **60–62**[28,63] (Scheme 28).



Scheme 28. Conversion of the nickel sandwich complex **17c** into the carbaboranylnickel sandwich complex **60c** and the bis(carbaboranyl)nickel complexes **61c** and **62c** [28, 29].

This transformation probably takes place via the elimination of hydrogen from **17**. The resulting hypothetical 16 VE complex **63** (an analogue of the platinum complex **22**) immediately yields the 18 VE carbaboranyl sandwich complex **60** through the transfer of a methylboranediyl fragment. If a boranediyl fragment is abstracted from **17**, a boracyclobutenyl complex should be formed. Trace amounts of the η^3-allyl-η^5-carbaboranyl complex **64b**[57] were isolated from the transformation reaction of **17b**. This complex is probably the result of an elimination of both boranediyls as well as the methylene group from **63b** and the capping of the C_2B_2C-ring by a Me–B moiety. The η^3-allyl ligand must be formed from the diethylethylene portion of the complexed ligand **1b**. The formation of the new η^5-2,3,5-tricarbahexaboranyl ligand **65** – H in the complex is the first access to the *nido*-2,3,5-tricarbahexaborane(7) **65**, which has not, as yet, been isolated in the free state. Alkyl derivatives of the isomeric 2,3,4-tricarbahexaborane as well as tricarbonylmanganese complexes $[(\eta^5\text{-}C_3B_3H_4R_2)Mn(CO)_3]$ (R = H, CH_3) are known.[64]



The complexes **60** (reddish orange), **61** (green) and **62** (turquoise) are the electronic analogues of the (η^5-cyclopentadienyl)(η^5-2,3-dihydro-1,3-diborolyl)nickel complexes **2**, **3**, and **46** since the isolobal ligands $C_3B_3H_6^{\ominus}$ and $C_5H_5^{\ominus}$ each contribute five electrons to the complexation. A com-

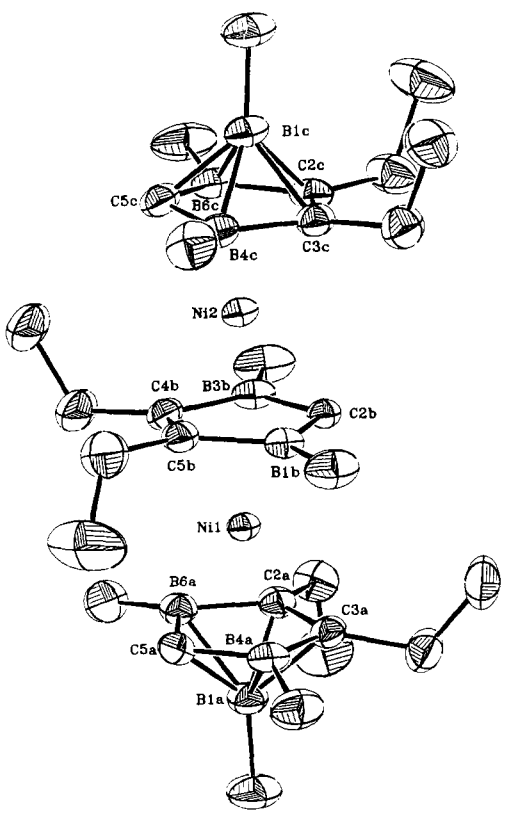
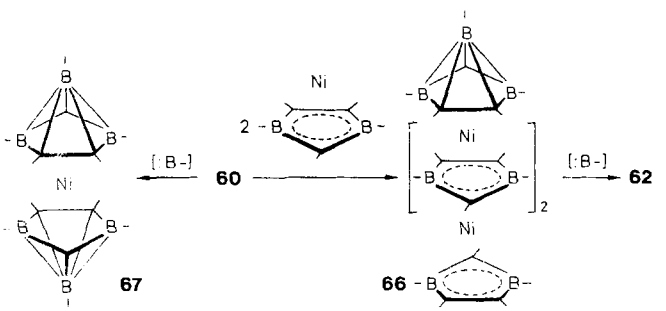


Fig. 8. Crystal structure of the bis(carbaboranyl) triple-decker **61b** [28].

parison of their physical and chemical properties as well as their spectroscopic data (color, stability, NMR, cyclovoltammetry) underline this analogy. The bond lengths and angles in the carbaboranyl sandwich **60b** are similar to those in the bis(carbaboranyl) triple-decker sandwich complex **61b** (Fig. 8). The planes passing through the central ring and the base of the carbaboranyl ligand (deviations ≤ 0.04 Å) are parallel. The nickel atoms are somewhat closer to the carbaboranyl rings than to the μ-ligand (1.69, 1.70 and 1.73, 1.74 Å, respectively). The structure and composition of the 46 VE trinuclear complex **62b** follow from the spectroscopic data.[63]

The formation of **62** can take place via the combination of two 18 VE complexes **60** with nickel or via the unsymmetrical carbaboranyl tetradecker **66**. The latter is capped by a methylboranediyl group to yield the bis(carbaboranyl) complex **62**. Two main reactions take place, of which the stacking of the 13 VE stack $Ni(C_2B_2C)$ must be faster than the capping with Me–B. Otherwise, only the formation of the complexes **60** and **61** is to be expected. It is interesting to note that the 18 VE complex is hardly capped to form the 20 VE complex **67** (Scheme 29); we only have MS evidence for **67b**.[31]



Scheme 29. Stacking of the carbaboranylnickel sandwich complex **60** with two (2,3-dihydro-1,3-diborolyl)nickel stacks to give **66**, the capping of the latter with methylboranediyl to give the bis(carbaboranyl)tetradecker sandwich complex **62** [29], and the capping of **60** to give **67** [31].

The stacking and capping reactions with **17c** take place with higher yields than with **17b**. After removal of **60c–62c** and the green bis(carbaboranyl) pentadecker complex, a dark-green residue is obtained. According to the EI-, FD- and FAB-mass spectra this residue contains oligomers up to and including the decadecker with differences in mass of 177 ($\triangleq {}^{58}Ni(C_3{}^{11}B_2Me_4H)$, stacking unit of the oligodeckers.[29,63]

6.7. Polydecker Sandwich Complexes

The synthesis of oligodecker complexes containing nickel atoms between the 2,3-dihydro-1,3-diborolyl ligands proves that the stacking unit $Ni(C_2B_2C)$ is a suitable building block for the construction of oligodeckers. Mass-spectral evidence of higher-molecular species formed in the synthesis of the bis(allyl) tetradeckers **53** also confirms this finding. The distillation residues contain oligodecker complexes with up to seven nickel atoms and six dihydrodiborolyl rings.[60,65] Furthermore, the isolation of the bis(carbaboranyl) complexes **61c** and **62c** as well as the mass-spectral evidence of pentadecker to decadecker complexes containing up to nine nickel atoms, eight dihydrodiborolyl ligands, and two terminal carbaboranyl groups, shows that these oligomers are formed under relatively mild conditions by a stacking of $Ni(C_2B_2C)$ units.

A single stacking unit contributes 13 VE ($d^{10}+\pi^3$) to the bonding, which in combination with the 5e ligands $C_5H_5^{\ominus}$ or $C_3B_3H_6^{\ominus}$ and an odd number of nickel atoms (for example n = 3: 46 VE, n = 5: 72 VE) yields the maximum number of valence electrons. 59 VE pentadecker complexes, which can be reduced to their diamagnetic anions, are formed with four nickel atoms and the ligands. In this connection it should be mentioned that the 13 VE stacking unit $Fe(C_5H_5)$ (Scheme 30) is completely unsuitable as a building block for polydecker complexes because of the weak acceptor properties of the bridging ligand and the high stability of ferrocene.



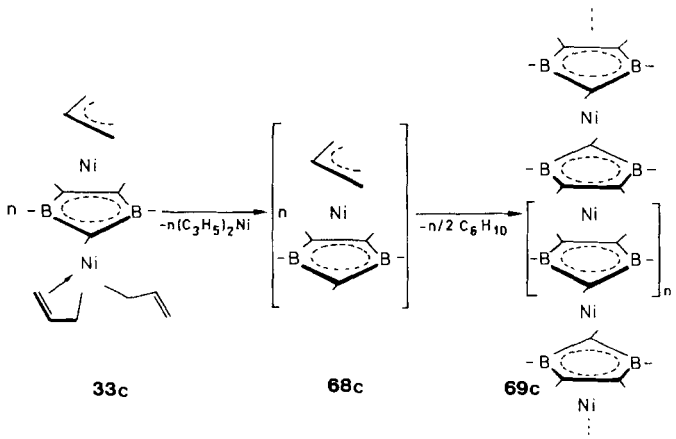
Scheme 30. 13 Valence-electron stacking unit (2,3-dihydro-1,3-diborolyl)nickel with donor properties of the metal and acceptor properties of the ligand. $Fe(C_5H_5)$ as a one-electron donor fragment.

Grimes et al.[36] were the first to predict that it should be possible to synthesize "multiple-decked stacked compounds" from metals and carbaborane rings $C_2B_3H_5$ (see **25**). Without a doubt the boron heterocycles[5,12,48–50,66] employed in the triple-decker sandwich complexes can also be used to synthesize oligodecker complexes.

The band structure of eleven one-dimensional polydecker sandwich compounds containing the metals Mn–Zn and different five-membered rings has been analyzed by *Böhm*[6] using a semi-empirical crystal-orbital method. Nine polydeckers contain 12 VE per stacking unit; two systems contain 14 VE. The 13 VE unit $Ni(C_2B_2C)$ described in this report is presently being studied.[67]

The yellowish brown tris(allyl) triple-decker **33c** was chosen as starting material for the synthesis of a $[Ni(C_3B_2)]_n$ polymer, since this complex already decomposes at room temperature with the elimination of bis(allyl)nickel and hexadiene to yield the bis(allyl) tetradecker **53c**.[29] The vacuum polycondensation of **33c** at temperatures > 120 °C produces bis(allyl)nickel, which is removed from the reaction zone, and the postulated η^3-allyl-η^5-diborolyl-nickel complex **68c** reacts with itself with elimination of allyl or secondary products to yield a black, film-like polymer **69c**. This product is characterized by an unusual thermal stability (Scheme 31).

The film cracks upon cooling and loosens itself from the sides of the glass. A C,H,B,Ni-analysis of the polymer yielded the empirical formula $C_7H_{13}B_2Ni$, which corresponds to a single stacking unit. The compound absorbs approximately two O_2 molecules per stacking unit.[68] Its



Scheme 31. Formation of the first polydecker sandwich complex **69c** from the tris(allyl)(μ-2,3-dihydro-1,3-diborolyl)dinickel triple-decker **33c** [29].

insolubility in inert organic solvents indicates a higher molecular arrangement. Mass spectral studies[69] up to 350°C have shown allyl to be the only fragment of any intensity. Solid-state ^{13}C- and ^{11}B-NMR studies show signals in the diamagnetic region although the polymer is paramagnetic.[76] Electrical conductivity measurements at 2500 bar using the two-point method[71,72] have yielded values of approximately 1 Siemen/cm, the four-point measurements[73] 10^{-2} S/cm. The observed temperature-dependency characterizes the polymer as a semiconductor. An EXAFS analysis supports a polydecker sandwich structure. However, two Ni–Ni and Ni–(C,B) distances (3.35, 3.8 Å and 2.17, 2.56 Å) indicate no regular stacking of $Ni(C_3B_2)$ units but most likely a Peierls distortion.[74]

7. Concluding Remarks

Thirteen years ago the first triple-decker sandwich complex opened up the field of classical sandwich chemistry towards "sky-scraper" molecules.[35] However, their predicted synthesis was not realized with carbacyclic bridging ligands. It was only the use of Lewis-acidic boron heterocycles that finally gave this field the necessary crucial impulses, which led to the synthesis of a wide range of oligodecker molecules using new synthetic strategies and theoretical models. Among the boron heterocycles the derivatives of 2,3-dihydro-1,3-diborole **1** described here occupy an exceptional position. On the one hand they can act as three-electron donors similar to an allyl ligand in the form of the 2,3-dihydro-1,3-diborolyls, while on the other they possess the necessary acceptor properties required to bind electron-rich metal atoms in a sandwich-like fashion with one another.

The previously introduced building blocks used to synthesize multilayered sandwich complexes contain the intact boron heterocycle **1** which acts as a four-electron donor. The synthetic potential of these compounds is based on the acidic C–H-bond of the ring-methylene group. We are convinced that the synthesis of oligodecker complexes containing more than six ligand planes is possible using C–H acidic triple-deckers. As already mentioned in this progress report, separation problems are often encountered. These difficulties are to be overcome with the help of middle pressure/low temperature chromatography.

The 2,3-dihydro-1,3-diborolyl metal complexes could someday attain practical significance as catalysts, as the recently published results of a 2,3-dihydro-1,3-diborolylcobalt complex-catalyzed pyridine synthesis by *Bönnemann* have shown.[75]

With the synthesis of the first polydecker sandwich complex, we have proven that the stacking of 2,3-dihydro-1,3-diborolylnickel units to a new type of semi-conducting polymer is possible. The optimization of the above-mentioned polycondensation as well as the introduction of other metals between the heterocyclic bridging ligands are the goals of further studies.

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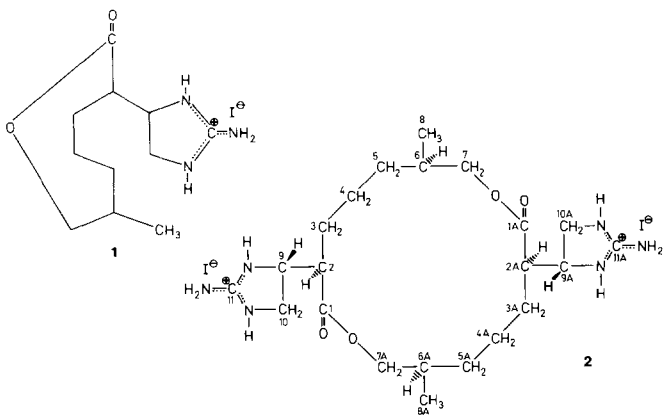
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The Revised Structure and Absolute Configuration of Chaksine**

By *Wolfgang Voelter,* Werner Winter, Viquar Uddin Ahmad,* and *Mohammad Usmanghani*

Dedicated to Professor Rolf Huisgen on the occasion of his 65th birthday

Chaksine was first isolated by *Siddiqui* and *Ahmad*[1] from the seeds of the plant *Cassia absus* (var. *Chaksa*) in 1935. Since then the natural product has been the subject of several structural[2] and pharmacological studies.[3] In 1958, Wiesner et al. proposed the monoterpenoid alkaloid structure **1** with an eight-membered lactone ring for chaksine iodide, which has been accepted till now.



1

2

For the isolation of chaksine, seeds of *Cassia absus* were extracted with ethanol and the extract was neutralized with aqueous ammonia, acidified with acetic acid, and evaporated under reduced pressure. The syrupy concentrate was suspended in distilled water and extracted successively with *n*-hexane, benzene, and ethyl acetate. The aqueous layer was acidified with dilute HCl, potassium iodide added, and the solution allowed to stand at +4°C. Chaksine iodide separated as a thick, whitish, crystalline mass, which was filtered, washed with 5% potassium iodide solution, ethanol, and acetone, and recrystallized from a mixture of ethanol and water (1 : 1).[4]

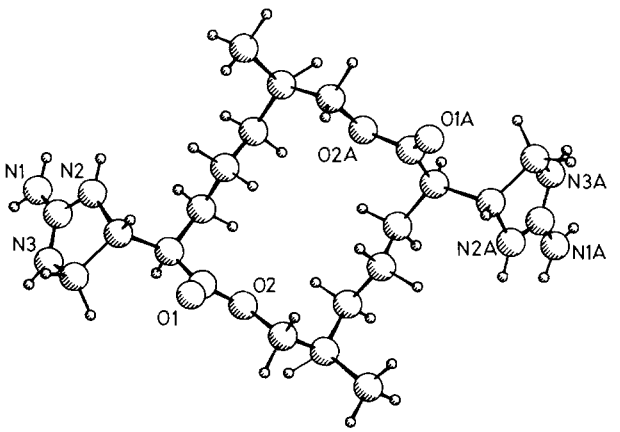


Fig. 1. Perspective view of the chaksine dication in **2** [5].

Although the elemental analysis and ^{1}H- and ^{13}C-NMR spectra were in agreement with the structure suggested by *Wiesner* et al.,[2] the field desorption mass spectrum, which showed a molecular ion of m/z 579, corresponding to the ionic species $(M^{2\oplus}I^{\ominus})^{\oplus}$, was not. This discrepancy prompted us to perform an X-ray crystallographic study. The results revealed that the structure of this alkaloid should be revised to **2**. Chaksine iodide consists of a 16-membered bislactone ring with two imino-imidazolidinyl groups at C-2 and C-2A, which form hydrogen bonds to both iodide anions. The molecule has a crystallographically imposed C_2 symmetry with *R,R,R* configuration at C-2, C-6, and C-9 as well as C-2A, C-6A, and C-9A.

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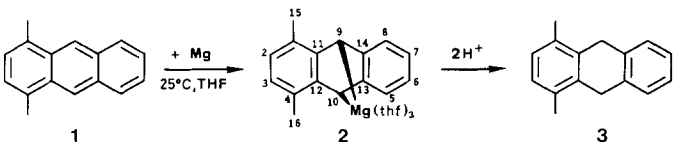
[1] S. Siddiqui, Z. Ahmad, *Indian Acad. Sci. 2* (1935) 421.
[2] K. Wiesner, Z. Valenta, B. S. Hurlbert, F. Bickelhaupt, L. R. Fowler, *J. Am. Chem. Soc. 80* (1958) 1521, 6701; L. R. Fowler, Z. Valenta, K. Wiesner, *Chem. Ind. (London) 1962*, 95.
[3] M. Haque, *Medicus 3* (1952) 195; A. Qayum, K. Khanum, M. Ahmad, S. Babar, *Pakistan J. Sci. Ind. Res. 12* (1970) 378.
[4] TLC (plates 60 F 254, Merck, 1-butanol/acetic acid/water, 3 : 1 : 1), $R_f = 0.4$; m.p. = 168°C; $[\alpha]_D = 38.05$ ($c = 1.5$, MeOH); IR (KBr): $\nu = 3340$ (NH, NH_2), 2960, 2930, 2920, 2840, 1720 (C=O), 1670, 1600, 1570, 1385, 1275, 1140, 980, 780, 760 cm^{-1}.
[5] $a = 18.406(7)$, $b = 5.194(3)$, $c = 17.239(3)$ Å, $\beta = 118.9(2)°$; C2, $Z = 2$. The structure was solved from low-temperature diffractometer data at −60°C (2349 reflections $I > 1\sigma(I)$, Nonius CAD4, $Mo_{K\alpha}$ radiation, graphite monochromator), using the heavy atom method, and refined to $R = 0.057$. The absolute configuration was derived from the Hamilton ratio at a probability level ≫ 99.5%. Further details of the crystal structure investigation are available on request from the Fachinformationszentrum Energie, Physik, Mathematik GmbH, D-7514 Eggenstein-Leopoldshafen 2, on quoting the depository number CSD-51556, the names of the authors, and the journal citation.

Synthesis and Structure of 1,4-Dimethylanthracenemagnesium·3thf and μ-Trichlorodimagnesium·6thf(1+) Anthracenide

By *Borislav Bogdanović,* Nikolaus Janke, Carl Krüger, Richard Mynott, Klaus Schlichte,* and *Uwe Westeppe*

Magnesium-anthracene systems are of interest owing to their catalytic properties.[1] We report here the synthesis, chemical and spectroscopic characterization, and crystal structure of 1,4-dimethylanthracenemagnesium·3thf **2** and of μ-trichlorodimagnesium·6thf(1+) anthracenide **6** (thf = tetrahydrofuran).

2 is prepared analogously to anthracenemagnesium·3thf[1c,2] **5**, from 1,4-dimethylanthracene **1** and magnesium in THF. Protolysis of the orange solid affords solely 1,4-dimethyl-9,10-dihydroanthracene **3**, along with THF and traces of **1**.



1 2 3

In the ^{13}C-NMR spectrum of **2**, eight signals are observed in addition to those of **3**; on the basis of their multiplet structure and relative intensities in the proton-coupled spectrum, they could be assigned to the 1,4-dimethylanthracene skeleton.[2] A detailed analysis of the ^{13}C-NMR spectrum of the analogous **5** has already been presented.[1c] Comparison of the NMR data of **2** with that of **5** shows that the methyl groups on the aromatic ring cause only small changes in the chemical shifts of C1/C4 and C11/C12. As in the case of **5**, the largest interaction of magnesium occurs with the carbon atoms C9 and C10 of the anthracene skeleton ($\delta = 54.1$, $^1J_{CH} = 137.3$ Hz). The signals for C9/C10 in the spectrum of **2** are shifted slightly to higher field ($\Delta\delta = 3.6$) compared with those of **5** on account of the γ-methyl groups. The corresponding coupling constants $^1J_{C\text{-}9,H}$ are the same in both spectra within the limits of detection and indicate the rehybridization of this carbon atom from sp^2 toward sp^3.

In contrast to **5**, compound **2** is sufficiently soluble in THF to obtain single crystals for an X-ray structure determination.[3] In the crystal, a monomeric structure is present, which was suggested earlier[1c] on the basis of nuclear magnetic resonance data for **5** (Fig. 1). Three coordination sites of the pentacoordinated magnesium are occupied by oxygen atoms of the THF molecules. The two independent molecules differ mainly in a slightly different folding of the solvate molecules. The geometries of the two independent anthracene moieties are identical, however, within the experimental accuracy. The folding angle of the two halves of the anthracene along the C9–C10 line has a mean value of 40.95°; the C9–Mg–C10 angle in the bicyclic metallacycle is 72.6°. The metal-carbon distances in this system were determined to be 2.32 Å (average). The structure of **2** and that of 9,10-bis(trimethylsilyl)anthracenemagnesium·3thf,[4] which exhibits the same structural features, suggest that **5**, with similar structural elements, is also present as a monomer, taking into consideration the nearly identical ^{13}C-NMR spectra.

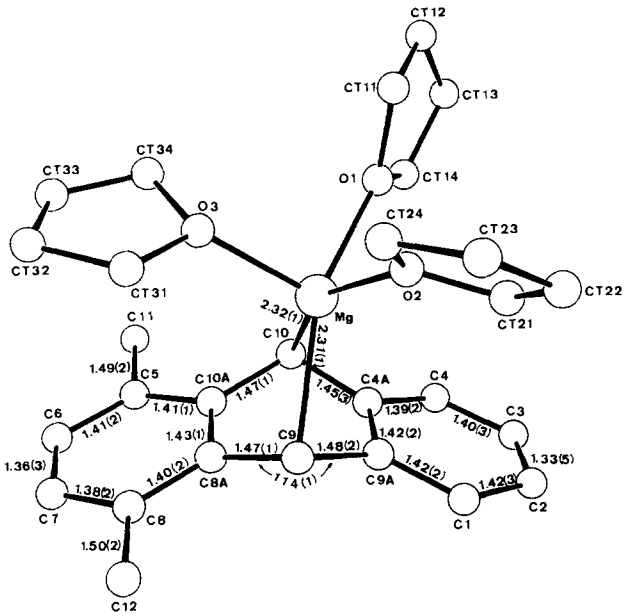
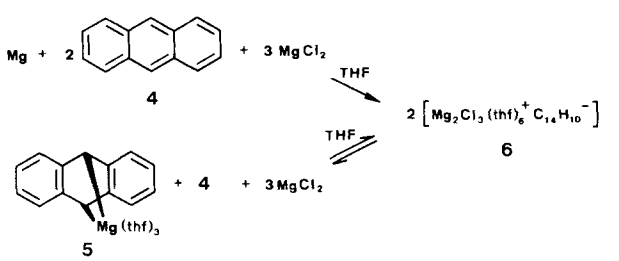


Fig. 1. Crystal structure of **2** (averaged over two independent molecules). Distances [Å], angles [°]. $P2_1/c$; $a = 8.090(1)$, $b = 21.301(4)$, $c = 29.992(5)$ Å, $\beta = 92.21(1)°$, $V = 5164.42$ Å^3, $Z = 8$, $\rho_{calcd} = 1.15$ gcm^{-3}, $\lambda = 0.71069$ Å, $\mu = 0.89$ cm^{-1}, $R = 0.088$, $R_w = 0.087$, 2632 observed reflections ($I \geq 2\sigma(I)$), 9046 unobserved reflections; 577 refined parameters [10].

The catalytic synthesis of magnesium hydride[1a] is improved by addition of $MgCl_2$.[5,6] For this reason, we studied the reaction of magnesium with anthracene **4** in THF in the presence of $MgCl_2$. The reaction, carried out in a solution saturated with $MgCl_2$, results in dark blue solutions, from which **6** separates out as a blue precipitate. **6** is also obtainable from **5** and **4** in the same solvent.[7]



4 6 5

UV and ESR spectroscopy show that anthracene radical anions are present in **6**. Hydrolysis of **6** results in disproportionation and the formation of a 1:1 mixture of **4** and 9,10-dihydroanthracene. **6** is present in equilibrium with **4** and **5**, the position of which is dependent on both the temperature and the concentration of $MgCl_2$.[5a] Accordingly, the Lewis acid $MgCl_2$ favors, at room temperature, the electron transfer from the dianion to **4**. Of interest is the elucidation of the structure of **6** and the comparison of its structure with that of **2** (Fig. 1) as well as with 9,10-bis(trimethylsilyl)anthracenemagnesium,[4] in which magnesium intramolecularly bridges the 9- and 10-positions of the anthracene skeleton. Crystals for a high-resolution structure determination[8] of **6** could be obtained by crystallization from a $MgCl_2$-saturated solution of **6**. In the crystal lattice,

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6 is present as distinct ions; a twofold axis of symmetry (as required by the space group) intersects a $Mg_2(thf)_6$ structural unit bridged by three chlorine atoms,[9] while the anthracene skeleton is characterized by a center of inversion (Fig. 2).

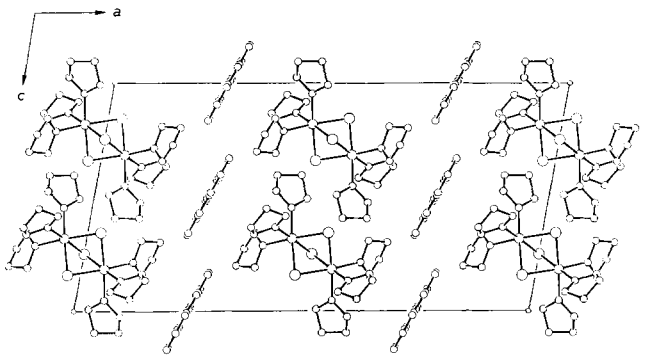


Fig. 2. Packing of **6** in the crystal lattice. C2/c, $a=28.212(3)$, $b=9.947(1)$, $c=14.520(3)$ Å, $\beta=100.043(9)°$, $Z=4$, $T=-173°C$, $\rho_{calcd}=1.27$ gcm^{-3}, $\lambda=0.71069$ Å, $\mu=2.99$ cm^{-1} (analytical absorption correction), $\theta_{max}=36°$, 44049 measured reflections, averaged to 6213 observed reflections ($R_{av}=0.027$), ($I\geq 2\sigma(I)$), 2301 unobserved reflections, 337 refined parameters, $R=0.039$, $R_w=0.039$, $R_{HO}=0.027$, $\sin\theta/\lambda\geq 0.65$ Å^{-1} [10].

Both the bond lengths and the electron deformation density (EDD) (Fig. 3) of the skeleton of the radical anion of anthracene, which, in this case, is present in a lattice as a distinct species for the first time, show unequivocally that in **6** the LUMO of anthracene is occupied by one electron. Thus, the C2–C3 (C6–C7) bonds are shortened by 0.02 Å, the EDD in this region being increased, whereas the C1–C2 and C3–C4 bonds are lengthened by 0.02 Å with decrease in the EDD. No changes were observed for the central C4A–C9A bond.

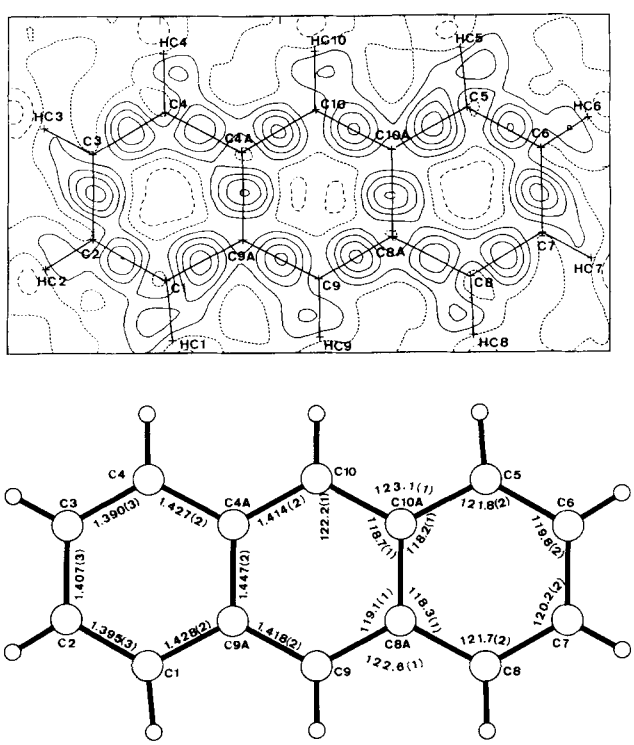
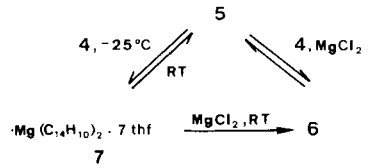


Fig. 3. EDD in the skeleton of the radical anion of **6** as well as the corresponding bond lengths.



Even in the absence of $MgCl_2$, **5** can transfer an electron to **4** in THF at −30°C. The insoluble magnesium bis(anthracenide)·7thf **7** is formed, which, after addition of $MgCl_2$ at room temperature (RT), affords **6**.

Compounds **5**, **6**, and **7** can accordingly be converted into one another.[5a]

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[1] B. Bogdanović, S. Liao, M. Schwickardi, P. Sikorsky, B. Spliethoff, *Angew. Chem. 92* (1980) 845; *Angew. Chem. Int. Ed. Engl. 19* (1980) 818; b) H. Bönnemann, B. Bogdanović, R. Brinkmann, D.-W. He, B. Spliethoff, *ibid. 95* (1983) 749 and *22* (1983) 728; c) B. Bogdanović, S. Liao, R. Mynott, K. Schlichte, U. Westeppe, *Chem. Ber. 117* (1984) 1378; d) review: B. Bogdanović, *Angew. Chem. 97* (1985) 253; *Angew. Chem. Int. Ed. Engl. 24* (1985) 262.

[2] Preparation (exclusion of air and moisture): Mg turnings (3.0 g, 123.4 mmol) and **1** (3.0 g, 15.5 mmol) were stirred for 3 d at room temperature. In order to activate the Mg, EtBr (0.01 mL) was added. The orange solid was separated from excess Mg, washed with THF, and dried in vacuum. Yield: 5.03 g (75.1%). Correct elemental analysis. For the crystallization, a saturated solution of **2** in THF was cooled from 35 to 0°C in 2 d. Orange-red needle-shaped crystals were obtained. ^{13}C-NMR (250 MHz, [D$_8$]THF, 40°C): δ(±1 rel. TMS, ^1J(CH) in Hz±1 Hz) = 118.0 (C1/C4), 114.7 (C5/C8; ^1J(CH) = 149.8), 119.5 (C2/C3; ^1J(CH) = 150.9), 118.2 (C6/C7; ^1J(CH) = 153.1), 54.1 (C9/C10; ^1J(CH) = 137.3), 142.6 (C11/C12), 145.9 (C13/C14), 20.3 (C15/C16; ^1J(CH) = 123.4).

[3] An attempt to obtain crystals of **5** suitable for X-ray structure determination failed.

[4] H. Lehmkuhl, A. Shakoor, K. Mehler, C. Krüger, K. Angermund, Y.-H. Tsay, *Chem. Ber. 118* (1985) 4239.

[5] a) U. Westeppe, *Dissertation*, Universität Bochum 1985; the experimental details will be reported later; b) B. Bogdanović, DE P-3410640.5 (March 23, 1984).

[6] By addition of a catalytic amount of $MgCl_2$ to the solution of catalyst, the reaction times can be reduced by a factor of 10–50 in comparison with those given in [1a].

[7] Experimental procedure for **6** (operations carried out with exclusion of air and moisture): **5** (6.12 g, 14.6 mmol) was stirred with **4** (2.61 g, 14.6 mmol) for 24 h in 150 mL of a 0.45 M $MgCl_2$ solution in THF and the blue precipitate was filtered, washed with THF and pentane, and dried (yield: 85%). Correct elemental analysis.

[8] K. Angermund, K. H. Claus, R. Goddard, C. Krüger, *Angew. Chem. 97* (1985) 241; *Angew. Chem. Int. Ed. Engl. 24* (1985) 237, and references cited therein.

[9] The μ-trichlorodimagnesium·6thf cation was recently detected in the complex [$Mg_2Cl_3\cdot 6thf$][$TiCl_5thf$] by X-ray analysis: P. Sobota, J. Utko, T. Lis, *J. Chem. Soc. Dalton Trans. 1984*, 2077.

[10] Further details of the crystal structure investigations are available on request from the Fachinformationszentrum Energie, Physik, Mathematik GmbH, D-7514 Eggenstein-Leopoldshafen 2, by quoting the depository numbers CSD-51453 (**2**) and CSD-51454 (**6**), the names of the authors, and the journal citation.

Nickel(0)-Catalyzed Synthesis of Sorbanilide from 1,3-Pentadiene and Phenyl Isocyanate

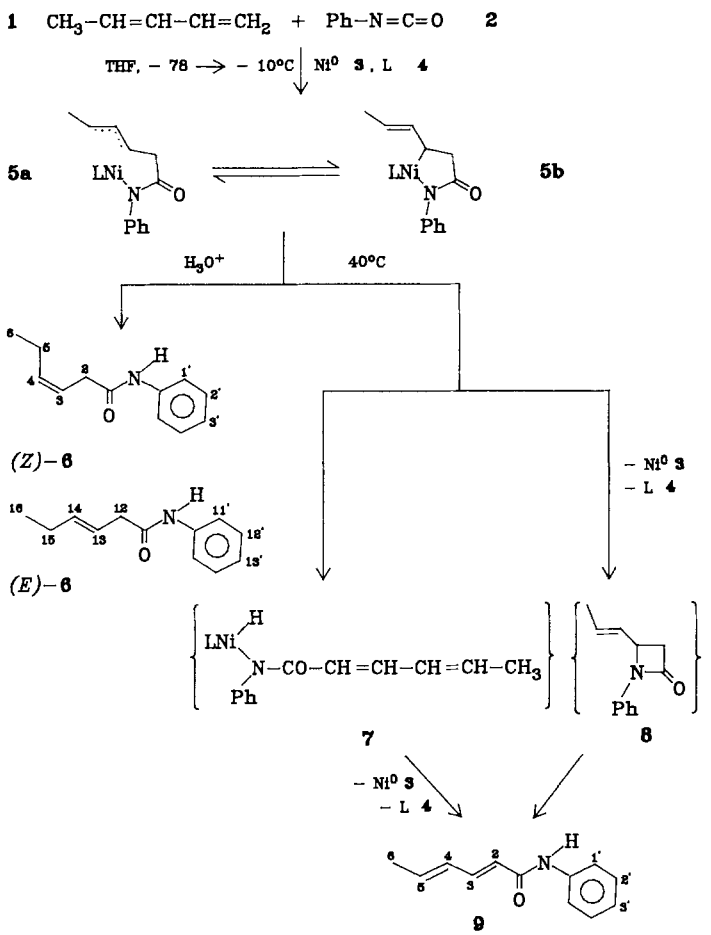
By *Heinz Hoberg** and *Elisa Hernandez*

We recently reported the preparation of acrylamides from ethylene and isocyanates on nickel(0) complexes in a

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stoichiometric sequence of reactions.[1] The corresponding 1:1 CC coupling reactions of 1,3-dienes and isocyanates with retention of the diene skeleton were unknown up to now.[2] We have now been able to obtain sorbanilide from 1,3-pentadiene (piperylene) and phenyl isocyanate using nickel compounds as catalysts.

Piperylene ($Z/E = 33:67$ mixture) **1** reacts with phenyl isocyanate **2** on nickel(0) complexes **3**[3] in the presence of a strongly basic, bulky ligand L such as (*cyclo*-$C_6H_{11})_3P$ **4** (mole ratio 2:1:1:1) with 1:1 CC bond formation to give the nickel complex **5** regioselectively[4] in 63% yield.[5] Protonolysis of **5** with 2 N H_2SO_4 affords **6** ($Z/E = 71:29$) in 55% yield.[6]



The mass spectrum of **5** shows no peak for the molecular ion, but does exhibit, along with the expected fragment ions of **4** and **6**, a peak that, as the molecular ion of the sum of **1** and **2** [*m/z* 187 (M^+)] indicates the formation of sorbanilide **9**. Under the conditions of mass spectrometric measurement, a reductive elimination thus takes place for **5**.

9 is also formed when **5** is heated. When **5**, which is only sparingly soluble in the conventional solvents (**5a** corresponds to a 14e and **5b** to a 16e complex, so that **5** is presumably present as an aggregate in the solid), is heated at 60°C for 24 h in tetrahydrofuran (THF), the protonolysis affords **9** in ca. 11% yield.

The stoichiometric synthesis of **9** can be made catalytic if special reaction conditions are employed. When a mixture of **1**, **2**, **3**, and **4** (mole ratio 10:5:1:1), initially prepared in a steel autoclave at −78°C in THF, is warmed with stirring to 20°C over ca. 10 h and then heated for ca. 48 h at 40°C, **9** is obtained in ca. 250% yield[7] (based on **3**) after hydrolytic work-up.[8]

The catalysis presumably begins with formation of a CC bond between **1** and **2** at L–Ni^0 in an oxidative addition reaction ($Ni^0 \rightarrow Ni^{2+}$) to give the nickel complex **5**, which, upon heating, forms **9** and the regenerated L–Ni^0 complex via intermediates **7** and/or **8** (with reductive elimination and H shift).

The formal addition of a vinylic C–H bond of 1,3-pentadiene to the CN double bond of phenyl isocyanate is the first metal-induced synthesis of a conjugated dienoic acid derivative.

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[1] H. Hoberg, K. Sümmermann, A. Milchereit, *Angew. Chem. 97* (1985) 321; *Angew. Chem. Int. Ed. Engl. 24* (1985) 325.

[2] Dienoic acids can also be prepared from the corresponding 1,3-dienes and carbon dioxide on nickel complexes in a stoichiometric reaction; cf. H. Hoberg, D. Schaefer, B. W. Oster, *J. Organomet. Chem. 266* (1984) 313; H. Hoberg, D. Schaefer, *ibid. 255* (1983) C 15; D. Walther, E. Dinjus, H. Görls, J. Sieler, O. Lindqvist, L. Anderson, *ibid. 286* (1985) 103.

[3] Ni^0: e.g., (cdt)Ni where cdt = 1,5,9-cyclododecatriene or $(cod)_2Ni$ where cod = 1,5-cyclooctadiene.

[4] **2** reacts exclusively at the C^1 atom of **1** to give **5**; the other three possible products of CC coupling could not be detected.

[5] **5**: A mixture of **1** (1.1 g, 15 mmol), **2** (0.95 g, 8 mmol), $(cod)_2Ni$ (1.96 g, 7.3 mmol), and **4** (1.97 g, 7.3 mmol) prepared under argon at −78°C in 30 mL of diethyl ether was warmed to −10°C within 48 h, forming an orange-brown suspension. After addition of ca. 30 mL of pentane, the precipitate was collected on a sintered glass filter and dried. Yield: 2.4 g (4.57 mmol) 62%. M.p. = 115°C (decomp.). IR (KBr): ν = 1532 (C=O) cm^{-1}. Correct elemental analysis.

[6] **6**: **5** (1.0 g, 1.9 mmol) was suspended in 20 mL of diethyl ether and treated with ca. 5 mL of 2 N H_2SO_4. After ca. 20 h, the reaction mixture was extracted with diethyl ether, the organic phase was dried with magnesium sulfate, the ether was removed, and the residue was chromatographed on silica gel 60 (eluent: toluene/diethyl ether 1:1). Yield: 199 mg (1.05 mmol) 55%. M.p. = 39°C. MS: *m/z* 189 (M^+). IR (KBr): 3247 ν(NH); 1548 δ(NH); 1657 ν(C=O); 1620 ν(C=C); 966 γ(CH,CC(*E*)); 760 γ(CH,CC(*Z*)) covered by C_6H_5 bands, cm^{-1}. The *E*/*Z* ratio was determined by ^{1}H-NMR spectroscopy. ^{1}H-NMR: the signals of (*Z*)-**6** and (*E*)-**6** were not completely resolved in the 200-MHz spectrum (except for H-2 and H-12, respectively, and H-6 and H-16); the integration gave $Z/E = 71:29$. ^{1}H-NMR ($CDCl_3$, TMS): [(*Z*)-**6**], δ = 1.01 (t, 3 H, H-6); 2.11 (quint, 2 H, H-5); 3.16 (d, 2 H, H-2); 5.7 (m, 2 H, H-3, H-4); 7.08 (t, 2 H, H-2'); 7.51 (d, 2 H, H-1'); 7.78 (s, 1 H, NH). [(*E*)-**6**] as for (*Z*)-**6** except for δ = 1.02 (H-16) and 3.08 (H-12).

[7] That only ca. 2.5 catalytic cycles occur is apparently due to inactivation of L–Ni^0 by **2**, forming nickel-containing six-membered rings; cf. H. Hoberg, B. W. Oster, C. Krüger, Y. H. Tsay, *J. Organomet. Chem. 252* (1983) 365.

[8] **9**: 1.88 g (20.3 mmol) **1**, 1.21 g (10.14 mmol) **2**, 0.56 g (2.03 mmol) $(cod)_2Ni$ and 0.57 g (2.03 mmol) **4** in 30 mL of THF were mixed at −78°C and warmed to 40°C (stirring) in a steel autoclave. The THF was subsequently distilled off and the residue hydrolyzed with 2 N H_2SO_4, diethyl ether being added. The organic phase was dried over magnesium sulfate and then chromatographically purified (silica gel 60, eluent: toluene/diethyl ether 1:1). Yield: 930 mg (4.93 mmol) 250% based on **3** [9]. M.p. = 143°C [10]. IR (KBr): 3303 ν(NH), 1534 δ(NH), 1656, 1630, 1611 ν(C=O,C=C), 1010 γ(CH,C=C–C=C) cm^{-1}. ^{1}H-NMR [$(CD_3)_2CO$, δ = 2.04, 200 MHz]: δ = 1.81 (d, 3 H, CH_3), 6.15 (m, 3 H, H-2, H-4, H-5), 7.02 (t, 1 H, H-3'), 7.28 (m, 4 H, H-3, H-2', N–H), 7.72 (d, 2 H, H-1').

[9] **1** was used as an $Z/E = 33:67$ mixture. If 97% (*Z*)-**1** or (*E*)-**1** is employed, the yield of **9** remains practically unchanged.

[10] O. S. Stepanova, D. A. Mazurenko, V. T. Nguyen, N. Ya. Derka, *Fiziol. Akt. Veshchestva 8* (1976) 86; *Chem. Abstr. 86* (1977) 189422d.

Reactivity of Bis(η^6-benzene)chromium(0) toward Sulfur Dioxide: Formation and Structure of $[(\eta^6\text{-}C_6H_6)_2Cr]_2S_4O_{10}$, a Salt Containing the Anion $[S_2O_6 \cdot 2SO_2]^{2\ominus}$**

By *Christoph Elschenbroich,* Rolf Gondrum,* and *Werner Massa*

Dedicated to Professor Max Schmidt on the occasion of his 60th birthday

An investigation of the reaction of bis(η^6-benzene)chromium **1** with SO_2 is of interest since the redox couples $\mathbf{1}/\mathbf{1}^{\oplus}$ and $2SO_2/S_2O_4^{2\ominus}$ ($E_{1/2} = -0.81$ and -0.79 V, respectively, DMF, versus SCE[2]) have nearly identical redox potentials, and since **1** reacts with liquid SO_2, undergoing extensive oxidation to $\mathbf{1}^{\oplus}$.[3] We have been concerned, above all, with the question whether, upon controlled addition of SO_2 to **1**, charge-transfer complexes $\mathbf{1}(SO_2)_n$ or, as for acceptors with more positive redox potentials,[4] radical salts $\mathbf{1}^{\oplus}SO_2^{\ominus}(SO_2)_{n-1}$ would be formed. In the latter case, the subsequent fate of the radical anion $SO_2^{\ominus}$ was of interest.

When dry, oxygen-free SO_2 gas is bubbled through a solution of **1** in toluene, a precipitate forms, which is initially red but subsequently turns black, and whose analytical composition corresponds to $\mathbf{1}(SO_2)_2$, the central metal atom of which, according to ESR spectroscopy, is present as Cr^I. At room temperature under high vacuum, this substance releases one equivalent of SO_2 and turns lighter in color. At temperatures above 80 °C, **1** sublimes from the precipitate. Recrystallization of the product from acetonitrile or direct reaction of **1** with SO_2 in acetonitrile affords brown crystals, whereby the solution transiently turns green. These crystals are only stable under SO_2; they also contain Cr and S in a ratio of 1:2 (approximately 60% yield from **1**). This substance, too, loses SO_2 in high vacuum; the residue has the composition $\mathbf{1}(SO_3)$.

Since the IR spectra do not allow unequivocal identification of the product, its structure was determined by X-ray analysis of the crystals obtained from acetonitrile.[5] To our surprise, the results showed that an $S_4O_{10}^{2\ominus}$ species is present as the counterion of two $\mathbf{1}^{\oplus}$ ions (Fig. 1). On the basis of the S2–O11 distance (243 pm), which lies between that corresponding to the sum of the van der Waals radii (330 pm) and that of an S–O single bond (176 pm), the $S_4O_{10}^{2\ominus}$ structural unit can be viewed either as a Lewis adduct with two extremely long S–O bonds or as a charge-transfer complex $S_2O_6^{2\ominus} \cdot 2SO_2$ of a dithionate ion with two molecules of SO_2. The interaction between SO_2 and $S_2O_6^{2\ominus}$ is fundamentally different from that between SO_2 and $SO_3^{2\ominus}$, which results in the formation of the unsymmetrical disulfite ion $S_2O_5^{2\ominus}$, in which, both in solution[6] and in the crystal,[7] SO_2 is bound covalently by an S–S bond. The formulation $S_2O_6^{2\ominus} \cdot 2SO_2$ places this structural unit in the class of "solvates," which have been frequently observed for SO_2[8] but only rarely characterized by X-ray analysis.[9] In the region of SO_2 coordination, the $S_2O_6^{2\ominus} \cdot 2SO_2$ structural unit exhibits similarities to the species 1,4-$(Me_2N)_2C_6H_4 \cdot 2SO_2$,[9f] the ion $ISO_2^{\oplus}$,[9g] and the ligand-bound SO_2 in $[Ru(CO)_2(PPh_3)_2(\eta^2\text{-}SO_2 \cdot SO_2)]$:[9d] the lengths of the donor-acceptor bonds lie, in each case, between those of van der Waals contacts and that of a covalent single bond; the pyramidal geometries around the S atom and the contractions of the bond angle O–S–O are comparable. An aggravating circumstance in the discussion of the S–O bond lengths is the strong thermal vibration of the loosely bound SO_2 molecule. However, correction for the effect of vibration using the "riding" model[11] leads to plausible, significantly longer S–O distances (Fig. 1), which are employed in the following discussion.

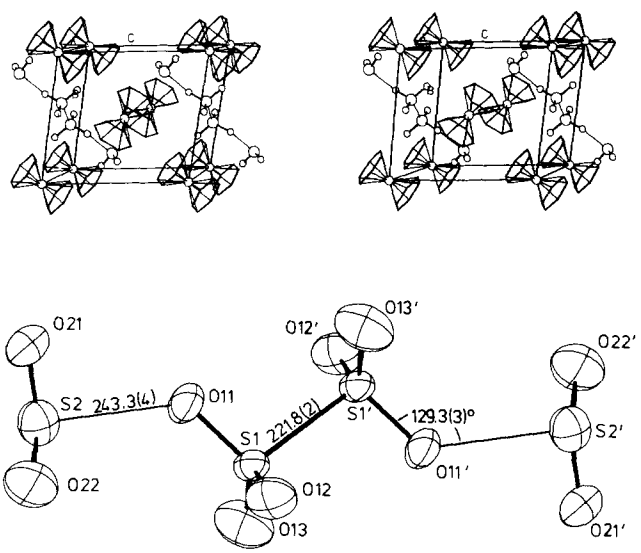


Fig. 1. Above: Stereoscopic view of a unit cell of $\mathbf{1}_2^{\oplus}S_2O_6^{2\ominus} \cdot 2SO_2$. Below: ORTEP plot of the anionic groups $S_2O_8^{2\ominus} \cdot 2SO_2$ (the ellipsoids of vibration represent 30% probability). A center of symmetry is present on the S1–S1′ bond. Bond lengths [pm]. Other important bond lengths [pm] (including values corrected for the effect of thermal vibration in brackets) and angles [°]: S1–O11 147.5(5) [153], S1–O12 142.1(6) [146], S1–O13 137.3(6) [143], S2–O21 137.9(7) [146], S2–O22 135.6(9) [144]; O12–S1–O13 113.4(4), O21–S2–O22 112.9(6). In $\mathbf{1}^{\oplus}$: mean value Cr–C 212.9, C–C 139.4.

The form and orientation of coordinated SO_2 in $S_2O_6^{2\ominus} \cdot 2SO_2$ can be explained in terms of the interaction between an occupied σ-donor orbital of the dithionate ion and the LUMO $2b_1(\pi)$ of SO_2, which is dominated by the contribution of the $3p_x$-AO on sulfur ($x \perp SO_2$ plane).[10] Since the O11–S2 bond is nearly perpendicular to the O21–S2–O22 plane, S2 is probably only slightly rehybridized. The LUMO $2b_1$ of SO_2 is S–O antibonding and O–O bonding. The contraction of the O21–S2–O22 angle and the lengthening of the S–O bonds of SO_2 in $S_2O_6^{2\ominus} \cdot 2SO_2$ can thus be viewed as a result of the charge transfer $S_2O_6^{2\ominus}(n) \rightarrow SO_2(\pi, 2b_1)$. The coordination of the acceptor SO_2 also influences the shape of the dithionate ion, which manifests itself primarily in the lengthening of the central S–S bond from 214 pm in $S_2O_6^{2\ominus}$[12] to 222 pm in $S_2O_6^{2\ominus} \cdot 2SO_2$ and of the S1–O11 bond from 145 to 152 pm. A significant interaction $SO_2/\eta^6\text{-}C_6H_6$ is not evident, the shortest S2–C(arene) separation (362 pm) being larger than the van der Waals distance.

The analysis of the IR spectrum of $\mathbf{1}_2^{\oplus}S_2O_6^{2\ominus} \cdot SO_2$ is complicated by the fact that the absorptions of the oxo anions of sulfur fall in a narrow range, the contribution of solvate formation to the shift cannot be predicted, and the counterion $\mathbf{1}^{\oplus}$ exhibits absorptions in the region around 1000 cm^{-1} where several of the IR bands for $S_2O_6^{2\ominus}$ are

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found.[13] Nevertheless, the bonding of the SO_2 molecule to the $S_2O_6^{2\ominus}$ ion causes shifts to lower wave numbers of the SO_2 vibrations ($\nu_{as} = 1314\ cm^{-1}$ [$\nu_{as}(SO_2, free) = 1340\ cm^{-1}$]) as well as of the dithionate ion vibrations ($\nu = 1209\ cm^{-1}$ [$\nu(Na_2S_2O_6, E_u) = 1235\ cm^{-1}$ [13a]]). Upon release of SO_2 in high vacuum, the band at 1314 cm^{-1} disappears and the band at 1209 cm^{-1} is displaced to 1224 cm^{-1}). These IR results are in accord with the structural data for $1_2^{\odot\oplus}S_2O_6^{2\ominus} \cdot 2SO_2$ as well as with earlier IR studies on the SO_2 solvates.[14]

The formation of two oxidation products, $1^{\odot\oplus}$ and $S_2O_6^{2\ominus}$, from the educts **1** and SO_2 requires the inclusion of a disproportionation step. As we were able to demonstrate by means of a flow experiment in which ESR spectra were recorded immediately after mixing solutions of **1** and SO_2 in acetonitrile, the reaction sequence is initiated by an electron transfer from **1** to SO_2, since, along with the ESR signal for $1^{\odot\oplus}$ ($\langle g \rangle = 1.9862$), the signal for $SO_2^{\odot\ominus}(SO_2)_n$ ($\langle g \rangle = 2.0068$[15]) is observed. The elucidation of the consecutive reactions leading to the product $1_2^{\odot\oplus}S_2O_6^{2\ominus} \cdot 2SO_2$ is the subject of further study. However, the formation of dithionate in the reduction of SO_2 is not without precedent. Thus, $S_2O_6^{2\ominus}$ was also found as a product of the discharge of Li/SO_2 cells and its formation ascribed to the following sequence of reactions.[16]

$$2SO_2 + 2e^{\ominus} \longrightarrow S_2O_4^{2\ominus} \xrightarrow{SO_2} S_3O_6^{2\ominus} \longrightarrow S_2O_6^{2\ominus} + S$$

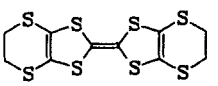
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[9] With the exception of metal complexes that contain SO_2 as a ligand directly bound to the metal [10], only structure determinations of the following "solvates" have, to the best of our knowledge, been carried out: a) $[Pt(CH_3)(PPh_3)_2I \cdot SO_2]$, I-S 339 pm, M. R. Snow, J. A. Ibers, *Inorg. Chem. 12* (1973) 224; b) $[\{(\mu\text{-}I)(PMePh_2)_2Cu\}_2 \cdot SO_2]$, I-S 341 pm, P. G. Eller, G. J. Kubas, R. R. Ryan, *ibid. 16* (1977) 2454; c) $[(PMePh_2)_3Cu(SPh) \cdot SO_2]$, S-S 253 pm, P. G. Eller, G. J. Kubas, *J. Am. Chem. Soc. 99* (1977) 4346; d) $[Ru(CO)_2(PPh_3)_2(\eta^2\text{-}SO_2 \cdot SO_2)]$, O-S 251 pm, D. C. Moody, R. R. Ryan, *J. Chem. Soc. Chem. Commun. 1980*, 1230; as well as for the metal-free SO_2 adducts: e) $Me_3N \cdot SO_2$, N-S 206 pm, D. van der Helm, J. D. Childs, S. D. Christian, *ibid. 1969*, 887; f) $1,4\text{-}(Me_2N)_2C_6H_4 \cdot 2SO_2$, N-S 234 pm, J. D. Childs, D. van der Helm, S. D. Christian, *Inorg. Chem. 14* (1975) 1386; g) $ISO_2^{\oplus}$, I-S 325 pm, P. G. Eller, G. J. Kubas, *ibid. 17* (1978) 894.
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β-$(ET)_2AuI_2$: An Organic Volume Superconductor with $T_c = 3.2$ K at Ambient Pressure**

By *Eberhard Amberger,* Helmut Fuchs,* and *Kurt Polborn*

Inorganic superconductors have been produced on an industrial scale for more than a decade.[1] The highest transition temperature T_c (transition from the metallic to the superconducting state) hitherto recorded, namely 23.2 K in the case of metastable Nb_3Ge, could not even be surpassed by A 15-Nb_3Si.[2] It would now appear, from theoretical considerations, that organic superconductors may offer more prospects of achieving higher critical temperatures.[3] The first organic ambient-pressure superconductor, the perchlorate of the radical-cation dimer of tetramethyltetraselenafulvalene $(TMTSF)_2ClO_4$ ($T_c = 1$ K), was discovered in 1981.[4] In 1983 the radical-cation salt $(ET)_2ReO_4$, obtained from bis(ethylenedithio)tetrathiafulvalene **1** ("BEDT-TTF" or "ET"), was found to be superconducting ($T_c \sim 2$ K), but only at high pressures ($p > 4.5$ kbar). Meanwhile,[***] four ambient-pressure superconductors of ET have been synthesized: β-$(ET)_2I_3$ ($T_c = 1.2$–1.6 K),[7, 8] γ-$(ET)_3(I_3)_{2.5}$ ($T_c \sim 2.5$ K),[7] ε-$(ET)_2I_3(I_8)_{0.5}$ ($T_c \sim 2.5$ K),[7] and β-$(ET)_2IBr_2$ ($T_c = 1.7$–2.8 K).[9, 10]



1

It would seem that superconductivity occurs in ET compounds only with certain layer arrangements of the nearly flat ET molecule. The ET radical cations are stacked in a fashion which is typical for all quasi one-dimensional "organic metals." However, the loosely packed ET stacks are not arranged along the shortest period of the crystal.[7b] Thus, the $(ET)_2X$ system belongs to a structurally novel class of organic conductors, in which the S···S interstack contact distances of the side-by-side arrangement of ET molecules are shorter than the intrastack S···S packing distances. The anions reside in channels and cavities between the ET stacks. We report here on the synthesis of $(ET)_2X$ compounds containing the anions $IBr_2^{\ominus}$, $I_2Br^{\ominus}$, and $AuI_2^{\ominus}$, which, like the isostructural $(ET)_2I_3$, are two-dimensional organic conductors (see Table 1).

Replacement of the linear $I_3^{\ominus}$ in β-$(ET)_2I_3$ by the smaller linear $IBr_2^{\ominus}$ anion leads to an increase in T_c from 1.2–1.6 K to 1.7–2.8 K. The design strategy described here for achieving still higher transition temperatures consists in the replacement of the interhalide ions by linear metal halide or

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[***] Almost concomitantly with the submission of this manuscript *Williams* et al. reported on β-$(ET)_2AuI_2$ as a superconductor at ambient pressure and quoted an onset temperature of 3.93–4.98 K [16].

cyanide ions $(X-M-X)^{\ominus}$, e.g. $AuI_2^{\ominus}$, $AuBr_2^{\ominus}$, and $Au(CN)_2^{\ominus}$. By electrocrystallization, the most important method for preparing single crystals of organic superconductors, we have obtained β-$(ET)_2AuI_2$, which is superconducting at $T_c = 3.2$ K at ambient pressure. This is the highest T_c recorded for any ambient-pressure organic superconductor without subsequent doping (e.g. with I_2 vapor) or tempering (see [16]). β-$(ET)_2AuI_2$, which was obtained as black, canted crystals in 1,1,2-trichloroethane (TCE), proved to be a volume superconductor. Besides strict adherence to the experimental conditions, especially important in the electrocrystallization is that $AuI_2^{\ominus}$ is synthesized chemically and not electrochemically. Non-superconducting, thin, black platelets were isolated from tetrahydrofuran (THF).

Table 1. Crystallographic data and T_c of superconducting and non-superconducting β-$(ET)_2AuI_2$ crystals and of polyhalide-ET compounds.

	β-$(ET)_2AuI_2$ [10] [a]	β-$(ET)_2AuI_2$ [10] [b]	β-$(ET)_2I_3$ [7]	β-$(ET)_2IBr_2$ [9, 10]	α-$(ET)_2I_3$ [7]
a [Å]	6.600(3)	6.603(1)	6.609	6.593(1)	10.785
b [Å]	8.986(3)	9.062(2)	9.083	8.975(2)	9.172
c [Å]	15.364(3)	15.285(2)	15.267	15.093(4)	17.39
α [°]	95.07(2)	94.48(2)	85.63	93.79(2)	82.08
β [°]	96.18(3)	95.65(2)	95.62	94.97(2)	96.92
γ [°]	110.66(3)	109.93(2)	70.22	110.54(2)	89.13
V [Å^3]	839.79	849.53	852.2	828.7(3)	1690.3
Space group	$P\bar{1}$	$P\bar{1}$	$P\bar{1}$	$P\bar{1}$	$P\bar{1}$
Z	1	1	1	1	2
ρ_{calc}	—	2.38	2.24	—	2.26
T_c [K]	3.2	< 1.2	1.2–1.6	1.7–2.8	(M – I) [c]

[a] With chemically prepared nBu_4NAuI_2. [b] With electrochemically prepared nBu_4NAuI_2. [c] Metal-insulator transition.

In the case of $(TMTSF)_2FSO_3$, less than 2% of the crystal volume is superconducting.[8] ET salts containing the centrosymmetric $(Br-I-Br)^{\ominus}$ anion and those containing the asymmetric $(I-I-Br)^{\ominus}$ anion, which have also been prepared by electrocrystallization, behave completely differently: Only β-$(ET)_2IBr_2$ is superconducting,[9b] thus verifying the importance of a centrosymmetric and crystallographically ordered anion. For the first time volume superconductivity has been observed in our β-$(ET)_2IBr_2$ with a T_c of 1.7 K. β-$(ET)_2I_2Br$, on the other hand, is not superconducting at ambient pressure nor under hydrostatic pressure. By electrocrystallization, we also obtained α- and β-like ET salts with the dibromoaurate ion $AuBr_2^{\ominus}$, but no superconductivity was observed up to the measured temperature of 1.2 K. As to whether superconducting crystals are obtained or not often depends very strongly on the experimental conditions.

Replacement of the $I_3^{\ominus}$ anion in the isostructural β-$(ET)_2X$ system by the ~7% shorter $IBr_2^{\ominus}$ anion leads to a decrease in the interstack S...S distances. Whether this is also true in the case of β-$(ET)_2AuI_2$ with the higher T_c and a unit cell volume about 11 Å^3 larger than that in the IBr_2 salt will have to be established by an X-ray structure analysis. Upon electrocrystallization of ET with halide ions ($F^{\ominus}$, $Cl^{\ominus}$, $Br^{\ominus}$) we have hitherto obtained only whiskers or thin, scaly-like platelets. Apparently, anions that are too small rarely yield useful single crystals.

Experimental

ET was prepared as previously described in the literature [11] and was recrystallized twice from toluene. The supporting electrolyte salt nBu_4NAuI_2 was synthesized chemically from AuI [12] and nBu_4NI [13] or from nBu_4NAuBr_2 and nBu_4NI. [14] The electrocrystallization of β-$(ET)_2AuI_2$ (2×10^{-3} M ET) was carried out galvanostatically at a current density of 0.5 μA/cm^2 in 25 mL of TCE at platinum electrodes in the presence of nBu_4NAuI_2 (3×10^{-3} M) using an H-type cell with two small porosity frits between cathode and anode vessels. After six days, black, canted needles with typical dimensions of maximally $3 \times 1 \times 1$ mm^3 were obtained. After electrocrystallization, the cathode was always found to be covered with a thin gold film. At current densities in excess of 1 μA/cm^2, compact separation of elemental gold took place at the anode and partial separation on the crystals. We have also succeeded in preparing thin, black platelets of $(ET)_2AuI_2$ from tetrahydrofuran (THF) by electrocrystallization (gold electrodes, 0.5 μA/cm^2, 2×10^{-3} M ET and 3.6×10^{-3} M nBu_4NAuI_2, room temperature). Preliminary X-ray crystallographic investigations indicate that only α-phases are obtained from THF.—Electrochemical synthesis of $(ET)_2AuI_2$ and its electrocrystallization: Stoichiometric oxidation of a gold wire in a solution of nBu_4NI in TCE furnished nBu_4NAuI_2. Neutral ET, dissolved in TCE, was then added. Electrocrystallization: 2×10^{-3} M ET, 5×10^{-3} M nBu_4NAuI_2, 23 °C, 2 μÅ/cm^2. The crystals have unit cell parameters similar to those of the β-$(ET)_2AuI_2$ crystals from chemically prepared nBu_4NAuI_2, but have a ca. 10 Å^3 larger unit cell (Table 1) and are not superconducting up to 1.2 K.—α- and β-$(ET)_2IBr_2$ and β-$(ET)_2I_2Br$ were crystallized from THF at 1–2 μA/cm^2 and 1 μA/cm^2, respectively. The supporting electrolyte salts nBu_4NIBr_2 and Et_4NI_2Br were prepared according to procedures given in the literature [15].—Superconductivity has been demonstrated in various batches of crystals using two samples of three crystals in each case and using a superconducting quantum interference device (SQUID magnetometer). The ratio of the Meissner effect to diamagnetic screening current of 38% and 67%, respectively, showed, analogously to the conclusions drawn from measurements with β-$(ET)_2I_3$ [8], that both β-$(ET)_2AuI_2$ and β-$(ET)_2IBr_2$ are volume superconductors.

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$(i\text{-}C_3H_7SGaI_2)_2$, the First "Butterfly" Molecule with Tetracoordinated Gallium**

By *Gerhard Georg Hoffmann** and *Christian Burschka*

Dedicated to Professor Max Schmidt on the occasion of his 60th birthday

Four-membered rings containing two tetracoordinated elements of the boron group are mostly planar. Only for aluminum have some folded ("butterfly") four-membered-ring structures been confirmed.[1] In contrast, no such example is known for gallium; all known four-membered rings containing sp^3-hybridized gallium atoms are strictly planar.[2] Folded systems are only found for pentacoordination of the metal.[3] We have now succeeded in synthesizing, along with further planar GaSGaS four-membered rings,[2b] the first compound of this kind that exhibits a "butterfly" structure in the crystal, bis[diiodo(isopropylthio)gallane].

A solution of diiodo(methylthio)gallane[4] reacts rapidly with 2-propanethiol in refluxing benzene, resulting in exchange of the alkylthio groups [Reaction (a)].[5]

$$CH_3SGaI_2 + i\text{-}C_3H_7SH \longrightarrow \underset{\mathbf{1}}{i\text{-}C_3H_7SGaI_2} + CH_3SH \qquad (a)$$

The gallane formed, **1**, is very sensitive to moisture and decomposes at 352 K. In the ^{1}H-NMR spectrum, the proton signal of the methine group is markedly shifted downfield compared with that of the free thiol; that of the methyl groups, on the other hand, is shifted upfield somewhat.[4] In contrast to the analogous compounds I_2GaSR ($R=CH_3$, C_2H_5, and n-C_3H_7), in which, already at room temperature, two (broad) groups of signals are present in the ^{1}H-NMR spectrum for both the methylene and the methyl groups,[4] no significant splitting is observed for **1**, even down to 200 K (400-MHz spectra), which would have indicated the presence of isomers. However, when **1** is stored for ca. 24 h at 213 K and its ^{1}H-NMR spectrum subsequently recorded, an additional signal for the methine protons appears at higher field. All signals are broadened and barely resolved. Recording of the spectrum once again at room temperature results in only one well-resolved signal for each type of proton.

Osmometric molecular weight determinations in benzene (318 K) using various concentrations of **1** (13 to 162 mmol/L, based on the empirical formula of the monomer) always give a molecular weight three times that calculated. The same degree of association is also found for the analogous compounds I_2GaSR ($R=CH_3$, C_2H_5, and n-C_3H_7), whereas the phenylthio derivative is present as a monomer in the same solvent.[4]

The X-ray structure analysis of the crystals obtained from $CHCl_3$/n-hexane, which are up to 3 mm in size, shows, however, that **1** adopts a folded four-membered-ring structure (Fig. 1) in the crystal, the two isopropyl groups being in *syn* positions. The molecule has C_2 symmetry in the crystal but deviates only slightly from C_{2v} symmetry. With a fold angle of 143.3(2)° on the diagonal Ga···Ga', the deviation from planarity (36.7(2)°) is more pronounced than in all folded four-membered-ring systems of aluminum and gallium known up to now. In the homologous series, only the "butterfly" ion $(Tl_2Te_2)^{2-}$[6] with 49.9° shows a greater folding; in this case, however, a Tl^I compound is involved. Both the Ga-S and the Ga-I bond lengths in $(\mathbf{1})_2$ are four to five standard deviations smaller than in the planar GaSGaS four-membered ring of $(CH_3SGaI_2)_2$, whose structure we[2b] and others[2c] have also elucidated recently.

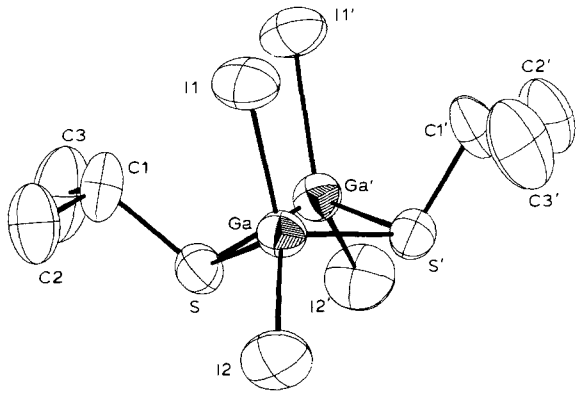


Fig. 1. Crystal structure of $(\mathbf{1})_2$: C2/c, $a=956.1(2)$, $b=1253.0(3)$, $c=1724.3(5)$ pm, $\beta=104.80(2)°$, $Z=4$, $\rho_{calcd}=2.65$, $\rho_{exp}=2.62$ gcm^{-3}, $R_1=0.053$ for 1303 independent reflections ($I_0 \geq 3\sigma(I_0)$), $Mo_{K\alpha}$ radiation. Atomic distances [pm]: Ga-S 232.7(3), Ga-S' 233.1(3), Ga-I1 248.2(2), Ga-I2 247.9(2), Ga···Ga' 313.7(2), S···S' 326.8(4); bond angles [°]: S-Ga-S' 89.1(1), Ga-S-Ga' 84.7(1), I1-Ga-I2 114.58(6). Further details of the crystal structure investigation are available on request from the Fachinformationszentrum Energie, Physik, Mathematik GmbH, D-7514 Eggenstein-Leopoldshafen 2, by quoting the depository number CSD-51366, the names of the authors, and the journal citation.

A satisfactory explanation of the striking differences in the degree of association of **1** in solution and in the crystal demands that an equilibrium between dimer and trimer

$$3(i\text{-}C_3H_7SGaI_2)_2 \rightleftharpoons 2(i\text{-}C_3H_7SGaI_2)_3 \qquad (b)$$

be established [Reaction (b)] by breaking of the four-membered-ring structure upon solvation of the substance; the equilibrium must be quickly established and lie strongly to the side of the trimer. Moreover, either only one conformer of the trimeric form is formed preferentially or an exchange between the various conformers takes place so rapidly, even at 200 K, that no significant additional groups of signals can be observed in the NMR spectrum.

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for 3 h. The solvent was then removed and the colorless residue recrystallized from $CHCl_3$/*n*-hexane. Yield: 1.39 g (70%) **1**, m.p. = 352 K (decomp.); correct elemental analysis; ^{1}H-NMR (60 MHz, C_6H_6): $\delta = 3.56$ (sep, 1H), 1.03 (d, 6H); (400 MHz, CD_2Cl_2, $J = 6.6$ Hz) 300 K: $\delta = 3.86$ (1H)*, 1.55 (d, 6H); 263 K: $\delta = 3.82$ (sep, 1H), 1.53 (d, 6H); 233 K: $\delta = 3.78$ (sep, 1H), 1.50 (d, 6H); 203 K: $\delta = 3.72$ (1H)*, 1.45 (d, 6H); 24 h at 213 K: $\delta = 3.72$ and 3.60 (1H)*, 1.44 (6H)*; the signals marked with an asterisk are unresolved.

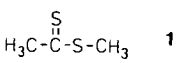
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A Dithioester as Allylic-Type 4e Ligand**

By *Wolfdieter A. Schenk,* Doris Rüb,* and *Christian Burschka*

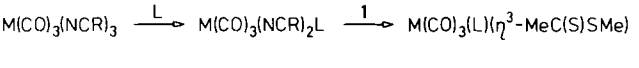
Dedicated to Professor Max Schmidt on the occasion of his 60th birthday

The coordination chemistry of simple organic thiocarbonyl compounds recently has attracted considerable attention. Thus, the normally unstable thioaldehydes and thioketones can be both stabilized[3,4] and activated to undergo novel reactions[4,5] by η^1- or η^2-coordination to a transition metal. Other C=S functional compounds, e.g., thioamides and thioureas, have frequently been employed as ligands;[6] their reactivity in the coordinated state, however, has not been investigated in detail. Herein we report on complexes of the simplest stable dithioester, methyl dithioacetate **1**, in which the ester acts as a four-electron donor toward the same metal center through both the C=S double bond and the second sulfur atom.[7]



1

The synthesis starts from the well-known tris(nitrile) complexes **2**–**4** with replacement of one nitrile ligand by a bulky phosphane, followed by replacement of the other two by the dithioester **1**. Complexes **5**–**7** are obtained as orange crystalline solids (correct elemental analyses).



2 – **4** **5** – **7**

2: M = Cr, R = Me **5**: M = Cr, L = PPh_3

3: M = Mo, R = Me **6**: M = Mo, L = PPh_2iPr

4: M = W, R = Et **7**: M = W, L = $PiPr_3$

The high CO stretching frequencies (Table 1) confirm the high π-acceptor ability of the dithioester ligand. In the ^{13}C-NMR spectra the dithiocarboxylate carbon gives rise to a resonance at approximately $\delta = 100$, well separated from the resonances for both the free ester ($\delta = 234.1$)[8] and the known η^2-complexes ($\delta = 47$–60).[2,9] An X-ray structure determination of **7** conclusively shows that the dithioester acts as an allylic-type four-electron ligand. The

Table 1. Spectroscopic data for the complexes **5**–**9**. THF = tetrahydrofuran. NMR measurements in CD_2Cl_2.

Complex	IR (THF) [cm^{-1}]	^{13}C-NMR δ [a]	^{31}P-NMR δ	^1J(W-P) [Hz]
5	1979 s, 1896 s	111.2	52.7	
6	1987 s, 1898 s, 1880 sh	103.2	38.9	
7	1983 s, 1885 s	85.3	29.0	181
8	2065 w, 1998 s, 1937 vs, 1894 s	84.0	29.1	188
9	2010 w, 1927 m, 1891 s	56.2	22.3	198

[a] Resonance of the dithiocarboxylate carbon.

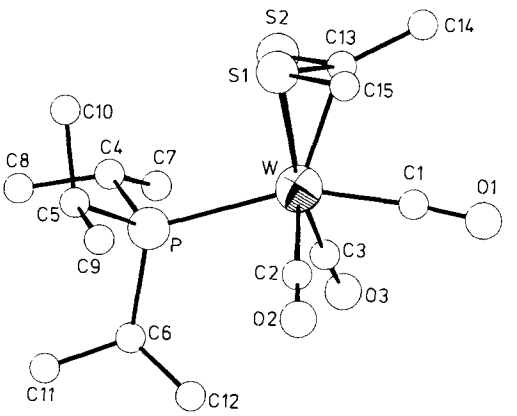
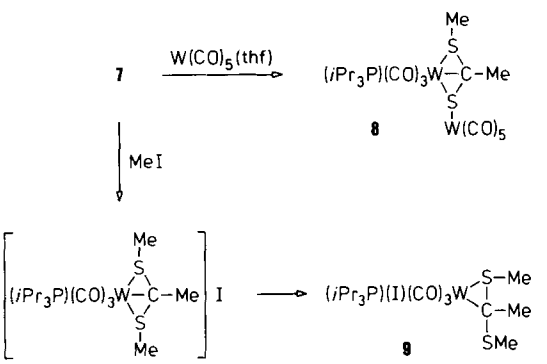


Fig. 1. Structure of **7** in the crystal. Space group $P2_1/c$ (No. 14), $Z = 4$, $a = 8.629(5)$, $b = 16.395(7)$, $c = 14.889(6)$ Å, $\beta = 104.22(4)°$, $\rho_{calcd} = 1.74$, $\rho_{exp} = 1.7$ mg/mm^3, $R_1 = 0.032$ (0.057), $R_2 = 0.029$ (0.031) for 2083 (3101) reflections ($I_{obs} \geq 3\sigma(I)$). Further details of the crystal structure investigation are available on request from the Fachinformationszentrum Energie, Physik, Mathematik GmbH, D-7514 Eggenstein-Leopoldshafen 2, on quoting the depository number CSD-51496, the names of the authors, and the journal citation.

atoms C15, S1, C13, and S2 are exactly coplanar. The bond lengths C13–S1 (1.79 Å), C13–S2 (1.75 Å), and W–C13 (2.154 Å) equal those of single bonds (Fig. 1).

The η^3-coordinated dithioester is still susceptible to electrophilic attack. Thus, **7** reacts with $W(CO)_5$(thf) to give the binuclear complex **8**.



With methyl iodide, **7** is converted into the yellow addition product **9**, which, surprisingly, is a nonelectrolyte. In the ^{13}C-NMR spectrum of **9**, the resonance of the dithiocarboxylate carbon is found at $\delta = 56.2$, a value typical for η^2-coordination. Apparently, the iodide ion produced in the first step nucleophilically attacks the metal center with displacement of one of the coordinated sulfur atoms. **9** contains a stabilized dithiocarbenium ion as two-electron

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donor and is thus analogous to the previously reported ionic compounds $[W(CO)_3(dppe)(RSC(H)SR')]X$ ($dppe = Ph_2P(CH_2)_2PPh_2$).[2]

Experimental procedure

5: A solution of **2** (1.30 g, 5.0 mmol) in acetonitrile (40 mL) was allowed to react at 20°C with Ph_3P (1.30 g, 5.0 mmol). After 16 h, the volume was reduced to 10 mL and diethyl ether (30 mL) was added to give a yellow precipitate. This was collected by filtration, washed with ether, and suspended in ethanol (50 mL). Upon addition of **1** (0.50 mL, 5.0 mmol), the mixture turned deep red. After 1 h, the volume was reduced to 25 mL and water (5 mL) was added to precipitate the orange product **5**. Yield 1.65 g (65%), decomp. p. 85°C.

6, **7**: **6** (80%, m.p. = 90°C (decomp.)) and **7** (70%, m.p. = 103–105°C (decomp.)) were obtained analogously.

8: A solution of $W(CO)_6$ (0.46 g, 1.30 mmol) in THF (100 mL) was irradiated until 1 equiv. of CO was liberated. After addition of **7** (0.64 g, 1.20 mmol), the volume was reduced to 5 mL and hexane (15 mL) was added to precipitate **8** as a yellow-orange powder. Yield 0.68 g (66%), m.p. = 107–110°C (decomp.).

9: A solution of **7** (1.44 g, 2.70 mmol) in acetone (20 mL) was treated at 20°C with methyl iodide (1.0 mL, 16.0 mmol). After 24 h, the solution was filtered and evaporated to 2 mL. Upon addition of diethyl ether (10 mL), **9** separated as a yellow crystalline powder. Yield 0.52 g (29%), m.p. = 115–120°C (decomp.).

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New Bicyclic Ketones and the Stereochemistry of Their Reaction with Carbanions**

By *Petra Baierweck, Detlef Hoell,* and *Klaus Müllen**

Dedicated to Professor Rolf C. Schulz on the occasion of his 65th birthday

Knowledge of the reaction profile of nucleophilic attack on carbonyl compounds is of great theoretical and practical importance.[1] If ketones of type **1** or **2** are allowed to react with carbanions, the question arises whether the transient associative interaction of the organometallic compound with the ethylene or benzene π-system can result in a diastereoselective addition. We have directed our attention to the ketones **2** and **3** since the results for **1a**[2] did not provide a clear picture. We describe here a remarkably simple preparation of the new ketones **2b** and **3** (Table 1) and report on the stereochemistry of their reaction with organometallic compounds.

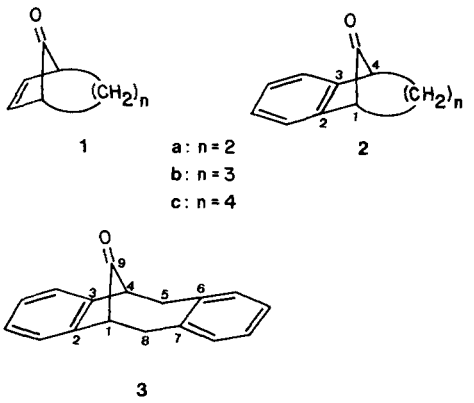


Table 1. Spectroscopic data for some of the new compounds [a].

2b: ^{13}C-NMR ($CDCl_3$, 20 MHz): δ = 217.4 (C-carbonyl), 139.1, 127.5, 122.6 (C-arom.), 52.4 (C-1, C-4), 34.3 (C-5, C-7), 17.4 (C-6); ^{1}H-NMR ($CDCl_3$, 90 MHz): δ = 7.25 (4H, arom.), 3.37 (2H, m), 2.15–1.90 (4H, m), 1.57–0.78 (2H, m); IR (KBr): ν(CO) = 1760 cm^{-1}

3: ^{13}C-NMR ($CDCl_3$, 100 MHz): δ = 219.0 (C-9); 140.3, 136.0, 131.5, 127.5, 126.9, 123.7 (C-arom.), 52.2 (C-4, C-1), 41.1 (C-5, C-8); ^{1}H-NMR ($CDCl_3$, 60 MHz): δ = 7.05 (4H, arom.), 6.90 (4H, arom.), 3.65 (2H, m), 3.20 (4H, m); IR (KBr): ν(CO) = 1750 cm^{-1}; m.p. = 153.5°C

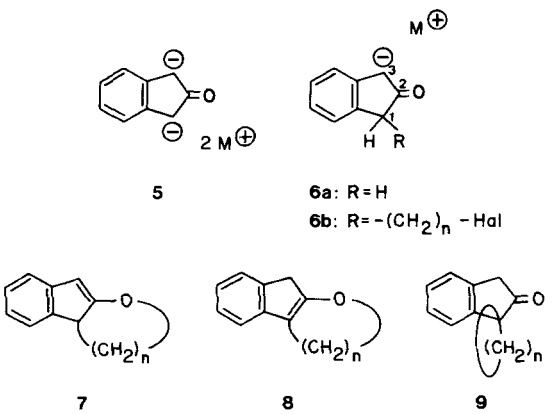
12a: ^{13}C-NMR ($CDCl_3$, 20 MHz): δ = 146.6 (*ipso*-phenyl), 143.6 (C-2, C-3); 127.7, 126.7, 126.5, 122.5 (C-arom.), 82.0 (C-8), 49.2 (C-1, C-4), 24.5 (C-5, C-7), 16.7 (C-6); ^{1}H-NMR ($CDCl_3$, 90 MHz): δ = 7.4–7.1 (9H, arom.), 3.32 (2H, m), 2.46–2.09 (2H, m), 1.99 (1H, s), 1.79–1.20 (3H, m), 1.02–0.5 (1H, m); m.p. = 70°C.

[a] All compounds gave correct elemental analyses.

Our most recent studies of the reductive alkylation of unsaturated hydrocarbons show[3] that the reaction of dianions with difunctional alkylating agents, e.g., 1,n-dihaloalkanes **4**, makes accessible a wide range of new cy-

$Hal-(CH_2)_n-Hal$ **4**

cloannelation and bridged products. In order to synthesize **2**, these results suggested the reaction of the dianion **5**, prepared by deprotonation of 2-indanone (1. NaH, 1.2 equiv., 0°C; 2. *n*-butyllithium, 1 equiv., tetrahydrofuran (THF), −78°C→0°C), with **4** (both **6a** and **5** were characterized by NMR spectroscopy[4]). The central question was



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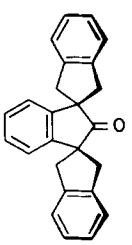
whether the monoanion **6b**, obtained by the first alkylation in the 1-position would tend to react via *C*-alkylation in position 3 (product **2**), by *O*-alkylation (products **7** and **8**), or—after proton migration—by *C*-alkylation in position 1 (product **9**).

We investigated this reaction as a function of the chain length of the alkylating agent, the halide leaving group, and the ion-pair structure:[5]

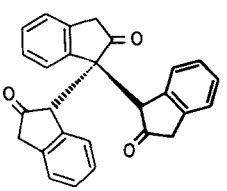
- 1,2-dibromoethane reacts with the dianion of 2-indanone to give solely the spiroannelated product **9a**; 1,3-dibromopropane affords a mixture of **2b** and **8b**;[6] 1,4-dibromobutane gives a complex mixture of products, which cannot be separated, but in which, according to NMR, no enol ether is present.
- The ratio of *C,C*- to *C,O*-alkylation products (**2b/8b**) increases in going from dibromo- to diiodopropane (a "softer" electrophile) from 2:1 to 5:1.
- This product ratio, observed in THF solution, is increased by addition of hexane and reduced by addition of hexamethylphosphoric triamide;[5] the product ratio **2b/8b** is 20:1 if THF/hexane (6:4) is used as solvent.

Even in dilute solution, considerable amounts of oligomeric products are formed; in a typical experiment (1,3-dibromopropane, THF), the yield of **2b/8b** is 31%. The separation of the products is achieved by column chromatography.

The variation of the alkylating agent demonstrates the limitations of the reaction. α,α'-Dibromo-*o*-xylene affords the ketone **3** (18%; side product, dispiro compound **10** (5%)), which is analogous to **2**; no *C,C*-alkylation product is formed with 1,2-bis(β-bromoethyl)benzene. When 1,2-dibromo-1,2-dihydrobenzocyclobutene is used, an electron transfer occurs. The trimer **11** is formed as the product of oxidative coupling.[7]



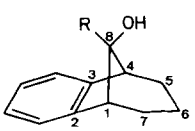
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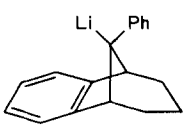
11

The reaction of the ketone **2b** with organometallic compounds (phenyllithium, phenylmagnesium bromide, methyllithium) exhibits pronounced diastereoselectivity: in the alcohol formed, **12**, the carbanion has always added *syn* to the benzene moiety. The configuration of the alcohol **12a** (Table 1) has been confirmed by an X-ray structure determination.[8] These results are in marked contrast to the results obtained for **1a**;[2] in the latter case, only a small amount of diastereoselectivity is observed, which, moreover, depends on the nature of the organometallic agent. Attack of phenyllithium on **3** also affords only the alcohol in which the phenyl group is *syn* to the neighboring benzene system.

The newly accessible ketones and alcohols described here are of further importance for the study of unusual carbanion structures. For example, the alcohol **12a**, formed from **2b**, can be transformed into the corresponding methyl ether. The reductive cleavage of the ether with lithium leads to the benzyllithium system **13**, which exhibits intramolecular "through-space" interaction between the carbanion moiety and the separated benzene π-system.[9]



12a: R = Ph
12b: R = CH_3



13

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Extensions of the Tricyclooctanone Concept. A General Principle for the Synthesis of Linearly and Angularly Annelated Triquinanes

By *Martin Demuth** and *Werner Hinsken*

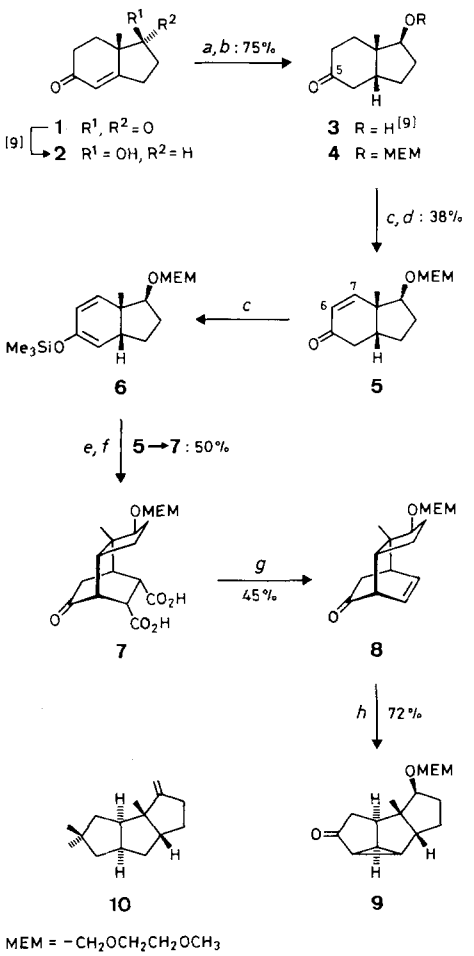
As an extension of our tricyclooctanone concept[1] for the synthesis of enantiomerically pure cyclopentanoid natural products, we present here a variant,[2] which leads to target structures that, using the original concept, would be difficult to obtain. Applying the new strategy, the linear *anti*-annelated triquinane skeleton **9**[3] and its isomer **15** with angularly joined rings are accessible in only a few steps.[4] They are, in our opinion, suitable precursors for hirsutene **10** and 5-oxosilphiperfol-6-ene **16**, respectively.[5]

The light-induced oxadi-π-methane rearrangement of bridged β,γ-unsaturated ketones again serves as the key step. Instead of constructing this type of chromophore via a Diels-Alder reaction of 1,3-dienes with ketene equivalents,[1] the addition of an acetylene equivalent (e.g., maleic anhydride) to siloxy-substituted dienes (**6** and **12**) is used.[6] From the adducts (**7** and **13**, respectively) the photoreactive substrates (**8** and **14**) are obtained and subsequently undergo triplet-sensitized rearrangement to **9** and **15**, respectively. The use of optically active dienes in this new route is advantageous. Both **6** and **12** are derived from a compound (**1** in Scheme 1) whose enantiomers are accessible in very good yields and high optical purities.[7] At first, racemic **1** was employed.

The *cis*-hydrindenone **5**[8] (Scheme 1, hirsutene project) could be prepared in good yield in four steps starting from the known compound **2** (**1** → **2**).[9] The *cis* configuration is

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established in the first step, a highly selective Birch reduction (**2**→**3**).[9] The introduction of the 6,7 double bond (→**5**) was achieved, after protection of the alcohol **3** (→methoxyethoxymethyl ether **4**),[8] by oxidative transformation of the trimethylsilyl C-5,6 enol ether of **4** (main product at −78 °C, 2 min). The method of kinetic formation of enol ethers[10] proved valuable both in this and in the following step. Thus, it was possible to synthesize the siloxydiene **6**[8] nearly quantitatively from **5** at −78 °C in 5 min and to react it, without purification, with maleic anhydride at room temperature. This addition took place in an *endo* manner, which is usual for Diels-Alder additions, and exclusively on the α side of **6** — thus determining the desired *anti* junction of the rings in the final product **9**. After hydrolysis of the resulting anhydride adduct, the diacid **7**[8] could be isolated in crystalline form and easily (in comparison, e.g., to the lead tetraacetate method) decarboxylated electrolytically to **8** (carbon electrodes, 200 V potential) (Table 1). In agreement with previous experience with simpler substrates, the β,γ-unsaturated ketone **8** underwent photochemical rearrangement to **9** upon irradiation at $\lambda = 300$ nm accompanied by the formation of a negligible amount of a side product[11] (reaction time 3 h, 72% yield after purification on silica gel) (Table 1).



Scheme 1. Synthesis of **9**. The sequence was carried out first with racemic material [14]. a) Li/NH_3, −78 °C [9]. b) Methoxyethoxymethyl chloride, ethyldiisopropylamine, CH_2Cl_2, room temperature. c) Lithium diisopropylamide, trimethylsilylchloride, −78 °C, analogous to [10]. d) 2,3-Dichloro-5,6-dicyano-*p*-benzoquinone, benzene, room temperature, 24 h. e) Maleic anhydride, no solvent, room temperature, 4 h. f) H_2O. g) 90% aqueous pyridine, triethylamine, 4-*tert*-butylcatechol, electrolysis, analogous to [12]. h) Acetone (1% solution), irradiation at $\lambda = 300$ nm (Rayonet apparatus with RPR-3000 lamps), room temperature, 3–4 h.

Table 1. Spectroscopic data for compounds **8**, **9**, **14**, and **15**. IR in $CHCl_3$; UV in ethanol; ^{1}H-NMR: 270 MHz, in $CDCl_3$; ^{13}C-NMR: in $CDCl_3$ [a].

8: IR: ν = 1718, 1610, 1120, 1000 cm^{-1}. MS: *m/z* 280 (M^+), 250, 146, 133, 89 (100%), 59. UV: $\lambda_{max}(\varepsilon)$ = 295 nm (140). ^{1}H-NMR: δ = 6.58 (ddd, *J* = 8, 6.5 and 1.2 Hz, 1 H), 6.13 (dddd, *J* = 8, 6.3, 1.6 and 1 Hz, 1 H), 4.73 (d, *J* = 7 Hz, 1 H), 4.68 (d, *J* = 7 Hz, 1 H), 4.0 (dd, *J* = 10 and 5.8 Hz, 1 H), 3.60–3.74 (m, 2 H), 3.5–3.56 (m, 2 H), 3.37 (s, 3 H), 2.94 (ddd, *J* = 6.3, 3.4 and 1.2 Hz, 1 H), 2.71 (dddd, *J* = 6.5, 4, 2.6 and 1 Hz, 1 H), 2.46 (dd, *J* = 19.1 and 2.6 Hz, 1 H), 1.94–2.07 (m, 1 H), 2.0 (dd, *J* = 19.1 and 4 Hz, 1 H), 1.85–1.94 (m, 1 H), 1.61–1.83 (m, 2 H), 1.03 (s, 3 H), 0.92–1.08 (m, 1 H). ^{13}C-NMR (100.6 MHz): δ = 212.9 s, 139.2 d, 127.3 d, 94.6 t, 79.5 d, 71.7 t, 66.8 t, 59.0 q, 54.9 d, 49.9 d, 47.3 s, 40.7 d, 36.9 t, 32.2 t, 25.3 t, 24.4 q

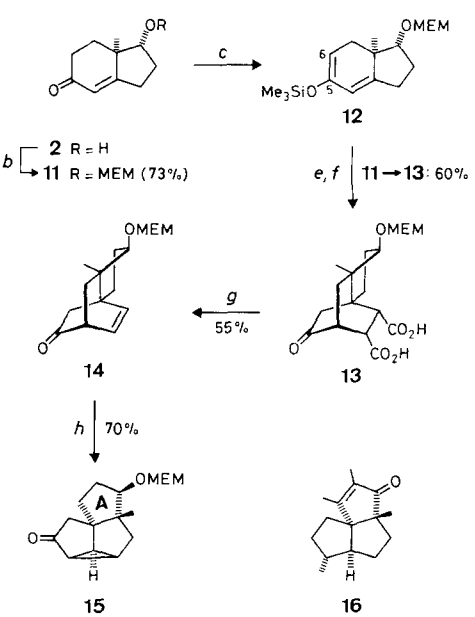
9: IR: ν = 1712, 1100, 1000 cm^{-1}. MS: *m/z* 280 (M^+), 204, 176, 148, 133, 89, 59 (100%). UV: $\lambda_{max}(\varepsilon)$ = 280 nm (65). ^{1}H-NMR: δ = 4.67 (d, *J* = 7 Hz, 1 H), 4.58 (d, *J* = 7 Hz, 1 H), 3.80 (dd, *J* = 6 und 6 Hz, 1 H), 3.61–3.65 (m, 2 H), 3.49–3.53 (m, 2 H), 3.36 (s, 3 H), 2.97 (dd, *J* = 5 and 10.8 Hz, 1 H), 2.56 (ddd, *J* = 6.3, 9.1 and 9.1 Hz, 1 H), 2.36–2.45 (m, 2 H), 2.20–2.30 (m, 1 H), 1.97–2.06 (m, 2 H), 1.66–1.86 (m, 3 H), 1.17 (s, 3 H), 1.09–1.22 (m, 1 H). ^{13}C-NMR (62.9 MHz): δ = 216.1 s, 94.4 t, 78.9 d, 71.8 t, 66.9 t, 63.3 s, 58.9 q, 55.1 d, 47.8 d, 44.9 t, 41.3 d, 36.7 d, 36.0 d, 34.3 d, 27.3 t, 24.4 q

14: IR: ν = 1715, 1610, 1100, 1050, 1005 cm^{-1}. MS: *m/z* 280 (M^+), 204, 175, 162, 147, 130, 118, 105, 89 (100%), 59. UV: $\lambda_{max}(\varepsilon)$ = 297 nm (118). ^{1}H-NMR: δ = 6.24 (d, *J* = 8 Hz, 1 H), 6.21 (dd, *J* = 5.2 and 8 Hz, 1 H), 4.66 (d, *J* = 7 Hz, 1 H), 4.62 (d, *J* = 7 Hz, 1 H), 3.76 (dd, *J* = 7.6 and 9.5 Hz, 1 H), 3.59–3.65 (m, 2 H), 3.47–3.51 (m, 2 H), 3.34 (s, 3 H), 2.98 (dddd, *J* = 2.6, 2.6, 3.3 and 5.2 Hz, 1 H), 2.23 (d, *J* = 18 Hz, 1 H), 2.13–2.28 (m, 1 H), 1.94 (d, *J* = Hz, 1 H), 1.78 (dd, *J* = 2.6 and 13 Hz, 1 H), 1.68–1.81 (m, 3 H), 1.62 (dd, *J* = 3.3 and 13 Hz, 1 H), 0.97 (s, 3 H). ^{13}C-NMR (75.5 MHz): δ = 213.9 s, 143.5 d, 129.5 d, 94.9 t, 85.4 d, 71.7 t, 66.8 t, 58.9 q, 50.5 d, 49.6 s, 46.9 s, 42.6 t, 39.2 t, 29.1 t, 28.4 t, 17.4 q

15: IR: ν = 1715, 1113, 1050, 1030 cm^{-1}. MS: *m/z* 280 (M^+), 224, 204, 190, 174, 149, 146, 105, 89 (100%), 59. UV: $\lambda_{max}(\varepsilon)$ = 284 nm (166). ^{1}H-NMR: δ = 4.75 (d, *J* = 7 Hz, 1 H), 4.7 (d, *J* = 7 Hz, 1 H), 4.2 (dd, *J* = 8.7 and 8.7 Hz, 1 H), 3.6–3.73 (m, 2 H), 3.5–3.57 (m, 2 H), 3.38 (s, 3 H), 2.41 (dd, *J* = 5.5 and 5.5 Hz, 1 H), 2.1–2.33 (m, 4 H), 1.52–1.98 (m, 5 H), 1.39 (dd, *J* = 2.2 and 14 Hz, 1 H), 0.81 (s, 3 H). ^{13}C-NMR (75.5 MHz): δ = 213.7 s, 95.4 t, 83.6 d, 71.8 t, 66.9 t, 60.3 s, 58.9 q, 56.1 s, 48.3 t, 43.6 d, 38.3 d, 36.5 t, 38.4 t, 28.3 t, 28.2 d, 13.7 q

[a] Correct elemental analyses.

The reaction sequence for the synthesis of the angularly fused isomeric triquinane **15** (Scheme 2, oxosilphiperfo-



Scheme 2. Synthesis of **15**. The sequence was carried out first with racemic material [4]. *b*, *c*, and *e*–*h* have the same meaning as in Scheme 1.

lene project) began with the facile synthesis of the diene **12**.[8] **12** could be prepared by kinetic deprotonation of **11**,[8] which gave, as expected,[13] exclusively the 5,6-enolate, and subsequent trapping of the enolate with trimethylsilyl chloride according to the method of *Corey*.[10] **12** was directly used for the subsequent step. The introduction of the etheno bridge [**12** → **13** (exclusively *endo* adduct) → **14** (Table 1)][8] was achieved analogously to the synthesis of **8** (from **6**) in comparable yields. The photorearrangement **14** → **15** (Table 1) (4 h irradiation time, 70% yield after purification on silica gel)[11] confirmed, along with the spectroscopic results, the structure of the enone chromophore of **14**. The possible isomeric arrangement in which the oxoethano and etheno bridges are interchanged would have resulted in a stereoisomer of **15** with an unrealistically strained *trans* ring junction for ring A. The successful oxadi-π-methane rearrangement of **14** to **15** was not predictable a priori. For instance, a few examples of bridgehead-substituted β,γ-enones have been found that are unreactive upon irradiation.[1, 14]

The efficiency and ease of the photorearrangements presented here further support the preparatively interesting applications of specific light-induced processes. The remaining functionalization of **9** to **15** and of **10** to **16** should be realizable using relatively simple procedures.[15]

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[15] According to preliminary experiments the crucial step, the lateral opening of the cyclopropane ring of **9** and **15**, can be achieved selectively under Birch-type conditions; moreover, **15** can be methylated regioselectively in the α-position to the keto group.

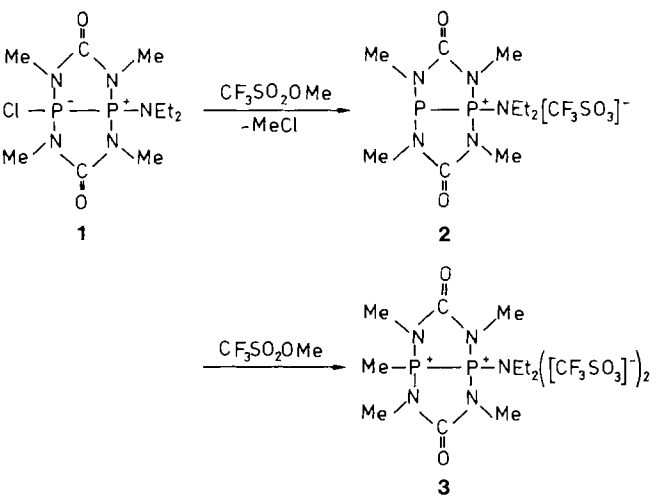
Preparation and Structure of a Diphosphorus Compound with Positive Charges on the Two Directly Bonded Phosphorus Atoms**

By *Dietmar Schomburg, Gerhard Bettermann, Ludger Ernst,* and *Reinhard Schmutzler**

The P–P single-bond distance in diphosphorus compounds varies only slightly, depending on the oxidation state and/or coordination number of the phosphorus atoms involved, and is usually around 220 pm.[1–4] It was therefore of particular interest to determine whether this constant P–P bond length is also observed when both phosphorus atoms bear a formal positive charge. Two opposing effects should be operative in this case: on the one hand, the electrostatic repulsion of the positive charges should lead to a lengthening of the P–P distance; on the other hand, the orbital contraction resulting from the proximity of two positive charges could lead to a shortening of the P–P distance.

To the best of our knowledge, the double quaternization of two directly bonded phosphorus atoms, for example, by alkylation of a $\lambda^3P\lambda^4P^+$ species, has not yet been achieved.[1] Presumably, the nucleophilicity of the λ^3 phosphorus atom is strongly decreased by the proximity of the positive charge.[1, 5] In studies carried out by *Nöth* et al.[6] and *Seidel*,[7] attempts to alkylate several diphosphanes with alkyl iodides resulted in cleavage of the P–P bond and disproportionation rather than quaternization of directly bonded phosphorus atoms. In the case of **2**, however, the bridging of the two phosphorus atoms by the *N,N'*-dimethylurea groups should render cleavage of the P–P bond more difficult.

We have developed a simple synthesis of compound **1** (and of its dimer resulting from chloride bridging).[8] The positive charge in **1** can, as part of the assumed zwitterionic system, presumably be delocalized optimally over three directly neighboring nitrogen atoms. Consequently,



1 **2** **3**

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[†] X-ray structure analysis.

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the nucleophilic properties of the low-valent phosphorus atom in **1** may be more strongly pronounced than in $\lambda^3P\lambda^4P^+$ compounds.

The validity of this assumption was confirmed by reaction of **1** with the strong methylating agent methyl trifluoromethanesulfonate.[9] The reaction proceeds via two steps, the first of which, the removal of the chlorine in **1** to form the salt **2**, takes place at 30°C.[10] The simultaneous formation of methyl chloride was demonstrated by IR spectroscopy. Upon heating of the reaction mixture in a heavy-walled glass tube, the quaternization of the λ^3P atom occurs with formation of the bis(trifluoromethanesulfonate) **3**.[11] **3** is the first compound to contain two directly bonded quaternary phosphorus atoms.

The structure of **3** was confirmed by elemental analysis, by ^1H-, ^{19}F-, and ^{31}P-NMR spectroscopy,[12] and by an X-ray structure determination (Fig. 1).

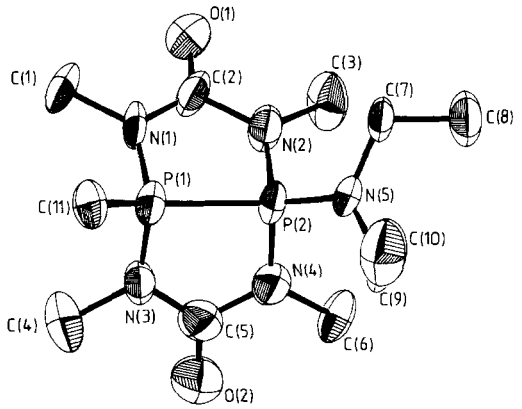


Fig. 1. Crystal structure of the cation of **3**.

The X-ray structure analysis[13] of **3** shows that the P^+–P^+ bond length (average value in the two crystallographically independent molecules 218.9 pm) exhibits, indeed, no significant deviation from the value normally found in diphosphorus compounds. On the other hand, the increased charge on the phosphorus atoms effects a marked shortening of the endocyclic P–N bonds to an average value of 163.7 pm, the corresponding bonds in uncharged phosphorus compounds being ca. 171 pm long.[3,4] The distance of the urea nitrogen atoms to phosphorus atoms bearing a formal negative charge is in the range of 174–176 pm.[3,4]

The bond between the phosphorus atom and the diethylamino nitrogen atom (158.7 pm) is significantly shorter than those to the urea nitrogen atoms. In particular, this very short bond indicates strong multiple bond character with delocalization of the positive charge over both phosphorus atoms and the amino nitrogen atom.

The geometry at both tetracoordinated phosphorus atoms exhibits a strong deviation from the ideal tetrahedral structure because of their incorporation into a bicyclic structure. Thus, the endocyclic N–P–P angle is reduced to 91.3–94.2° while the P–P–X angles (X = Me, NEt_2) are between 132.3 and 136.9°.

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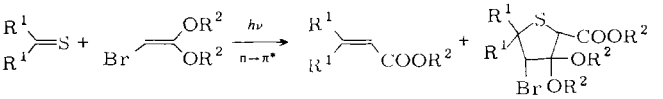
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[10] Characterization of **2**: Elemental analysis, IR, NMR spectroscopy (CD_2Cl_2) [^{31}P-NMR (162 MHz, ext. H_3PO_4): $\delta = 42.7$ (without ^1H): $^1J(PP)$-doublet with unresolved multiplet structure, λ^4P); 16.2 (sept., $^3J(PH) = 9.9$, $^1J(PP) = 170.6$ Hz, λ^3P). ^1H-NMR (400 MHz, $CHDCl_2$, $\delta = 5.32$): $\delta = 3.31$ (ddq, $^3J(PH) = 13.8$, $^4J(PH) = 1.4$, $^3J(HH) = 7.2$ Hz (NCH_2)); 3.15 (dd, $^3J(PH) = 9.8$, $^4J(PH) = 1.9$ Hz (NCH_3)); 3.11 (d, $^3J(PH) = 7.3$ Hz (NCH_3)); 1.34 (t, $^3J(HH) = 7.2$ Hz (CCH_3)). ^{19}F-NMR (56 MHz, CH_2Cl_2, ext. $CFCl_3$): $\delta = -78.8$].
[11] The reaction was carried out with exclusion of moisture in a three-necked flask. Methyl trifluoromethanesulfonate (7 g, 0.043 mol) was added via a syringe to **1** (5.5 g, 0.016 mol) in 30 mL of dichloromethane; the temperature of the solution was then maintained for 5 min at 30 C. After cessation of gas evolution (ca. 1 h), the reaction mixture was transferred to a heavy-walled glass tube and, after sealing of the tube, maintained at 90°C for 3 d. A two-phase system was formed, the dichloromethane being practically free of **3**. After cooling to room temperature, the product phase solidified and the dichloromethane was poured off. The isolated crude product afforded crystals of the pure product after recrystallization from acetonitrile (6.7 g; 67%), m.p. = 204°C (decomp.).
[12] $^{31}P\{^1H\}$-NMR (162 MHz, ca. 32°C, CD_3CN, ext. H_3PO_4): $\delta = 42.7$ ($\nu(1/2) \approx 25$ Hz ($PNEt_2$)); 21.3 ($\nu(1/2) = 16$ Hz (PCH_3); $^1J(PP) = 219$ Hz). The assignment could not be experimentally verified since the fine structure was not resolved on account of the large line width in the spectrum measured without ^1H decoupling. Upon heating of the sample to ca. 70°C, the line widths remained roughly constant. ^1H-NMR (400 MHz, ca. 25°C, CD_3CN, $\delta(CHD_2CN) = 1.98$): $\delta = 3.51$ (br. s with $\nu(1/2) \approx 60$ Hz (NCH_2)); 3.28 (dd, $^3J(PH) = 8.3$, $^4J(PH) = 0.8$ Hz (NCH_3)$_3$); 3.25 (d, $^3J(PH) = 7.7$ Hz (NCH_3)); 3.24 (dd, $^2J(PH) = 16.2$, $^3J(PH) = 7.7$ Hz (PCH_3)); 1.36 (t, $^3J(HH) = 7.0$ Hz (CCH_3)). ^{19}F-NMR (56 MHz, CD_3CN, ext. $CFCl_3$): $\delta = -78.8$ (s).
[13] X-ray structure analysis: $P2_1/c$, $a = 1890.2(2)$, $b = 1327.0(1)$, $c = 2141.2(2)$ pm, $\beta = 103.25(1)°$, $\rho_{calcd} = 1.574$ g cm^{-3}, $Z = 8$, 6911 independent reflections, 3893 observed ($I \geq 2.0\sigma(I)$), $R = 0.099$, Syntex $P2_1$ four-circle diffractometer, $\lambda = 154.178$ pm ($Cu_{K\alpha}$), $2\theta_{max} = 135°$. Empirical absorption correction. Further details of the crystal structure investigation are available on request from the Fachinformationszentrum Energie, Physik, Mathematik GmbH, D-7514 Eggenstein-Leopoldshafen 2, by quoting the depository number CSD-51630, the names of the authors, and the journal citation.

Photoreaction of Thiones with Bromoketene Acetals

By *Pieter H. J. Ooms** and *Willy Hartmann*

Dedicated to Professor Rolf Huisgen on the occasion of his 65th birthday

Thiocarbonyl compounds such as **1** combine with ketene acetals upon n,π* excitation to give 2,2- or 3,3-dialkoxythietanes.[1] We have now investigated the photoreactions of the thiones **1**[2] with the bromoketene acetals **2**[3] and found an unexpected course of reaction.

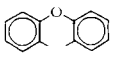
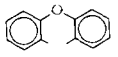
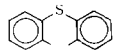
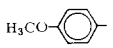
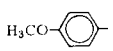


1 **2a**, $R^2 = CH_3$ **3** **4**
2b, $R^2 = C_2H_5$

When a solution of xanthione and bromoketene dimethyl acetal **2a** or bromoketene diethyl acetal **2b** in benzene is irradiated at room temperature the corresponding acrylates **3** are obtained in high yield. Thioxanthione and 4,4′-

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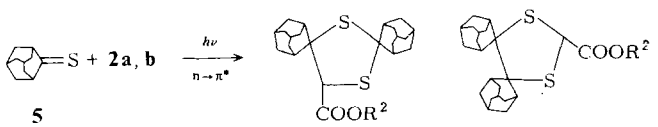
Table 1. Some data of the acrylates **3** [a].

R^1–	R^2	Yield [%]	M.p. [°C]	IR [cm^{-1}] ν(C=O)	^{1}H-NMR (δ values, in $CDCl_3$)
1/2 	CH_3	91	85-86 (85-85.5 [5])	1703 [b]	8.08 (br. d, 1H, J=8.0 Hz), 7.70 (br. d, 1H, J=8.0 Hz), 7.58-7.00 (m, 6H), arom. H, 6.19 (s, 1H, =CH), 3.76 (s, 3H, OCH_3)
1/2 	C_2H_5	82	54.5-55.5 (54-54.5 [6])	1718 [b]	8.09 (br. d, 1H, J=8.0 Hz), 7.71 (br. d, 1H, J=8.0 Hz), 7.58-7.00 (m, 6H), arom. H, 6.18 (s, 1H, =CH), 4.23 (q, 2H, J=7.2 Hz, OCH_2), 1.30 (t, 3H, CH_3)
1/2 	C_2H_5	87	44-45.5	1718 [b]	7.75-7.05 (m, 8H, arom. H), 6.12 (s, 1H, =CH), 4.13 (q, 2H, J=7.2 Hz, OCH_2), 1.80 (t, 3H, CH_3)
	C_2H_5	33	oil	1718 [c]	7.26 (d, 2H), 7.15 (d, 2H), 6.90 (d, 2H), 6.80 (d, 2H), J=8.3 Hz, arom. H, 6.22 (s, 1H, =CH), 4.05 (q, 2H, J=7.2 Hz, OCH_2), 3.82 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 1.14 (t, 3H, CH_3)
	CH_3	23	oil	1721 [c]	7.24 (d, 2H), 7.16 (d, 2H), 6.90 (d, 2H), 6.83 (d, 2H), J=8.8 Hz, arom. H, 6.22 (s, 1H, =CH), 3.83 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 3.61 (s, 3H, OCH_3)

[a] All compounds give correct elemental analyses. [b] KBr pellet. [c] Thin film.

dimethoxythiobenzophenone react similarly (Table 1). If the irradiation of xanthione and **2a** in toluene is carried out at −70°C, besides **3** the stereoisomeric tetrahydrothiophenecarboxylates **4** can be isolated in small yields.[4]

Upon reaction of electronically excited adamantanethione **5** with **2a** or **2b**, the formation of acrylic acid esters **3** does not take place. Instead, a 1,3-dithiolanecarboxylate is obtained in yields of 60-65%. Reductive desulfurization

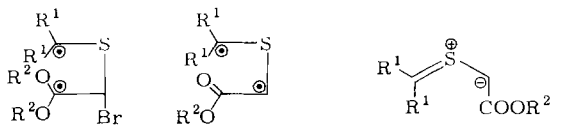


5 **6a, b** **7a, b**

a, R^2 = CH_3; **b**, R^2 = C_2H_5

of the ethyl ester with Raney nickel in methanol furnishes adamantane and (2-adamantyl)acetic acid ethyl ester;[7] thus, it is confirmed that **6b**[8] and not its isomer **7b** is formed. **6b** is also obtained via an alternative route by reaction of **5** with ethyl diazoacetate (ether, 50°C, 1 h, 60%).

For the reaction of n,π*-excited thiones **1** and **5** with bromoketene acetals **2**, we propose the formation of the diradical **8** as the first step.[1] By subsequent heterolytic dissociation[9] of the C-Br bond and dealkylation, the 1,3-diradical **9**, a resonance structure of the thiocarbonyl ylide **10**,[10] is formed.



8 **9** **10**

In the case of the aromatic thiones **1** the main reaction of the thiocarbonyl ylide **10** is cyclization and extrusion of sulfur to give the unsaturated esters **3**.[11] Concomitantly, **10** reacts with **2** leading to the tetrahydrothiophene **4**. Upon reaction of the cycloaliphatic thione **5** with **2**, the 1,3-dipolar cycloaddition predominates. The ylide **10** is trapped by **5** to give the 1,3-dithiolane **6**. We regard the independent synthesis of **6** from **5** and diazoethyl acetate as substantial support for the formulated mechanism. For this type of reaction the intermediate formation of thiocarbonyl ylides is established.[11]

Experimental

3: A solution of **1** (0.01 mol) and **2** (0.05 mol) in benzene (100 mL) was irradiated for 4 to 6 h at room temperature under N_2. A mercury high-pressure lamp (Philips HPK 125W) mounted in a water-cooled shaft (FW161 glass, Glasshütte Wertheim) transparent to light of wavelength $\lambda > 500$ nm was used as light source. After complete decoloration the solution was evaporated to dryness; the acrylates **3** were isolated by column chromatography (Merck silica gel 60F 254, petroleum ether/ethyl acetate 15:1).

6: In the reactions with **5**, a solution of **5** (0.01 mol) and **2** (0.20 mol) in pentane (100 mL) was irradiated for 14 h using a GWV glass filter (Glashütte Wertheim) transparent to light of wavelength $\lambda > 400$ nm. After evaporation to dryness the 1,3-dithiolanes **6** are obtained by recrystallization from ether.

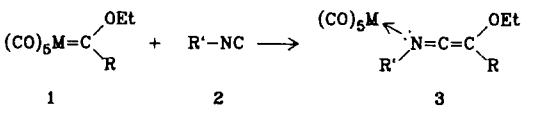
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revised: August 19, 1985 [Z 1330 IE]
German version: *Angew. Chem. 97* (1985) 999

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[2] J. W. Scheeren, P. H. J. Ooms, R. J. F. Nivard, *Synthesis 1973*, 149; J. W. Greidanus, *Can. J. Chem. 48* (1970) 3530.
[3] S. M. McElvain, M. J. Curry, *J. Am. Chem. Soc. 70* (1948) 3781; F. Beyerstedt, S. M. McElvain, *ibid. 59* (1937) 2266.
[4] **4**, R^2=CH_3, isomer A: Yield 5%; unstable oil; ^{1}H-NMR ($CDCl_3$): δ=8.52 (br. d, 1H), 8.04 (br. d, 1H), 7.50-6.93 (m, 6H, arom. H), 4.67 (s, 1H, CHS), 4.42 (s, 1H, CHBr), 3.89 (s, 3H, OCH_3), 3.43 (s, 3H, OCH_3), 3.31 (s, 3H, OCH_3); IR (thin film [cm^{-1}]): ν=1748 (C=O), 760 (C-Br); MS (70 eV): *m/z* 420/418 ($M^{\oplus}-CH_3OH$, 6%), 387/385 (3%), 339 (100%).—**4**, R^2=CH_3, isomer B: Yield 5%; m.p. 182-183.5°C; ^{1}H-NMR ($CDCl_3$): δ=8.46 (br. d, 1H), 8.07 (br. d, 1H), 7.50-6.90 (m, 6H), arom. H, 4.95 (s, 1H, CHS), 4.49 (s, 1H, CHBr), 3.85 (s, 3H, OCH_3), 3.42 (s, 3H, OCH_3), 3.38 (s, 3H, OCH_3); IR (KBr) [cm^{-1}]: ν=1738 (C=O), 743 (C-Br); MS (70 eV): *m/z* 452/450 ($M^{\oplus}$, 4%), 421/419 ($M^{\oplus}-CH_3O$, 2%), 339 (15%), 267 (100%).
[5] H. Gotthardt, *Chem. Ber. 107* (1974) 1856.
[6] H. J. T. Bos, H. T. van der Bend, J. S. M. Boley, C. J. A. Everaars, H. Polman, *Recl. Trav. Chim. Pays-Bas 91* (1972) 65.
[7] (2-Adamantyl)acetic acid ethyl ester: Yield 92%; b.p. 150°C/0.045 torr (Kugelrohr distillation); n_D^{20}=1.4930; ^{1}H-NMR ($CDCl_3$): δ=4.14 (q, 2H, J=7.2 Hz, OCH_2), 2.60-1.40 (m, 15H, adamantane-H), 1.26 (t, 3H, J=7.2 Hz, CH_3); IR (thin film): ν(C=O)=1736 cm^{-1}.
[8] **6a**, yield 65%; m.p. 147.5-148.5°C; IR (KBr): ν(C=O)=1736 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ=4.45 (s, 1H), 3.70 (s, 3H, OCH_3), 2.93-1.43 (m, 28H, adamantane-H); MS (70 eV): *m/z* 404 ($M^{\oplus}$, 5%), 345 ($M^{\oplus}-COOCH_3$, 2%), 238 ($M^{\oplus}$ – Ad=S, 8%), 198 ($M^{\oplus}$ – Ad=CHCOOCH$_3$, 100%).—**6b**, yield 60%; m.p. 151-153°C; IR (KBr): ν(C=O)=1736 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ=4.42 (s, 1H), 4.19/4.16 (dq, 2H, J=7.0 Hz, OCH_2), 2.95-1.40 (m, 28H, adamantane-H), 1.26 (t, 3H, J=7.0 Hz, CH_3); MS (70 eV): *m/z* 418 ($M^{\oplus}$, 6%), 345 ($M^{\oplus}-COOC_2H_5$, 2%), 252 ($M^{\oplus}$ – Ad=S, 8%), 198 ($M^{\oplus}$ – Ad=CHCOOC$_2$H$_5$, 100%).—Ad = 2,2-adamantylidene.
[9] G. Behrens, E. Bothe, G. Koltzenburg, D. Schulte-Frohlinde, *J. Chem. Soc. Perkin Trans. 2 1980*, 883.
[10] R. M. Kellogg, *Tetrahedron 32* (1976) 2165.
[11] R. Huisgen, G. Mloston, *Tetrahedron Lett. 26* (1985) 1049; I. Kalwinsch, R. Huisgen, *ibid. 22* (1981) 3941.

3-Aminoindoles, Imidazolidines, and Oxazolidines from Isocyanides and Carbene Complexes by Metal-Induced [4+2]- and [3+2]-Cycloadditions**

By *Rudolf Aumann,* Eberhard Kuckert,* and *Heinrich Heinen*

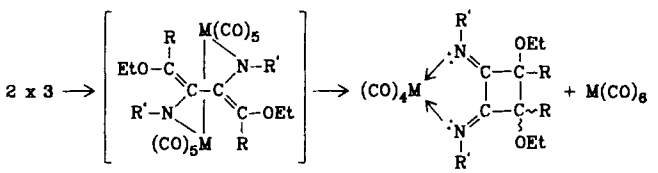
Carbene complexes **1** react with isocyanides **2** to give ketenimine complexes **3**[2] in good yields. Complexes **3** prove to be versatile synthons for organic reactions.[3,4] They are capable of undergoing novel [2+2]-,[3] [3+2]-, and [4+2]-cycloadditions, all of which are characteristically controlled by the carbonylmetal fragment.



1 **2** **3**

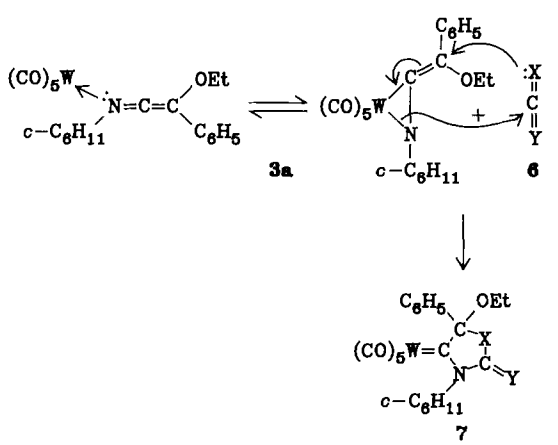
M = Cr, Mo, W; R = C_6H_5, 2-Thienyl;
R' = C_6H_5, o-CH_3O-C_6H_4, c-C_6H_{11}

In inert solvents, **3** is slowly converted at 40–70°C into 1,2-bis(imino)cyclobutane complexes **5** and $M(CO)_6$ by a template-controlled symmetric [2+2]-cycloaddition of two C=C bonds, presumably via the intermediates **4**.[3]



4 **5**

3a reacts rapidly with the C=O and C=N-groups of aldehydes **6a** and isocyanates **6b**, respectively, undergoing [3+2] cycloaddition[5] to give the oxazolidine complexes **7a–c** and imidazolidine complexes **7d–i**, respectively. In each case formation of a M=C bond to the central C atom of the CCN moiety takes place (Table 1).



3a **6**

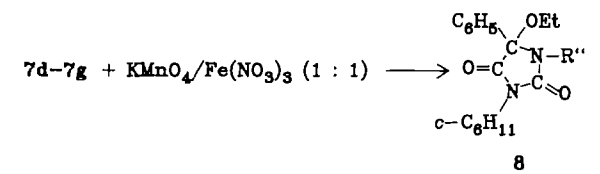
a: X = O, Y = R", H; **b**: X = N–R", Y = O; **c**: X = Y = N–R"

Table 1. Synthesis and physical data of the complexes **7**.

	X	Y	Yield [%]	$\delta(^{13}C_{carbene})$	ν(C=O) [cm^{-1}]	M.p. [°C]
7a	O	C_6H_5, H	78	241.9, 243.3	–	142 [a]
7b	O	CH_3, H	75	[b]	–	119 [a]
7c	O	C_2H_5, H	70	243.7, 243.3	–	131 [a]
7d	N-C_6H_5	O	69	267.2	1766	168
7e	N-CH_3	O	66	267.3	1757	120
7f	N-*n*-C_4H_9	O	63	267.1	1770	114
7g	N-*t*-C_4H_9	O	15	264.8	1760	128
7h	N-C_6H_5	N-C_6H_5	7	[b]	–	80
7i	N-*c*-C_6H_{11}	N-*c*-C_6H_{11}	24	[b]	–	156

[a] As diastereomeric mixture (for composition see below). [b] Not determined.

7 is synthesized in a one-pot process by reaction of **1**, **2**, and **6** in ether. The ketenimine complex **3a**, which is formed in the first step of the reaction, does not need to be isolated. With increasing bulkiness of **6** the [2+2]-cycloaddition to give **5** supersedes the [3+2]-cycloaddition leading to **7**. **7a–7c** each have two chirality centers and accordingly are obtained as diastereomeric mixtures (*S,R*)/(*R,S*):(*S/S*)/(*R/R*) = 1:2 (**7a**), 1:1 (**7b**), 1:1 (**7c**), which can be separated on silica gel. The hydantoins **8** are obtained in high yields by oxidative decomposition of **7d–7g** with $KMnO_4/Fe(NO_3)_3$ in acetone/water (Table 2).



8

Table 2. Synthesis and physical data of the hydantoins **8**.

	R"	Yield [%]	M.p. [°C]	ν(C=O) [cm^{-1}]
8a	C_6H_5	73	128	1770, 1705
8b	CH_3	78	95	1770, 1715
8c	*n*-C_4H_9	80	Oil	1775, 1706
8d	*t*-C_4H_9	84	118	1764, 1708

The ketenimine complexes **3b** prepared from aromatic isocyanides react differently to the aliphatic derivatives. Complexes **3b** rapidly add two further molecules of aryl isocyanide;[6] cycloaddition by *ortho*-attack at the *N*-aryl groups leads to formation of the 3-aminoindole derivatives **11** and **12** – presumably via the intermediates **9** and **10** (Table 3).

The dipolar intermediate **10** dimerizes in anhydrous ether to the pyrazinodiindole **11**, which precipitates as colorless crystals (50%, m.p. 250°C). In the presence of water, **10** hydrolyze to 3-arylamino-2-arylcarbonylindoles **12a–c**, which are readily accessible in this way in a one-pot process.

Experimental:

7a: A solution of cyclohexyl isocyanide (95 mg, 0.87 mmol) in ether (1 mL) was added dropwise to a vigorously stirred solution of $[(CO)_5W{=}C(OEt)C_6H_5]$ (400 mg, 0.87 mmol) and benzaldehyde (250 mg, 2.36 mmol) in anhydrous ether (4 mL) under an inert gas (N_2). After 20 h at 25°C, the reaction mixture was evaporated to dryness and the residue taken up in a small volume of toluene and chromatographed on silica gel (column 10 × 2 cm, petroleum ether/ether 4:1). The yellow main fraction contained **7a**. The separation of the diastereomers was carried out on a 40 × 2 cm column with petroleum ether/dichloromethane 5:1 (1st fraction 137 mg (23%), m.p. 164°C; 2nd fraction 270 mg (47%), m.p. 150°C).

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[**] Organic Synthesis with Transition Metals, Part 14. This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie. We thank Prof. *I. Ugi* for a sample of *o*-CH_3O-C_6H_5-NC. – Part 13: [1].

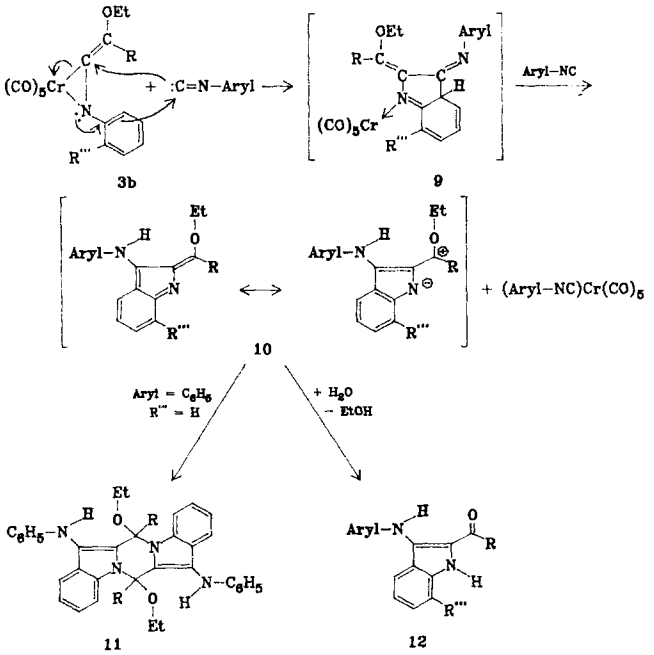


Table 3. Synthesis and melting points of the 3-aminoindole derivatives **12**.

	R	R'''	Yield [%]	M.p. [°C]
12a	C_6H_5	H	72	143
12b	C_6H_5	OCH_3	65–70	oil
12c	2-Thienyl	H	71	138

7d: A solution of $[(CO)_5W{=}C(OEt)C_6H_5]$ (500 mg, 1.09 mmol) and phenyl isocyanate (650 mg, 5 mmol) in anhydrous ether was treated (under the same conditions as given above) with 120 mg (0.13 mL, 1.09 mmol) of cyclohexyl isocyanide. After work-up and column separation **7d** was isolated from the orange fraction. Yield 520 mg (69%), m.p. 168 °C.

12a: $[(CO)_5Cr{=}C(OEt)C_6H_5]$ (326 mg, 1 mmol) was dissolved in tetrahydrofuran (1 mL; ca. 5% water) in an air-tight 5-mL glass vessel and treated dropwise with vigorous stirring with a solution of phenyl isocyanide (309 mg, 3 mmol) in tetrahydrofuran (3 mL) (ca. 30 min). After 4 h at 70 °C the reaction mixture was evaporated to dryness and the residue taken up in a small volume of benzene and chromatographed on silica gel (2 × 20 cm column, elution with petroleum ether/ether 7:3 with continually increasing proportion of ether). **12a** was isolated from the yellow main fraction. Yield 224 mg (72%), m.p. 143 °C (from dichloromethane/petroleum ether at − 15 °C).[7] The colorless first runnings contained ca. 250 mg of $[(C_6H_5NC)Cr(CO)_5]$.

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1 (M = W, R = Ph), 36834-98-7; **1** (M = Cr, R = Ph), 26160-57-6; **1** (M = W, R = *c*-C_6H_{11}), 98481-78-8; **1** (M = Cr, R = 2-thienyl), 29998-70-7; **2** (R' = *c*-C_6H_{11}), 931-53-3; **2** (R' = Ph), 931-54-4; **2** (R' = *o*-CH_3O-C_6H_4), 20771-60-2; **3** (M = W, R = Ph, R' = *c*-C_6H_{11}), 98481-79-9; **3** (M = Cr, R = Ph, R' = Ph), 98481-80-2; **3** (M = Cr, R = Ph, R' = 2-MeOC_6H_4), 98481-81-3; **3** (M = Cr, R = 2-thienyl, R' = Ph), 98481-82-4; **6a** (R'' = Ph), 100-52-7; **6a** (R'' = Me), 75-07-0; **6a** (R'' = Et), 123-38-6; **6b** (R'' = Ph), 103-71-9; **6b** (R'' = Me), 624-83-9; **6b** (R'' = *n*-Bu), 111-36-4; **6b** (R'' = *t*-Bu), 1609-86-5; **6c** (R'' = Ph), 622-16-2; **6c** (R'' = *c*-C_6H_{11}), 538-75-0; *cis*-**7a**, 98481-83-5; *trans*-**7a**, 98574-20-0; *cis*-**7b**, 98481-84-6; *trans*-**7b**, 98574-21-1; *cis*-**7c**, 98481-85-7; *trans*-**7c**, 98575-29-2; **7d**, 98481-86-8; **7e**, 98481-87-9; **7f**, 98481-88-0; **7g**, 98481-89-1; **7h**, 98509-08-1; **7i**, 98481-90-4; **8a**, 98481-91-5; **8b**, 98481-92-6; **8c**, 98481-93-7; **8d**, 98481-94-8; **11**, 98481-95-9; **12a**, 98481-96-0; **12b**, 98481-97-1; **12c**, 98481-98-2; $(C_6H_5NC)Cr(CO)_5$, 14782-94-6.

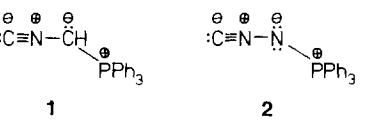
[1] R. Aumann, E. Kuckert, *Chem. Ber.*, in press.
[2] R. Aumann, E. O. Fischer, *Chem. Ber. 101* (1968) 954; C. G. Kreiter, R. Aumann, *ibid. 111* (1978) 1223.
[3] R. Aumann, H. Heinen, *Chem. Ber. 118* (1985) 952; R. Aumann, H. Heinen, C. Krüger, *Angew. Chem. 96* (1984) 234; *Angew. Chem. Int. Ed. Engl. 23* (1984) 223.
[4] R. Aumann, H. Heinen, *Chem. Ber.*, in press.
[5] E. Kuckert, *Diplomarbeit*, Universität Münster 1984.
[6] Both addition steps proceed almost equally rapidly; hence, two equivalents of aryl isocyanide are required for complete reaction of **3b**. As to whether the isocyanide-ketenimine coupling is metal-induced or takes place after previous removal of ligand cannot be answered by simply changing the stoichiometric ratios.
[7] **12a**: ^{1}H NMR: $\delta = 8.80$ (br, 1H, exchangeable with D_2O, N-H indole), 7.95 (br, 1H, exchangeable with D_2O, N-H, NH-Ph), 7.85 ("d", 2H, *o*-H, CO-Ph), 7.50 (m, 3H, *m*- and *p*-CO-Ph), 7.42 (d, 1H, H^4 indole), 7.32 (m, 2H, $H^{6,7}$ indole), 7.28 ("t", 2H, *m*-H, HN-Ph), 7.16 ("d", 2H, *o*-H, HN-Ph), 7.03 (1H, *p*-H, HN-Ph), 6.93 (t, 1H, H^5 indole).—^{13}C NMR: $\delta = 186.16$ (s, CO-Ph), 142.25 (s, C^{7a} indole), 138.93 (s, *i*-C, HN-Ph), 137.66 (s, *i*-C, CO-Ph), 134.09 (s, C^3 indole), 131.39 (d, C^6 indole), 128.94 and 128.12 (each d, each 2C, *o*- and *m*-CO-Ph), 128.64 (d, 2C, *m*-C, HN-Pa), 127.52 (d, *p*-C, CO-Ph), 123.60 (d, C^4 indole), 122.14 (d, C^5 indole), 120.78 (s, C^2 indole), 119.77 (d, 2C, *o*-C, HN-Ph), 119.39 (s, C^{3a} indole), 119.00 (d, *p*-C, HN-Ph), 112.33 (d, C^7 indole).—IR (KBr): ν(N-H) = 3400 (sharp) and 3320 (br), 1590 (st, 2 sh), 1570 (s), 1530 (s), 1490 cm^{-1} (s).—FD-MS: *m/z* 312.—Molar mass (Beckmann) 304.—UV (acetonitrile): $\lambda_{max}(\lg\varepsilon) = 258$ nm (4.37), 326 (4.20), 426 (3.99).

Isocyanomethylenetriphenylphosphorane**

By *Gerhard Zinner* and *Wolf Peter Fehlhammer**

Dedicated to Professor Max Schmidt on the occasion of his 60th birthday

Among the numerous reactions of 'in situ' generated α-metalated isocyanides is carbonyl olefination, which supplements the Wittig reaction without really competing with it.[1] We became interested in isocyanomethylenetriphenylphosphorane **1**, which combines the structural elements (and thus the reaction possibilities) of both synthons; in view of its internal stabilization, this α-carbanionic isocyanide was expected to be isolable. Its *N*-analogue **2** is known and has proved to be a key substance in *N*-isocyanide chemistry.[2]



1 **2**

As a consequence of the unavailability of suitable α-halo isocyanides,[3] the most straightforward synthetic route to **1**, namely, nucleophilic substitution, was blocked. Surprisingly, however, the reaction of trimethylsilylmethyl isocyanide[4] with Ph_3PCl_2 or with PPh_3 and C_2Cl_6[5] in tetrahydrofuran (THF) under very mild conditions was successful [Reaction (a)]: After only 1 h, the phosphonium salt **3a** starts to crystallize out.[6] Its conversion into the hexafluorophosphate **3b** was carried out in neutral aqueous solution

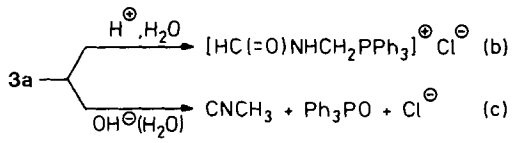
$$CNCH_2SiMe_3 + PPh_3 + C_2Cl_6 \longrightarrow [CNCH_2PPh_3]^{\oplus}\,X^{\ominus} + C_2Cl_4 + SiMe_3Cl \qquad \text{(a)}$$

3a, X = Cl
3b, X = PF_6

by reaction with NH_4PF_6.[6] In acidic media, addition of water takes place to give the corresponding formamide [Reaction (b)]; in basic media, on the other hand, fast

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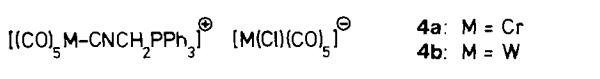
[**] Metal Complexes of Functionalized Isocyanides, Part 12. This work was supported by the Fonds der Chemischen Industrie.—Part 11: [14].



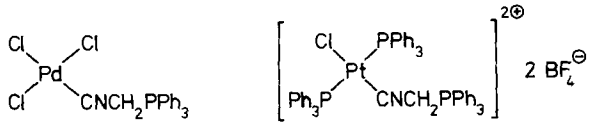
cleavage of the P-C bond occurs with formation of triphenylphosphane oxide and methyl isocyanide [Reaction (c)].

Deprotonation of **3a** by sodium amide in THF gives the yellow neutral compound **1**, which, even in the coordinated form, is extremely sensitive to moisture, decomposing in analogy with Reaction (c). The α-isocyanocarbanionic nature of **1** becomes particularly obvious by comparing its spectroscopic data with those of **3a**.[7]

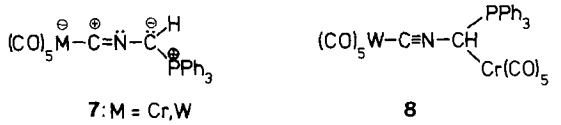
1 and its "storable" form **3** are unusually reactive. For instance, upon heating in toluene to 70°C, **1** undergoes isomerization to the corresponding cyanide, which may be detected by its ν(CN) band at 2139 cm^{-1}. Despite its positive charge, **3** exhibits a pronounced tendency to undergo coordination (formation of **4** and **5**), even with cationic metal complex fragments (formation of **6**).[8]



4a: M = Cr
4b: M = W

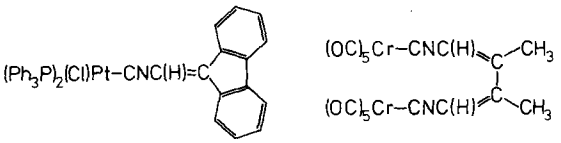


5 **6**



7: M = Cr, W **8**

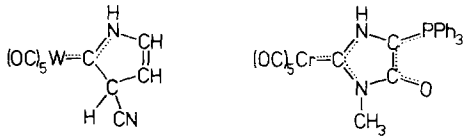
The complex-bound cation of **3** may also be deprotonated; the ylides **7a**, **b** thus formed from **4a**, **b** can coordinate to a second Lewis acidic metal center via the ylide carbon atom (formation of **8**).[8, 9] With carbonyl compounds such as fluorenone or 2,3-butanedione, **1** and **3** as well as their metal complexes (e.g., **4a** or **6**) react to give free and coordinated vinyl isocyanides (e.g., **9**)[10] and bis(vinyl isocyanides) (e.g., **10**[10] (mixture of isomers)); in this respect, **1** and **3** are similar to *Schöllkopf*'s $CNCH_2P(O)(OEt)_2$.[11]



9 **10**

Finally, coordinated **1** undergoes [3+2] cycloadditions with reactive multiple bond systems such as heteroallenes, nitriles, acetylenes, and olefins to give metal-*C*-bonded five-membered heterocycles, PPh_3 being cleaved (e.g., formation of **11**[12]) or remaining bonded (e.g., formation of **12**[12]). In each case, only one product is formed both rapidly and in good yield, i.e., the reactions proceed regiospecifically and (with unsymmetrical heteroallenes) chemoselectively.

Pentacarbonyl(isocyanomethylenetriphenylphosphorane)chromium and -tungsten, **7a**, **b**, are the first stable



11 **12**

1,3-dipoles of the metal nitrile ylide type. Their representation by resonance structure **7**, however, indicates that they are more similar to organic nitrile oxides (or nitrile imines) than to alkyl- or aryl-substituted nitrile ylides, the HOMOs of which, in complete contrast, have the largest coefficient on the twofold coordinated carbon atom.[13]

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[1] U. Schöllkopf, *Angew. Chem. 89* (1977) 351; *Angew. Chem. Int. Ed. Engl. 16* (1977) 339.

[2] B. Weinberger, W. P. Fehlhammer, *Angew. Chem. 92* (1980) 478; *Angew. Chem. Int. Ed. Engl. 19* (1980) 480; B. Weinberger, F. Degel, W. P. Fehlhammer, *Chem. Ber. 118* (1985) 51.

[3] In contrast to α-monohalo isocyanides, di- and trihalo isocyanides are readily accessible in complex-stabilized form: W. P. Fehlhammer, F. Degel, *Angew. Chem. 91* (1979) 80; *Angew. Chem. Int. Ed. Engl. 18* (1979) 75.

[4] R. West, G. A. Gornowicz, *J. Organomet. Chem. 25* (1970) 385; R. Smith, T. Livinghouse, *Synth. Commun. 14* (1984) 639.

[5] R. Appel, *Angew. Chem. 87* (1975) 863; *Angew. Chem. Int. Ed. Engl. 14* (1975) 801. We thank Prof. *Appel* for valuable suggestions.

[6] *Experimental procedure*: **3a**: Trimethylsilylmethyl isocyanide (3.0 mL, 21.2 mmol) [4], PPh_3 (3.5 g, 13.4 mmol), and C_2Cl_6 (3.2 g, 13.4 mmol) were stirred in 100 mL of THF under argon for 18 h at room temperature. The pale yellow precipitate was filtered off, washed with 2 × 10 mL of cold CH_2Cl_2, and dried under vacuum. After recrystallization from CH_2Cl_2/petroleum ether, colorless and odorless crystals were obtained (3.3 g, 73% based on PPh_3).—**3b**: On combination of concentrated aqueous solutions of **3a** and NH_4PF_6 (1 : 1), **3b** precipitated quantitatively.—**1**: **3a** (2.0 g, 5.9 mmol) and $NaNH_2$ (0.7 g, 17.9 mmol) were dispersed in 100 mL of THF at −78°C over 1 h (Ultra-Turrax, 20000 rpm). The filtered solution was concentrated to ca. 1/3 of its original volume under oil-pump vacuum and treated with 15 mL of *n*-hexane. At −15°C yellow **1** crystallized (1.65 g, 93%).

[7] **3a**: IR [KBr]: ν(CN) = 2140 (s) cm^{-1}; ^{1}H-NMR [90 MHz, $CDCl_3$]: δ = 7.19 (d, $^2J_{PH}$ = 10.5 Hz, 2H, CH_2), 7.89 (m, 15H, C_6H_5); $^{31}P\{^1H\}$-NMR [$CDCl_3$, 85% H_3PO_4 ext.]: δ = 22.0; $^{13}C\{^1H\}$-NMR [$CDCl_3$]: δ = 164.8 (s, CN), 38.1 (d, J_{PC} = 56.9 Hz, CH_2).—**1**: IR [KBr]: ν(CN) = 2059 (w) cm^{-1}; ^{1}H-NMR [90 MHz, −30°C, CD_2Cl_2]: δ = 2.99 (d, $^2J_{PH}$ = 28.5 Hz, 1H, CH), 7.63 (m, 15H, C_6H_5); $^{31}P\{^1H\}$-NMR [−30°C, CD_2Cl_2, 85% H_3PO_4 ext.]: δ = 18.9; $^{13}C\{^1H\}$-NMR [−30°C, CD_2Cl_2]: δ = 154.6 (s, CN), 22.4 (d, J_{PC} = 137 Hz, CH); MS [80 eV, 130°C]: *m/z* 301 ($M^{\oplus}$, 51%), 300 ($[M-H]^{\oplus}$, 100%).

[8] Elemental analyses, conductivity measurements, and IR, ^{1}H-NMR, and ^{31}P-NMR spectra are in agreement with the structures given.

[9] W. C. Kaska, *Coord. Chem. Rev. 48* (1983) 1.

[10] **9**: IR [KBr]: ν(CN) = 2180 (s) cm^{-1}; ^{1}H-NMR [CD_2Cl_2]: δ = 7.50 (m, $C_6H_5 + C_6H_4$), 6.16 (s + ^{195}Pt satellites, $^4J_{PtH}$ = 19 Hz, CH); $^{31}P\{^1H\}$-NMR [CD_2Cl_2, 85% H_3PO_4 ext.]: δ = 18.4 (s + ^{195}Pt satellites, J_{PtP} = 2170 Hz).—**10**: IR [*n*-hexane]: ν(CN) = 2120 (m) cm^{-1}; ^{1}H-NMR [$CDCl_3$]: δ = 6.10 (m, 2H, CH), 2.03 (m, 6H, CH_3); MS [80 eV, 110°C]: *m/z* 516 ($M^{\oplus}$, 38%), 376 ($[M-5CO]^{\oplus}$, 100%).

[11] U. Schöllkopf, R. Schröder, *Tetrahedron Lett. 1973*, 633; U. Schöllkopf, R. Schröder, D. Stafforst, *Justus Liebigs Ann. Chem. 1974*, 44.

[12] **11**: IR [KBr]: ν(NH) = 3427 (s), ν(N=C) = 1419 (m) cm^{-1}; ^{1}H-NMR ([D$_6$]acetone): δ = 7.81 (m, 1H, N-CH), 7.02 (m, 1H, C=CH−C), 6.65 (m, 1H, CH−CN); $^{13}C\{^1H\}$-NMR ([D$_6$]acetone): δ = 200.4 (s, *trans*-CO), 196.7 (s, *cis*-CO), 191.7 (carbene C), 129.6 (s, N−CH), 120.9 (s, C=CH−C), 112.1 (s, CH−CN), 89.7 (s, CN); MS [80 eV, 40°C]: *m/z* 416 ($M^{\oplus}$, 2%), 92 ($C_2H_4N_2^{\oplus}$, 100%).—**12**: IR [KBr]: ν(NH) = 3459 (w), ν(>C=O) = 1595 (s), ν_{as}(N=C=N) = 1455 (m) cm^{-1}; ^{1}H-NMR ([D$_6$]DMSO): δ = 11.18 (s, 1H, NH), 7.74 (m, 15H, C_6H_5), 3.39 (s, 3H, CH_3); $^{31}P\{^1H\}$-NMR ([D$_6$]DMSO, 85% H_3PO_4 ext.): δ = 4.8; $^{13}C\{^1H\}$-NMR ([D$_6$]DMSO): δ = 222.6 (s, *trans*-CO), 218.2 (s, *cis*-CO), 187.0 (d, $^3J_{PC}$ = 2 Hz, carbene C), 164.5 (d, $^2J_{PC}$ = 22 Hz, >C=O), 134.0–120.3 (m, C_6H_5), 66.7 (d, J_{PC} = 146 Hz, C=PPh$_3$), 30.4 (s, CH_3).

[13] P. Caramella, K. N. Houk, *J. Am. Chem. Soc. 98* (1976) 6397; cf., however, K. Burger, H. Goth, E. Daltrozzo, *Z. Naturforsch. B37* (1982) 473.

[14] W. P. Fehlhammer, K. Bartel, U. Plaia, A. Völkl, A. T. Liu, *Chem. Ber. 118* (1985) 2235.

$[\mu\text{-}N_2H_2\{Ru(PPh_3)dttd\}_2]$, the First Diazene Complex with Sulfur-Coordinated Transition Metal Centers (dttd = 2,3,8,9-Dibenzo-1,4,7,10-tetrathiadecane(2 –))**

By *Dieter Sellmann,** *Elmar Böhlen, Michael Waeber, Gottfried Huttner,* and *Laslo Zsolnai*

The coordination of N_2 and reduction products N_2H_2 and NH_3 to sulfur-coordinated transition-metal centers is a central problem in the elucidation of the molecular course of N_2-fixation in nitrogenases. Numerous findings indicate that activation and subsequent reduction of the N_2-molecule are achieved by coordination to the sulfur-coordinated iron and/or molybdenum centers of the nitrogenase; nevertheless, all attempts to detect N_2 or N_2H_2 in complexes with metal-sulfur centers have hitherto met without success.[1]

In the search for model compounds for nitrogenase we have now isolated a complex in which diazene HN=NH is bound to sulfur-coordinated ruthenium centers. Diazene is extremely unstable in the free state;[2] it is probably the key compound of the reduction of N_2 in N_2-fixation,[3] but it has so far only proven possible to demonstrate its formation from molecular nitrogen indirectly.[4] As we have previously been able to show, diazene can be stabilized considerably by complexation; however, this has so far only been accomplished with the organometal complex fragments $M(CO)_5$, M = Cr, Mo, W and $C_5H_5M(CO)_2$, M = Mn, Re.[5]

In the reaction

$$[Ru(N_2H_4)(PPh_3)dttd][6] \xrightarrow[20\,^\circ C/1\,d]{O_2/CH_2Cl_2} [\mu\text{-}N_2H_2\{Ru(PPh_3)dttd\}_2] + \cdots$$
1

the color of the solution gradually changes from yellow to deep green. Filtration and subsequent concentration and cooling of the filtrate afford blackish-green crystals whose composition according to an elemental analysis is consistent with the compound $\mathbf{1}\cdot 2CH_2Cl_2$. A spectroscopic confirmation of this formulation was not possible.[7] Besides the intense color, a weak signal in the ^{1}H-NMR spectrum ($CDCl_2$) at $\delta = 14.5$ alone indicated that a diazene unit was formed from the N_2H_4 ligand of the starting complex.

An X-ray structure analysis of the crystals confirmed this indication.[8] A *trans*-N_2H_2 ligand couples two Ru centers, which are additionally surrounded pseudooctahedrally by four S atoms and one P atom (Fig. 1).

The molecule has a crystallographically established inversion center in the mid-point of the N=N bond. The structure could be determined accurately enough to establish the positions of all H atoms and to refine the parameters of the diazene hydrogen atoms. Accordingly, the Ru, N, H_N and the S1 and S4-thiolate atoms lie in a plane, to which the (S2RuP)- and (S2′Ru′P′)-axes are oriented orthogonally. The bond lengths and angles characterize **1** as a *trans*-diazene complex. The N=N distance (130.1 pm) is slightly larger than the corresponding distance in $[\mu\text{-}N_2H_2\{Cr(CO)_5\}_2]\cdot 2thf$ (125 pm),[9] but nevertheless still much shorter than is to be expected for a N-N bond; the Ru-N distance is relatively short (202.6 pm). (The corresponding distances in the methylhydrazine complex $[Ru(CH_3NHNH_2)PPh_3(dttd)]$ are N-N = 143 and Ru-N = 217 pm.[10]) The angles too are consistent with sp^2 hybridized N atoms; consequently, the Ru-diazene moiety is best described in terms of a Ru=N=N=Ru 4c-π-system. The intense color typical for diazene complexes is also in agreement with this description.

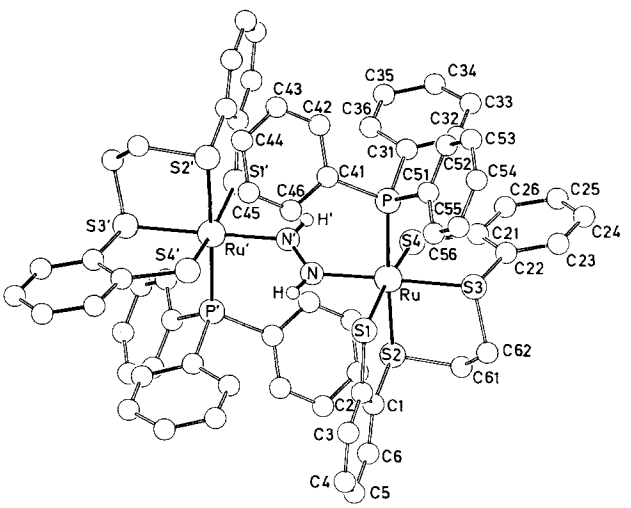


Fig. 1. Structure of **1** in the crystal of $\mathbf{1}\cdot 2CH_2Cl_2$.

These results show that the unstable HN=NH can be stabilized also by coordination to sulfur-coordinated metal centers. Generally, the formation of the M=N=N=M four-center system might be responsible for this stabilization. A second stabilizing factor in the case of **1** is certainly the good steric shielding of this system. The third stabilizing factor is caused by the sulfur ligand. As is shown in Figure 2, the mean $S\cdots H(N_2H_2)$ distances are ≈288 pm (Fig. 2). They are thus about 20 pm shorter than the sum of the corresponding van der Waals radii (≈305 pm[11]), indicating H-bridges between the diazene H-atoms and thiolate S-atoms.

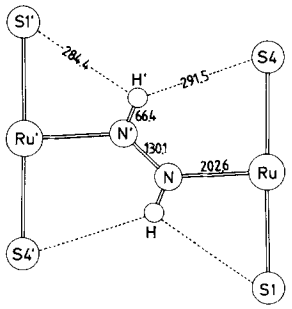


Fig. 2. View onto the $Ru\text{-}N_2H_2\text{-}Ru$ coordination plane in **1** with $S\cdots H(N_2H_2)$ distances [pm].

Such an interaction between diazene and sulfur ligands—observed here for the first time—should favor the formation of diazene upon N_2-reduction at sulfur-coordinated metal centers and lower the energy that is necessary

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[**] Transition Metal Complexes with Sulfur Ligands, Part 17. This work was supported by the Deutsche Forschungsgemeinschaft, the Fonds der Chemischen Industrie, and by the Dr.-Otto-Röhm-Gedächtnisstiftung. – The IUPAC name for the ligand is 2,2′-ethylenedithiobis(benzenethiolate). Part 16: D. Sellmann, W. Reisser, *J. Organomet. Chem.*, in press.

for the conversion of a $M-N_2$ moiety into a $M-N_2H_2$ moiety.[12]

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[2] S. N. Foner, R. L. Hudson, *J. Chem. Phys. 28* (1958) 719; S. Hünig, H. R. Müller, W. Thier, *Angew. Chem. 77* (1965) 368; *Angew. Chem. Int. Ed. Engl. 4* (1965) 271; N. Wiberg, G. Fischer, H. Bachhuber, *ibid. 84* (1972) 889 and *11* (1976) 829.

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[4] Cf. also a) G. N. Schrauzer, *Angew. Chem. 87* (1975) 579; *Angew. Chem. Int. Ed. Engl. 14* (1975) 514; b) the intermediary occurrence of N_2H_2 can also be concluded from the hydrolysis products N_2 and N_2H_4 of N_2-complexes such as $[\{(C_5H_5)_2Ti\}_2N_2]$ or $[\{(C_5H_5)_2TiPh\}_2N_2]$: Y. G. Borodko, I. N. Ivleva, L. N. Kachapina, S. I. Salienko, A. K. Shilova, A. E. Shilov, *J. Chem. Soc. Chem. Commun. 1972*, 1178; F. W. van der Weij, J. H. Teuben, *J. Organomet. Chem. 120* (1976) 223.

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[7] No NH-bands can be observed in the IR spectrum of **1**. Only fragment ions occur in the FD-mass spectrum, and a Raman spectrum for the identification, e.g., of the NN double bond could not be recorded because of fluorescence and decomposition. In the visible region of the electronic spectrum (in CH_2Cl_2) two bands can be observed at 480 nm ($\varepsilon_{max}=6980$ L/mol cm) and 610 nm ($\varepsilon_{max}=2860$ L/mol cm), which are missing in the case of other $[Ru(PPh_3)_3dttd]$ complexes.

[8] X-ray structure analysis of $1\cdot 2CH_2Cl_2$: $P\bar{1}$, $a=1152.7(6)$, $b=1256.6(8)$, $c=1391.1(8)$ pm, $\alpha=116.54(4)$, $\beta=110.41(4)$, $\gamma=98.86(5)°$; $V_{calc}=1569.97\times 10^6$ pm^3; $Z=1$. $T=-35°C$, $\lambda Mo_{K\alpha}$, ω scan $1.6<\omega<29.3°$ min^{-1}, $4<2\theta<46°$. Of 4371 independent reflections, 3870 with $I>2\sigma(I)$. (SHELXTL, direct methods, $R_1=0.051$, $R_2=0.057$. The positions of all H atoms were determined by difference Fourier synthesis, but only the positions of the H atoms on N were refined). Important bond lengths [ppm] and angles [°]. NN' 130.1(1.4), NH 66.4(15.5), RuN 202.6(5), RuS1 237.2(3), RuS2 234.4(3), RuS3 228.2(2), RuS4 237.4(3), RuP 231.8(2), S1C2 174.8(9), S2C1 176.6(1.1), S2C61 182.1(7); RuNN' 129.3(9), N'NH 113.5(8.5), RuNH 116.8(8.2), S1RuS4 168.7(1), S1RuS2 86.1(1), S2RuP 176.0(1), S2RuS3 88.4(1), S1RuN 87.3(3), S4RuN 92.2(3). Further details of the crystal structure investigation are available on request from the Fachinformationszentrum Energie, Physik, Mathematik GmbH, D-7514 Eggenstein-Leopoldshafen 2, on quoting the depository number CSD-51487, the names of the authors, and the full citation of the journal.

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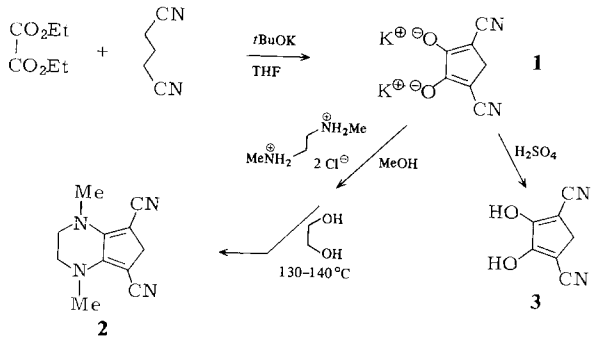
[12] Estimating a bonding enthalpy of only 12 kJ/mol per H-bridge, the four $S-H(N_2H_2)$ bridges in the title complex would lower by about 25% the bonding enthalpy of the complexed N_2H_2 compared to that of the free N_2H_2 of $\Delta H_{f(298)}=212$ kJ [13].

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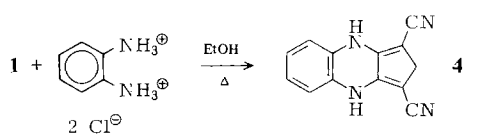
Donor-Acceptor Substituted Anions and Cations in the Cyclopentadienyl System**

By *Rudolf Gompper** and *Thomas Gessner*

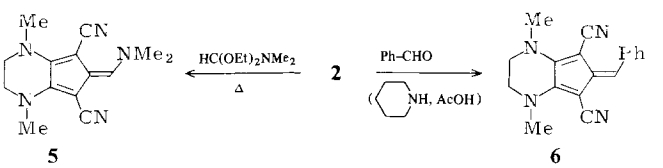
In connection with studies on the color and reactivity of pyridiniocyclopentadienides[1] we have concerned ourselves with the preparation of donor-acceptor substituted cyclopentadienes, since the pyridiniocyclopentadienides obtained from them should absorb at longer wavelengths than analogues without substituents in the five-membered ring. Donor-acceptor substituted derivatives should at the same time, however, be more stable than donor-substituted derivatives, which are likewise expected to exhibit bathochromism.



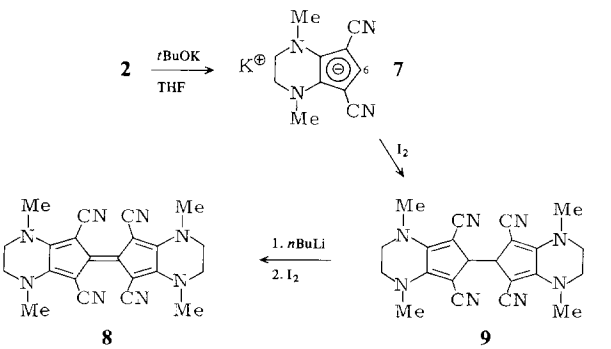
The well known reaction of glutaric acid dinitrile with diethyl oxalate[2] can be considerably improved by the use of potassium *tert*-butoxide/tetrahydrofuran (THF). The dipotassium salt **1** is formed in quantitative crude yields. It reacts with *N,N'*-dimethylethylenediamine dihydrochloride to yield the ammonium salt, which can be converted by heating in ethylene glycol into the desired donor-acceptor substituted cyclopentadiene **2** (yield 52%, colorless needles, m.p. 248 °C (decomp.)). Protonation of **1** provides the dihydroxy compound **3** (colorless powder, m.p. 222 °C (decomp.)). The analogous reaction of **1** with *o*-phenylenediamine dihydrochloride affords the cyclopentadiene derivative **4** (yield 57%, orange-yellow crystals, decomp. above 250 °C).



Like other cyclopentadienes, **2** is suitable for the preparation of fulvenes. Reaction with dimethylformamide di-



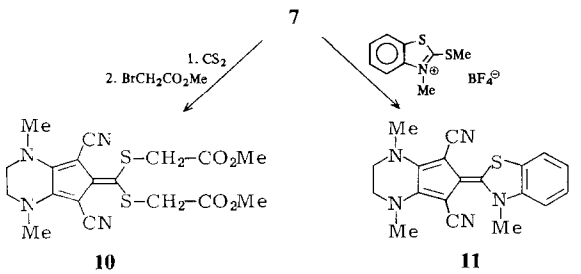
ethyl acetal affords the 6-dimethylaminofulvene **5** (yield 65%, orange-yellow needles, m.p. 128–130 °C), while reaction with benzaldehyde furnishes the 6-phenylfulvene **6**



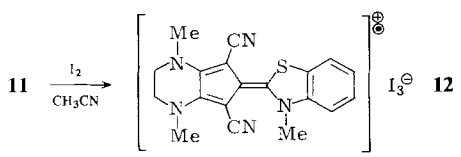
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(yield 51%, orange-yellow needles, m.p. 228–230°C). Fulvalenes are also accessible from **2**. The yellowish potassium salt **7** [^{1}H NMR (CD_3CN): $\delta = 2.66$ (s; 6H, NCH_3), 2.79 (s; 4H, NCH_2), 6.05 (s; 1H, 5-ring-H)], obtained from **2** with potassium *tert*-butoxide, reacts with iodine to give the colorless dihydrofulvalene **9** (m.p. 190°C (decomp.)), from which the donor-acceptor substituted fulvalene **8** is formed by reaction with *n*-butyllithium and then with iodine [yield 66%, shiny green prisms, m.p. 317–318°C; UV/VIS (CH_3CN): $\lambda_{max}(\log\varepsilon) = 230$ (4.44), 265 (sh, 3.94), 301 (sh, 3.68), 335 (sh, 3.33), 520 nm (4.47)].



7 also reacts with carbon disulfide. The resulting dithiocarboxylic salt reacts, e.g. with methyl bromoacetate to give the bis(methoxycarbonylthio)fulvene **10** (yield 71%, orange-yellow needles, m.p. 190°C). Treatment of **7** with 3-methyl-2-methylthiobenzothiazolium tetrafluoroborate leads to the thiaazafulvalene **11** [yield 57%, shiny metallic green prisms, m.p. 248–250°C; UV/VIS (CH_3CN): $\lambda_{max}(\log\varepsilon) = 225$ (4.52), 520 nm (4.58)], which can be oxidized with iodine to the blackish-violet radical cation salt **12**



[yield 91%, m.p. 156°C; UV/VIS (CH_3CN): $\lambda_{max}(\log\varepsilon) = 212$ (4.53), 236 (4.36), 291 (4.71), 365 (4.50), 424 (4.39), 568 (sh, 3.66), 609 (3.79), >900 nm].

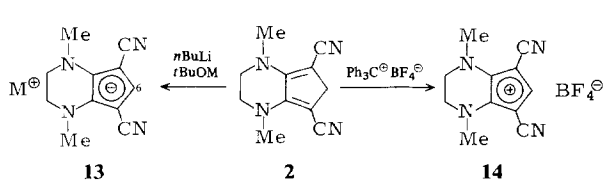
The distinctive effect of the combination of donor- and acceptor-substituents in **2** is illustrated in a dramatic way by the fact that not only can the (yellow) cyclopentadienides **13** be prepared (e.g. **7**, M = K), which contain the "aromatic" 6π system of the cyclopentadienide anion, from **2**, but also the green cyclopentadienylium tetrafluoroborate **14**, which contains the "antiaromatic" 4π system of the cyclopentadienylium cation [yield practically quantitative, m.p. 160°C (decomp.); UV/VIS (CH_3CN): $\lambda_{max}(\log\varepsilon) = 225$ (4.25), 307 (4.13), 350 (sh, 3.59), 426 (sh, 2.46), 810 nm (2.52); ^{1}H NMR (CD_3CN): $\delta = 3.65$ (s; 6H, NCH_3), 4.00 (s; 4H, NCH_2), 8.15 (s; 1H, 5-ring-H)]. The signal of the five-membered ring H atom in the anion of **7** (δ(H-6) = 6.05) is shifted somewhat downfield compared to that of the (unsubstituted) cyclopentadienide anion[3] ($\delta = 5.49$). This difference, taking into account the relationship between charge density (according to PPP: $q_{C\text{-}6} = -0.128$[4]) and chemical shift ($\Delta\delta_q = (10.7\,\Delta q_\mu)$ ppm[5]) shows **7** to be a typical aromatic compound with diamagnetic ring current. As expected, the substituents in **7** do not influence the aromatic properties of the anionic cyclopentadienide system. The signal of the corresponding proton in the cation of **14** ($\delta = 8.15$) appears between the proton signals of the tropylium ion ($\delta = 9.26$[6]) and of benzene ($\delta = 7.27$[7]) and not, as one would expect from the size of the ring, between those of the cyclopropenylium ion ($\delta = 11.1$[8]) and of the tropylium ion. The charge-induced shift on going from **13** to **14** ($\Delta\delta_q = 3.58$ ppm) calculated from the charge density on C-6 of **14** (according to PPP: $q = +0.207$[4]) using the above equation is considerably larger than that observed ($\Delta\delta = 2.10$ ppm) and leads to a calculated paratropic shift of $\Delta\delta_p = 1.48$ ppm in **14**. This value is actually smaller than, for instance, that in the bicyclo[5.4.1]dodecapentaenide anion (3.7–6.8 ppm),[9] but is comparable with that observed in tri-*tert*-butylcyclobutadiene (1.04 ppm).[10] Like other paratropic compounds (cf., e.g.,[11]) **14** may therefore be counted among the antiaromatic systems. The yellow salt **15**[12] ($\lambda_{max} = 421$ nm) can be regarded as a non-aromatic compound for comparison with **14**.



Compared to this model (^{1}H NMR: δ(H-3) = 8.3; PPP: $q_{C\text{-}3} = +0.129$[4]) the signal of H-6 in the ^{1}H NMR spectrum of **14** shows a small upfield shift. Particularly striking is the enormous difference in color (green/yellow, $\Delta\lambda_{max}$ ca. 400 nm) between **14** and its open-chain analogue **15**.

As in **13**, the substituents in **14** also change the properties of the parent compound only slightly. **14** is more stable than the unsubstituted cyclopentadienylium cation (inter alia because of the removal of degeneration of the frontier orbitals), but the paratropic and thus antiaromatic properties are retained, albeit to a lesser extent.

There are only very few fully conjugated monocyclic systems which, with the same ring size and same substituents, exist both as a cation as well as an anion, with the latter possessing two additional π-electrons. In the case of the pentachloro- and pentaphenylcyclopentadienide derivatives, the (aromatic) metal cyclopentadienides are stable,[14] whereas the (antiaromatic) cyclopentadienylium salts could previously only be obtained in solution.[13] **13** and **14** are, in contrast, the first pair of carboxylic ions in which the partners have comparable stability.

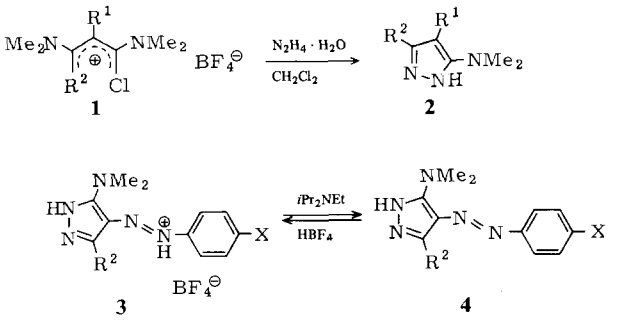


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1, 98689-16-8; **2**, 98689-19-1; **3**, 10528-59-3; **4**, 98689-20-4; **5**, 98689-21-5; **6**, 98689-22-6; **7**, 98689-23-7; **8**, 98689-25-9; **9**, 98689-24-8; **10**, 98689-27-1; **11**, 98689-28-2; **12**, 98689-30-6; **14**, 98703-78-7; $(EtO)_2CCO_2Et$, 95-92-1; $NC(CH_2)_3CN$, 544-13-8; $MeNH(CH_2)_2NHMe \cdot 2HCl$, 5752-40-9; $2\text{-}H_2NC_6H_4NH_2 \cdot 2HCl$, 615-28-1; $(EtO)_2CHNMe_2$, 1188-33-6; PhCHO, 100-52-7; CS_2, 75-15-0; $BrCH_2CO_2Me$, 96-32-2; 4,5-dioxo-1,3-cyclopentandicarbonitrile *N,N'*-dimethylethylenediamine salt, 98689-18-0; 5,7-dicyano-1,4-dimethyl-1,2,3,4-tetrahydro-6*H*-cyclopentapyrazine-6-dithiocarboxylic acid potassium salt, 98689-26-0; 3-methyl-2-(methylthio)benzothiazolium tetrafluoroborate, 36530-03-1.

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1/2	R^1	R^2	3/4	R^2	X
a	H	H	**a**	H	OMe
b	H	NMe_2	**b**	H	NO_2
c	Ph	H	**c**	NMe_2	OMe
d	Ph	NMe_2	**d**	NMe_2	NMe_2

Dimethylamino-Pyrazoles and Pyrazolylium Salts**

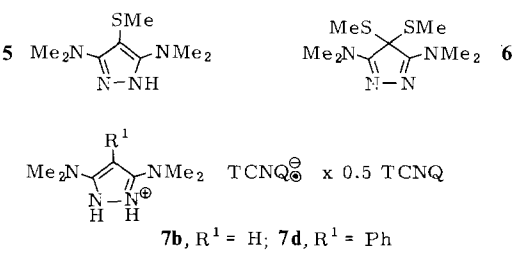
By *Rudolf Gompper,* Rainer Guggenberger,* and *Rolf Zentgraf*

In investigations into stable five-membered ring cations which are formally to be counted among the antiaromatic species, we have previously prepared imidazolylium salts,[1] pyrrolylium salts,[2] and finally also crystallized cyclopentadienylium salts.[3] The gradation in the color of these compounds (yellow/red/blue to green) is consistent with the HOMO-LUMO distances calculated by HMO. According to these calculations the longest wavelength absorption maxima in the electronic spectra of pyrazolylium salts, i.e. of 1,2-diazacyclopentadienylium salts, should approach the maxima of the cyclopentadienylium salts, and the stabilities of the two systems should also be comparable. Since dialkylamino groups had proven to be stabilizing groups for the previously prepared five-membered ring cations, it seemed to us that 3-dialkylamino- and 3,5-bis(dialkylamino)pyrazoles would be the most suitable starting materials. Due to their richness in electrons, they ought to be more susceptible to electrophilic substitution than simple pyrazoles, and, moreover, they ought to be easily oxidizable.

1-Substituted dialkylaminopyrazoles have long been known,[4] while compounds not substituted in the 1-position are relatively new.[5-7] *Viehe* et al.[8] have prepared 3,5-dichlorovinamidinium salts, but only in the case of one 4-phenoxy derivative has a corresponding 1-unsubstituted pyrazole been reported.

We have now found that the 5-dimethylamino- and 3,5-bis(dimethylamino)pyrazoles **2a–d**[9] are readily accessible in good yields by reaction of the 1-chloro- and 1,3-dichloro-vinamidinium tetrafluoroborates **1a–d**, respectively, with hydrazine in dichloromethane. The chlorides **1**, $Cl^{\ominus}$ instead of $BF_4^{\ominus}$, are sensitive to hydrolysis and are therefore unsuitable for this reaction.

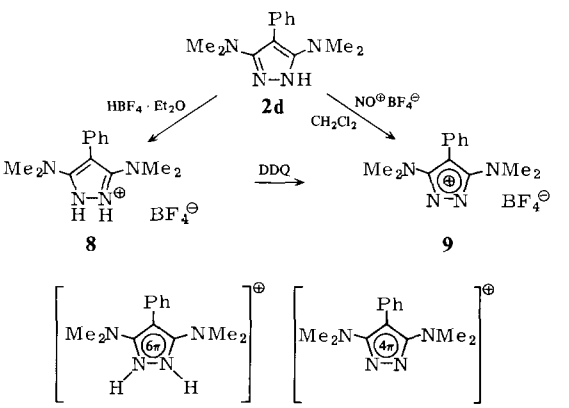
Upon coupling **2a** and **2b** with benzenediazonium chlorides in dilute mineral acids and subsequent addition of sodium acetate, or benzenediazonium tetrafluoroborates in acetonitrile (in the case of **2b** this usually leads to improved yields), the azo dyes **4** and their salts **3**[10] are obtained. **2b** reacts with dimethyl(methylthio)sulfonium tetrafluoroborate[11] in dichloromethane to give, depending on the molar ratio, either the 3,5-bis(dimethylamino)-4-methylthio-1*H*-pyrazole **5** (yield 82%, m.p. 101–102 °C) or the 3,5-bis(dimethylamino)-4,4-bis(methylthio)-4*H*-pyrazole **6** (yield 70%, m.p. 151 °C).



7b, R^1 = H; **7d**, R^1 = Ph

When a hot saturated solution of tetracyanoquinodimethane (TCNQ) in acetonitrile is treated with **2b** or **2d** the solution immediately turns deep-green, the color typical for the TCNQ radical anion, and upon cooling, blackish-blue needles of **7b** and **7d**, respectively, crystallize out (**7b**: m.p. 234 °C (decomp.); **7d**: m.p. 216–218 °C (decomp.)). The electrical conductivities (two-electrode measurement, $P = 1800$ kp/cm^2) of pellets of these salts at room temperature are $\sigma = 1.6 \times 10^{-3}$ S/cm and 6.1×10^{-3} S/cm, respectively.

Attempts to eliminate a methylthio group from **6** to give a pyrazolyl cation met without success. However, oxida-



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tion of **2d** with nitrosyl tetrafluoroborate furnishes 3,5-bis(dimethylamino)-4-phenylpyrazolium tetrafluoroborate **9** in 72% yield as dark blue crystals.[12] On a preparative scale it was found that protonation of **2d** with tetrafluoroboric acid and subsequent oxidation of the isolable pyrazolium salt **8**, with dichlorodicyano-*p*-benzoquinone (DDQ), was more favorable.

The electronic spectrum of **9**[12] is, as expected, similar to that of a structurally related cyclopentadienylium salt (6-dimethylamino-1,4-dimethyl-5,7-diphenyl-1,2,3,4-tetrahydrocyclopentapyrazine-6-ylium tetrafluoroborate: $\lambda_{max} = 624$ nm[3]). Also informative with respect to the electronic properties of the 4π system **9** is a comparison with the 6π system **8**: In the ^{1}H-NMR spectrum of **9**, two signals appear at $\delta = 3.91$ and 2.90, which are assigned to the protons of the dimethylamino groups. Upon increasing the temperature these signals broaden and the coalescence temperature is 121°C. From this, an energy barrier of $\Delta G^* = 19.45$ kcal/mol is calculated for the rotation about the ring-NMe_2 bond. The ^{1}H-NMR spectrum of **8**, on the other hand, shows only one signal for these protons, indicative of a rapid rotation of the dimethylamino groups. Apparently—and as expected—the 4π system of **9** is a very much stronger electron acceptor than the 6π system of **8**.

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1a, 98635-07-5; **1b**, 98635-09-7; **1c**, 98635-10-0; **1d**, 98635-12-2; **2a**, 26387-78-0; **2b**, 98635-13-3; **2c**, 98635-14-4; **2d**, 98635-15-5; **3a**, 98635-17-7; **3b**, 98635-19-9; **3c**, 98635-21-3; **3d**, 98635-23-5; **4a**, 98635-16-6; **4b**, 98635-18-8; **4c**, 98635-20-2; **4d**, 98635-22-4; **5**, 98635-24-6; **6**, 98635-25-7; **7b**, 98651-86-6; **7d**, 98651-89-9; **8**, 98651-90-2; **9**, 98635-27-9; 4-methoxybenzenediazonium tetrafluoroborate, 459-64-3; 4-nitrobenzenediazonium tetrafluoroborate, 456-27-9.

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[9] **2a**: Yield 81%, colorless oil, b.p. 104°C/10^{-3} torr (Ref. [6]: b.p. 85°C/10^{-4} torr); **2b**: yield 87%, m.p. 122–123°C; **2c**: yield 47%, m.p. 149.5–150°C; **2d**: yield 46%, m.p. 162–162.5°C.
[10] **3/4** [m.p., UV/VIS (CH_3CN): $\lambda_{max}(\log\varepsilon)$]: **3a**: 194°C, 468 nm (4.42); **4a**: 208°C, 423 nm (sh, 4.17); **3b**: 254°C, 443 nm (4.46); **4b**: 269°C, 467 nm (4.35); **3c**: 166°C, 435 nm (4.32); **4c**: 178–179°C, 420 nm (sh, 4.06); **3d**: 404 nm (4.25); **4d**: 206–206.5°C, 448 nm (4.36).
[11] H. Meerwein, K. F. Zenner, R. Gipp, *Justus Liebigs Ann. Chem. 688* (1965) 67; S. H. Smallcombe, M. C. Caserio, *J. Am. Chem. Soc. 93* (1971) 5826.
[12] **9**: m.p. 160–161°C; UV/VIS (CH_3CN): $\lambda_{max}(\log\varepsilon) = 209$ (3.67), 229 (3.52), 267 (3.73), 337 (s, 3.06), 583 nm (3.71); ^{1}H NMR (CD_3CN): $\delta = 2.90$ (s; 6H, NCH_3), 3.91 (s; 6H, NCH_3), 7.36 (mc; 5H, phenyl-H); ^{13}C NMR (CD_3CN): $\delta = 41.89$ (q; NCH_3), 44.07 (q; NCH_3), 87.02 (s; C-4), 129.24 (s; Ph-C-*i*), 129.79 (d; Ph-C-*m*), 130.09 (d; Ph-C-*p*), 133.27 (Ph-C-*o*), 168.35 (s; C-3, C-5).

A Novel Route to Pentamethylcyclopentadienyllutetium Alkoxides and Thiolates**

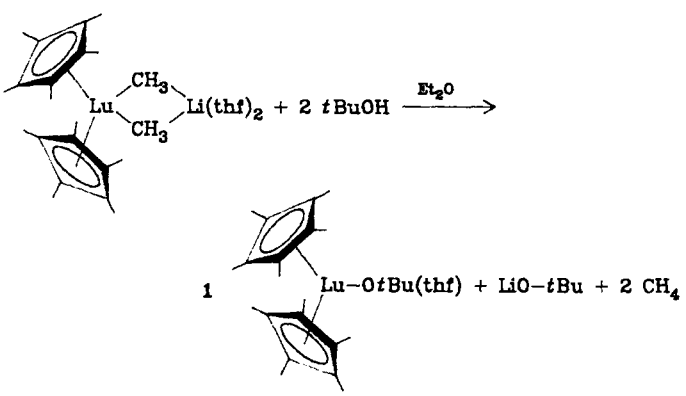
By *Herbert Schumann,* Ilse Albrecht,* and *Ekkehard Hahn*

Dedicated to Professor Max Schmidt on the occasion of his 60th birthday

Only very few organometallic compounds of the "hard" electropositive metals of the lanthanoid series are known in which, aside from organic groups, other ligands are bonded via "soft" atoms such as sulfur, phosphorus or silicon.[1] Such compounds are, however, of particular interest as reagents for organic syntheses because of their very reactive, and possibly strong covalent Ln–X bonds. To our knowledge only one organolanthanoid-sulfur compound, $(C_5Me_5)_2YbS_2CNEt_2$,[2] has so far been characterized, whereas several bis(cyclopentadienyl)lanthanoid-phosphane derivatives have been described.[3] However, their unequivocal characterization by X-ray structural determination was, in contrast to that of the first organolanthanoid-silicon complex, $[Li(dme)_3][(C_5H_5)_2Sm(SiMe_3)_2]$[4] (dme = 1,2-dimethoxyethane), hitherto not possible.

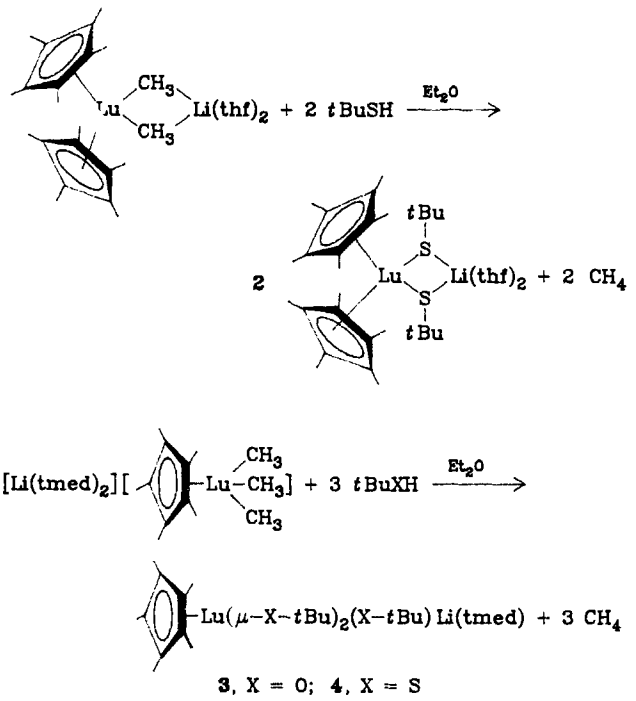
We have now found a simple, versatile route to this interesting class of compounds. Bis(pentamethylcyclopentadienyl)lutetiumdi(μ-methyl)bis(tetrahydrofuran)lithium[5] reacts in ether with *tert*-butyl alcohol at −78°C with formation of bis(pentamethylcyclopentadienyl)lutetium *tert*-butylate, **1**, whereas with *tert*-butyl hydrosulfide the compound **2** (thf = tetrahydrofuran) is obtained with retention of the bridged structure. $[Li(tmed)_2][C_5Me_5Lu(CH_3)_3]$[6] (tmed = tetramethylethylenediamine), which exists as an ion pair, reacts with both *t*BuOH and *t*BuSH with formation of the bridged organolanthanoid compounds **3** and **4**, respectively.[7]

Both **3** and **4** are also assumed to contain a $Lu(\mu\text{-}X)_2Li$ unit since in each case only one molecule of tmeda is bound to lithium. The NMR spectra of both compounds, however, show only one signal for the three *tert*-butyl ligands, which can be explained in terms of a rapid exchange of the terminal X*t*Bu group with the two bridging ligands. An analogous process was observed in the case of $[Li(tmed)]_3[Th(CH_3)_7]$ where six bridging CH_3 groups and



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one terminal CH_3 group give only one CH_3 signal in solution.[8]

The X-ray structural analysis (Fig. 1) shows that **2** is a bis(*tert*-butylthio)-bridged, dinuclear lutetium-lithium complex. The lutetium atom is in a distorted tetrahedral environment consisting of the centroids of two cyclopentadienyl rings and the two bridging sulfur atoms, whereas the two sulfur atoms, and the oxygen atoms of two THF molecules form the coordination sphere of the lithium. In the bis(cyclopentadienyl)lanthanoid complexes so far investigated X-ray crystallographically, $[Cp_2Ln(\mu\text{-}X)_2Li(B)_{1,2}]$, $Cp = C_5Me_5$, $Ln = Yb$, $B = Et_2O$, $X = Cl$, I,[10] $Cp = C_5H_5$, B = tmed, $X = CH_3$, $Ln = Er$,[11] Lu[11] a planar four-atom unit $Ln(\mu\text{-}X)_2Li$ was observed. In **2**, on the other hand, a dihedral angle of 168.1(7)° is found between the S1-Lu-S2 and S1-Li-S2 planes. To our knowledge, a puckered $Ln(\mu\text{-}X)_2Li$ unit with two Cp ligands on the Ln atom is unique and does not even occur in the four-membered rings of $(C_5Me_5)Yb(\mu\text{-}Cl)_2AlCl_2$,[10] $(C_5Me_5)_2Lu(\mu\text{-}CH_2)_2P(CH_3)_2$[12] or in the one other crystallographically characterized organolanthanoid-sulfur compound $(C_5Me_5)_2YbS_2CNEt_2$.[2]

The Cp1-Lu-Cp2 angle (Cp signifies the centroid of a cyclopentadienyl group) and the mean value of the ten $LuC(\eta^5)$ distances (2.66(2) Å) lie in the expected range. The cyclopentadienyl rings are planar (maximum deviation from the medial plane 0.015 Å). The Lu-S distance (2.709(3) and 2.723(3) Å) is comparable with the Yb-S distance in $(C_5Me_5)_2YbS_2CNEt_2$ (2.70(1) Å[2]) (ionic radii for Yb and Lu with coordination number 8 : 0.985 and 0.977 Å, respectively[13]). The S1-Lu-S2 angle is, of course, larger than the S-Yb-S angle in the dithiocarbamate.[2]

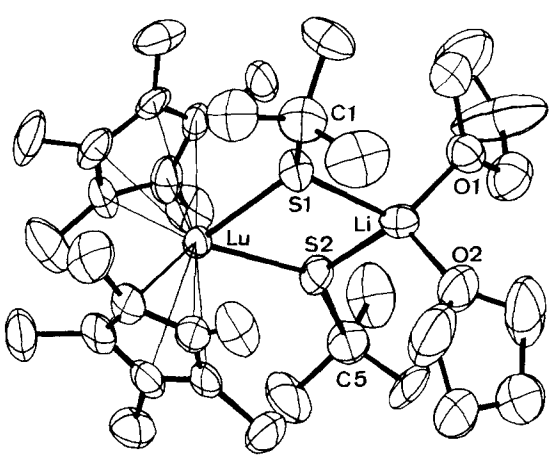


Fig. 1. ORTEP-plot of $[(C_5Me_5)_2Lu(\mu\text{-}S\text{-}t\text{Bu})_2Li(thf)_2]$ in the crystal [9]. Selected bond lengths [Å] and angles [°]: Lu···Li 3.89(2), S1···S2 3.252(4), Lu-S1 2.709(3), Lu-S2 2.723(3), Lu-Cp1 2.364(10), Lu-Cp2 2.370(10), average Lu-C(η^5) 2.66(2), S1-C1 1.853(12), S2-C5 1.863(12), S1-Li 2.41(2), S2-Li 2.48(2), Li-O1 1.95(2), Li-O2 1.95(2); Cp1-Lu-Cp2 131.5(3), S1-Lu-S2 73.6(1), Lu-S1-Li 101.8(4), Lu-S2-Li 99.7(4), S1-Li-S2 83.5(6), O1-Li-O2 102.6(10); dihedral angle between the S1-Lu-S2 and S1-Li-S2 planes 168.1(7) (Cp1 and Cp2 signify the centroids of the top and bottom cyclopentadienyl groups.

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[7] **1** to **4** were characterized by complete elemental analyses. Decomposition point and ^{1}H- as well as ^{13}C-NMR spectra (25°C, C_6D_6 (**1** and **3**), C_4D_8O (**2** and **4**), rel. TMS): **1**: decomposition point 139°C; ^{1}H NMR (80 MHz): $\delta = 1.92$ (s, $C_5(CH_3)_5$), 1.22 (s, *t*Bu), 1.73 and 3.59 (m, thf); ^{13}C NMR (20.149 MHz): $\delta = 12.34$ (s, $C_5(CH_3)_5$), 115.81 (s, $C_5(CH_3)_5$, 72.16 (s, C_α), 35.36 (s, C_β), 25.31 and 72.69 (thf); **2**: decomposition point: 260°C; ^{1}H NMR (80 MHz): $\delta = 2.03$ (s, $C_5(CH_3)_5$), 1.40 (s, *t*Bu), 1.72 and 3.58 (m, thf); ^{13}C-NMR (67.922 MHz): $\delta = 13.42$ (s, $C_5(CH_3)_5$), 117.50 (s, $C_5(CH_3)_5$), 44.21 (s, C_α), 38.86 (s, C_β), 26.25 and 68.13 (thf); **3**: decomposition point: 120°C; ^{1}H NMR (80 MHz): $\delta = 2.13$ (s, $C_5(CH_3)_5$), 1.27 (s, *t*Bu), 2.25 and 2.40 (s, tmed); ^{13}C NMR (20.149 MHz): $\delta = 12.27$ (s, $C_5(CH_3)_5$), 114.51 (s, $C_5(CH_3)_5$), 69.88 (s, C_α), 34.94 (s, C_β), 46.94 and 57.82 (s, tmed); **4**: decomposition point: 260°C; ^{1}H NMR (80 MHz): $\delta = 2.14$ (s, $C_5(CH_3)_5$), 1.57 (s, *t*Bu), 2.26 and 2.40 (tmed); ^{13}C NMR (67.922 MHz): $\delta = 12.60$ (s, $C_5(CH_3)_5$), 117.30 (s, $C_5(CH_3)_5$), 43.75 (s, C_α), 39.05 (s, C_β), 46.14 and 58.67 (tmed).

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[9] **2**: $P2_1/n$, non standard setting of $P2_1/c$, $a = 19.016(7)$, $b = 17.206(6)$, $c = 11.899(4)$ Å, $\beta = 101.82(3)°$, $V = 3810.7$ Å^3, $Z = 4$, $\rho_{calc} = 1.351$ g cm^{-3}; $Mo_{K\alpha}$ radiation at $-105(3)$°C, 1°-ω scans in the 2θ-range $3.0° \leq 2\theta \leq 48.0°$, 5979 independent intensities. Data reduction with Lorentz and polarization correction, empirical absorption correction ($\mu = 25.9$ cm^{-1}) 6 ψ-scans in the 2θ region $5.25° \leq 2\theta \leq 34.20°$. Solution and refinement by Patterson and Fourier techniques (SHELX-76); $R = 0.0517$, $R_w = 0.0641$ ($w = k/[\sigma(F_0)^2 + gF_0^2]$, $k = 1.2339$, $g = 0.001650$) for 4228 observed reflections ($I > 2\sigma(I)$) and 403 refined parameters (reflection-parameter ration 10.5 : 1). Further details of the crystal structure investigation are available on request from the Fachinformationszentrum Energie, Physik, Mathematik GmbH, D-7514 Eggenstein-Leopoldshafen 2, on quoting the depository number CSD-51471, the names of the authors, and the full citation of the journal.

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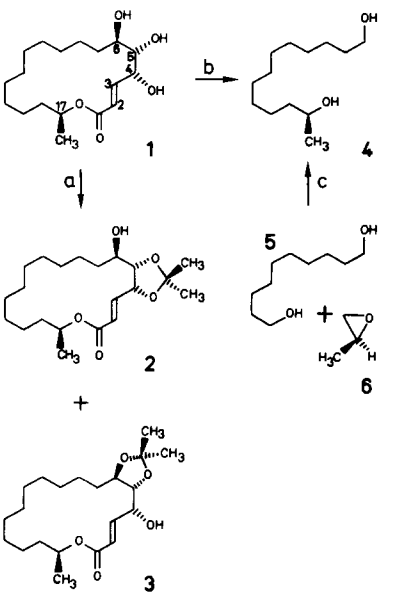
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The Structure of the Lichen Macrolide (+)-Aspicilin**

By *Gerhard Quinkert,* Nana Heim, Jan W. Bats, Hartmut Oschkinat,* and *Horst Kessler*

Dedicated to Hans Musso on the occasion of his 60th birthday

(+)-Aspicilin **1** (Scheme 1) was first isolated in 1900 from a crustose lichen belonging to the genus *Lecanora*.[2] It took nearly 75 years to realize that the substance was a macrolide: the constitution is that of a 4,5,6-trihydroxy-17-methyl-2-heptadecenolide, and the orientation of the ligands on the C(2)–C(3) double bond is *E*.[3] We have now determined its configuration to be 4*R*,5*S*,6*R*,17*S* (Fig. 1).



Scheme 1. a) Conversion of **1** into the acetonides **2** and **3**: 2,2-dimethoxypropane, PPTS, room temperature, 7 h. b) Degradation of **1** to **4**: $NaIO_4$, $MeOH/H_2O$ (9:1), room temperature, 5 h; $LiAlH_4$, ether, room temperature, 12 h. c) Synthesis of **4** from **5** and **6**: aq. HBr, petroleum ether, 80°C; dihydropyran, PPTS, CH_2Cl_2, room temperature, 4 h; Mg, tetrahydrofuran; 1,5-cyclooctadiene/CuCl [4], **6** [9]. *ent*-**6** is analogously converted into [10] *ent*-**4**. PPTS: pyridinium *p*-toluenesulfonate.

The relative configuration was established by single-crystal X-ray analysis of **1** (with respect to C(4), C(5), C(6), and C(17); see Fig. 1A)[5] as well as by ^{1}H-NMR spectroscopy of **2** and **3** (with regard to C(4), C(5), and C(6); see Fig. 2 and Table 1).

In order to obtain unequivocally interpretable NMR data, it is necessary to reduce the conformational flexibility of **1** at centers C(4), C(5), and C(6) by acetonide formation. The constitution of the acetonide moiety for **2** and **3** is obtainable provided the signals for H-C(2) to H-C(6) can be assigned for both substances. This is achieved by determination of the homonuclear coupling (H,H-COSY),[7] in which the coupling between the exchangeable OH proton and the vicinal CH proton makes it possible to distinguish between the acetonides. This coupling depends both on the water content and the temperature of the sample. The NOE build-up rates for **2** and **3** were determined by NOESY spectroscopy (with shorter mixing time than

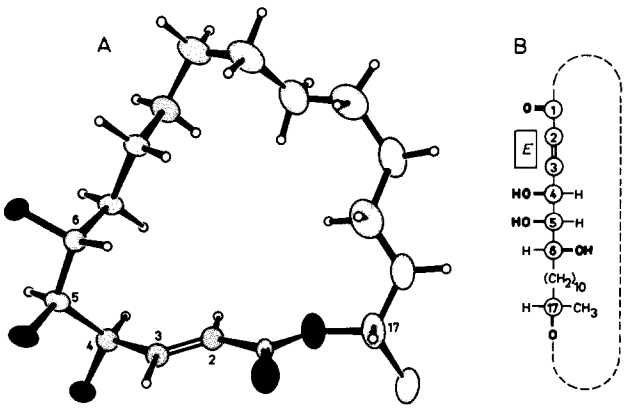


Fig. 1. A) Conformation and B) absolute configuration of (+)-aspicilin **1** (Fischer projection).

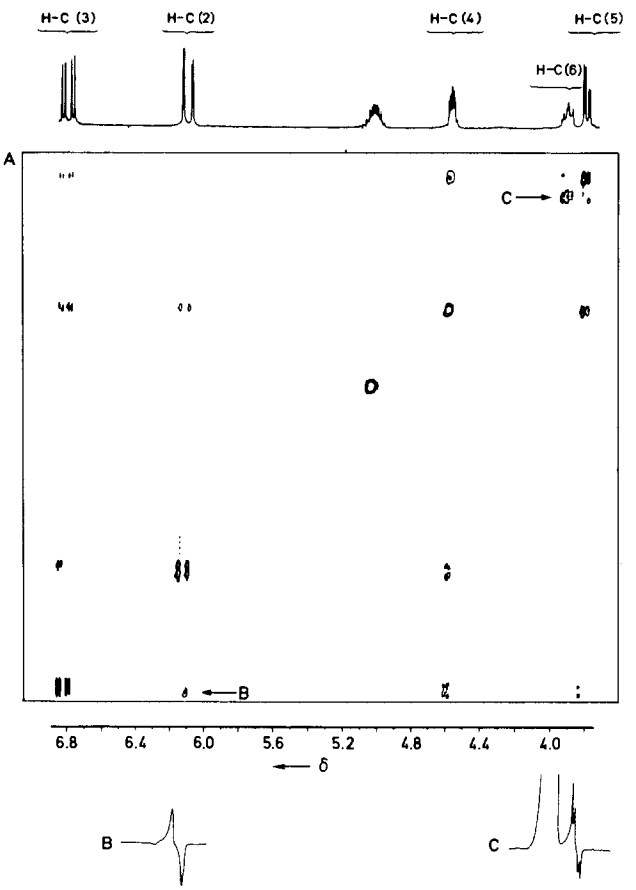


Fig. 2. A) Phase sensitive NOESY spectrum [6] of **3** in $CDCl_3$ at room temperature, recorded at 300 MHz by the TPPI method; the mixing time was 1.2 s ≈ 1.1 T_1). The signals along the diagonal from bottom left to top right have positive intensities and all cross peaks negative intensities. The cross peaks of H-C(4) and H-C(5) exhibit a strong NOE, while only weak artifacts occur between H-C(5) and H-C(6). B) Cross-section through the cross peak of H-C(3) and H-C(2) along the arrow marked with B in Fig. 2A. The antiphase structure arises due to scalar coupling; no NOE is observed. C) Cross-section through the cross peak marked with C in Fig. 2A; antiphase magnetization due to scalar coupling.

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Table 1. Physical data for the compounds **2**, **3**, **4**, and *ent*-**4**.

2: m.p. = 114–115 °C (ether/*n*-pentane); UV (*n*-hexane): $\lambda_{max}(\varepsilon) = 200$ nm (13600); IR (KBr): $\nu = 3470$ (s, OH), 1710 (s, ester carbonyl), 1650 (w, C=C), 990 (C=C, *trans*) cm^{-1}; ^{1}H-NMR ($CDCl_3$): $\delta = 1.23$–1.59 (m, H-C(7) to H-C(16), CH_3-C(17), $CH_{3\,gem}$), 3.61–3.77 (m, H-C(6)), 4.02–4.07 (dd, H-C(5)), 4.56–4.61 (dd, H-C(4)), 5.07–5.13 (m, H-C(17)), 5.98 (dd, H-C(2)), 6.85 (dd, H-C(3)); $[\alpha]_\lambda^{20}$ ($c = 0.817$ in $CHCl_3$) +57 (589), +60 (578), +68 (546), +116 (436), +184 (365 nm)

3: m.p. = 30 °C (*n*-pentane); UV (*n*-hexane): $\lambda_{max}(\varepsilon) = 209$ nm (12460); IR (KBr): $\nu = 3410$ (s, OH), 1710 (s, ester carbonyl), 1650 (w, C=C), 985 (C=C, *trans*) cm^{-1}; ^{1}H-NMR ($CDCl_3$): $\delta = 1.21$–1.62 (m, H-C(7) to H-C(16), CH_3-C(17), $CH_{3\,gem}$), 3.80 (dd, H-C(5)), 3.91 (m, H-C(6)), 4.57 (m, H-C(4)), 5.03 (m, H-C(17)), 6.11 (dd, H-C(2)), 6.79 (dd, H-C(3)); $[\alpha]_\lambda^{20}$ ($c = 1.436$ in $CHCl_3$) +45 (589), +48 (578), +55 (546), +95 (436), +152 (365 nm)

4: m.p. = 55–56 °C (ether/*n*-pentane); ^{1}H-NMR ($CDCl_3$): $\delta = 1.18$ (d, CH_3), 1.28–1.59 (m, H-C(2) to H-C(11)), 1.69 (s, OH), 3.69 (t, $J = 6.5$ Hz, H-C(1)), 3.73–3.85 (m, H-C(12)); $[\alpha]_\lambda^{20}$ ($c = 0.911$ in CH_3OH) +5.8 (589), +6.2 (578), +7.1 (546), +11.9 (436), +17.6 (365 nm) (by degradation); $[\alpha]_\lambda^{20}$ ($c = 1.068$ in CH_3OH) +6.3 (589), +6.7 (578), +7.7 (546), +12.6 (436), +19.1 (365 nm) (by synthesis)

ent-**4** (by synthesis): m.p. = 55–56 °C (ether/*n*-pentane); ^{1}H-NMR ($CDCl_3$): as for **4**; $[\alpha]_\lambda^{20}$ ($c = 0.939$ in CH_3OH) −6.2 (589), −6.4 (578), −7.6 (546), −12.3 (436), −17.7 (365 nm)

for recording the spectrum in Fig. 2A) or by difference spectroscopy. The results obtained—large NOE with a high build-up rate for H-C(4)/H-C(5), small NOE with a low build-up rate for H-C(5)/H-C(6)—show that the dioxolane ring is *cis*-fused to the 18-membered lactone ring in **2** and *trans*-fused in **3**.

The absolute configuration was determined by synthesis of both **4** and *ent*-**4** (see Scheme 1 and Table 1).[8]

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[5] 1: $a = 5.512(2)$, $b = 8.920(2)$, $c = 19.719(8)$ Å, $\beta = 96.07(3)°$, $V = 964(1)$ Å^3; monoclinic, $P2_1$, $Z = 2$; $\rho_{calcd} = 1.13$ g/cm^3, 23 °C, Enraf-Nonius CAD4 diffractometer, $Cu_{K\alpha}$ radiation, quadrant $(\sin\theta/\lambda)_{max} = 0.53$ Å^{-1}, 1437 independent reflections, with $I > \sigma$, $R(F) = 0.075$, $R_w = 0.098$, SDP program system. Further details of the crystal structure investigation are available on request from the Fachinformationszentrum Energie, Physik, Mathematik GmbH, D-7514 Eggenstein-Leopoldshafen 2, by quoting the depository number CSD-51441, the names of the authors, and the journal citation.
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[8] **1**, **2**, **3**, **4**, and *ent*-**4** gave correct elemental analyses.
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Reaction of Phenylcarbene with Oxygen

By *Wolfram Sander**

Since 1958, when *Horner* and *Kirmse* et al.[1] described the reaction of diphenylcarbene with oxygen, the mechanism of the oxidation of free carbenes has been in dispute. Frequently, a carbonyl oxide is postulated to be the primary product.[1,2] The carbonyl oxide reacts with O_2 to give ozone and the carbonyl compound[2,9] or with unreacted carbene to give two molecules of the carbonyl compound,[1] or it rearranges to give a carboxyl compound.[5,6,9] In some cases, chemiluminescence has been observed during the oxidation of carbenes.[2–5] Direct observation of the carbonyl oxide was achieved in the case of cyclopentadienylidene by matrix isolation in argon[6] and in the case of diphenylcarbene by time-resolved spectroscopy.[7]

We have studied the oxidation of phenylcarbene **2** in an O_2-doped argon matrix. The O_2 content of the matrix was varied between 0.5% and 15%; the carbene **2** was generated by photolysis of matrix-isolated phenyldiazomethane **1**.[8]

$$\underset{\mathbf{1}}{PhCHN_2} \xrightarrow{h\nu} \underset{\mathbf{2}}{{}^3PhHC:}$$

After irradiation ($\lambda > 475$ nm, 8 K) of **1**, phenylcarbene **2** (IR: $\nu = 747$, 668 cm^{-1}), benzaldehyde **3** (1717, 830 cm^{-1}), and benzoic acid **4** (1757, 712 cm^{-1}) were found along with small amounts of unreacted starting material. The ratio of these products depends on the O_2 content and on the thermal treatment of the matrix. For an O_2 content of 0.5%, **2** was the main product; only traces of **3** and **4** were formed. At this O_2 content, the probability is low that an oxygen molecule is present near the carbene formed upon photolysis. The rate of diffusion of O_2 in solid argon at 8 K is too small for significant reaction to occur. At an O_2 content of 4%, the conversion was almost complete; in the IR spectrum, the characteristic band of **2** at 668 cm^{-1}[8] was absent. At 1% O_2, free carbene and oxidation products were present in roughly equal amounts and could be simultaneously detected by IR spectroscopy.

The ratio of **3** to **4** depends on the thermal treatment of the matrix. For short irradiation times (1 h) and the lowest temperature possible (8 K), **3** was the only detectable oxidation product. For longer irradiation times (15 h), which were necessary for complete conversion of **1**, some **4** was also formed (Fig. 1). By warming the matrix over a short period of time to 27 K following irradiation, the proportion of **4** increased significantly and that of **2** and of **3** decreased.

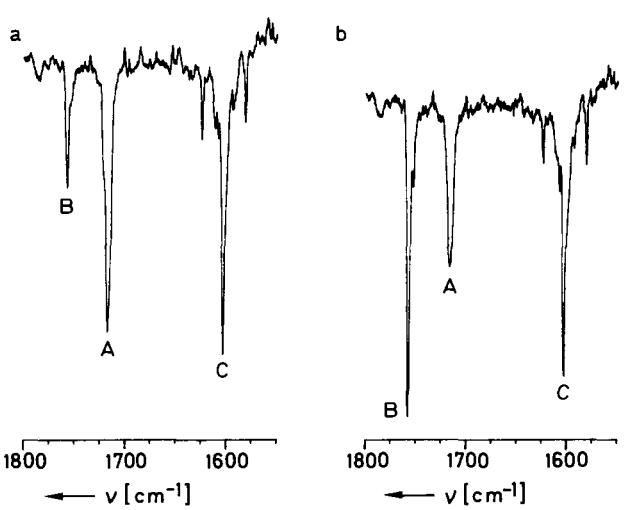


Fig. 1. Thermal reaction of benzaldehyde **3** and $O(^3P)$ to give benzoic acid **4**. IR spectra in the region of the carbonyl vibrations of **3** (A, 1717 cm^{-1}) and **4** (B, 1757 cm^{-1}). A band of unreacted phenyldiazomethane (C, 1603 cm^{-1}) serves to compare intensities. a) 5 h irradiation ($\lambda > 475$ nm, 8 K) of **1** in Ar with 1% O_2; b) as in a) but with subsequent annealing at 27 K for 15 min.

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The maximum in the rate of reaction for the conversion **3** → **4** was found at 27 K. After several minutes of annealing at this temperature, no further reaction was observed to take place. Unreacted **2** only underwent significant oxidation at $T > 35$ K by the O_2 present in excess.

$$^3\text{PhHC:} + {}^3O_2 \longrightarrow [{}^*\text{PhHC}{=}\overset{\oplus}{O}{-}\overset{\ominus}{O}] \longrightarrow \underset{\mathbf{3}}{\text{PhCHO}} + O(^3P) \quad (1)$$
$$\mathbf{2}$$

$$^3\text{PhHC:} + O(^3P) \longrightarrow {}^3\text{PhCHO} \longrightarrow \underset{\mathbf{3}}{\text{PhCHO}} + h\nu \quad (2)$$
$$\mathbf{2}$$

$$\underset{\mathbf{3}}{\text{PhCHO}} + O(^3P) \longrightarrow \underset{\mathbf{4}}{\text{PhCOOH}} \quad (3)$$

$$^3O_2 + O(^3P) \longrightarrow O_3 \quad (4)$$

Atomic oxygen is the only oxidizing agent in question that has a sufficiently high rate of diffusion at 27 K.[10] The oxygen atoms are trapped by phenylcarbene **2** or benzaldehyde **3** [Reactions (2) and (3)]. For an O_2 content of 15%, **3** was also obtained as the main product; however, larger proportions of ozone were also formed. Warming the matrix to 27 K following irradiation resulted in no changes in the IR spectrum; accordingly, O_2 in large excess can compete successfully with **2** and **3** for the oxygen atoms[11] [Reaction (4)]. In an N_2 matrix containing 1% O_2, we obtained no N_2O, which is formed from $O(^1S)$ and N_2 but not from $O(^3P)$ and N_2.[12] Thus, the oxygen atoms are formed in the $O(^3P)$ electronic state.

The reaction of **2** with $O(^3P)$ can be followed directly by observing the chemiluminescence upon warming the matrix. The temperature dependence of the total emission of the matrix (glow curve) was recorded using a photomultiplier (Fig. 2). Spectra at several points along the curve were obtained using an optical multichannel analyzer. In all cases, the phosphorescence spectrum of benzaldehyde[13] with maxima at 401, 430, 462, and 500 nm was found, independent of oxygen content and temperature.

For an O_2 content of the matrix of 1%, the glow curve exhibits an initial increase at 20 K followed by a plateau and a maximum at 44 K (Fig. 2a). If the matrix is warmed to 27 K for several minutes before recording the glow curve the initial increase is absent, the maximum remaining unchanged (Fig. 2b). The emission in the region between 20 and 32 K is due to the reaction of free $O(^3P)$ with phenylcarbene **2** [Reaction (2)], which was also observed by IR spectroscopy. At higher temperatures, the diffusion of O_2 and thus the formation of new $O(^3P)$ begins to take place [Reaction (1)]. This reaction is not sufficiently exothermic to generate **3** in a triplet state.[14] The excess energy of the reaction is partly transferred to $O(^3P)$, which thus receives sufficient translational energy to leave the matrix cage.

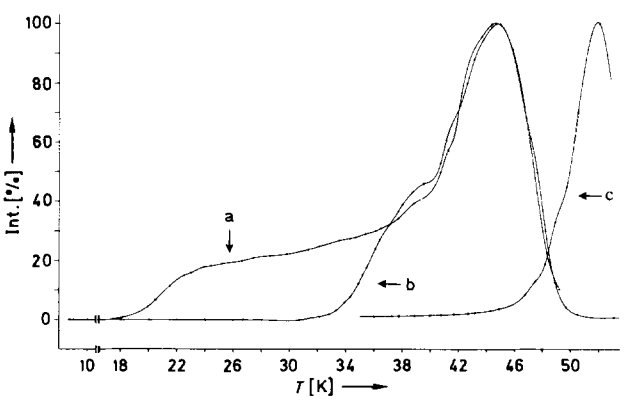


Fig. 2. Chemiluminescence intensities as a function of temperature (glow curve) normalized to the highest intensity (100%). Rate of warming ca. 1 K/min. a) Warming experiment directly after the irradiation; b) warming experiment after 15 min of annealing at 27 K and subsequent cooling to 8 K; c) control experiment as in a) but without O_2 in the matrix. The chemiluminescence on evaporation of the matrix (51 K) is caused by reaction of phenylcarbene **2** with a layer of air (from small leaks) on top of the matrix.

A carbonyl oxide as intermediate could not be detected either directly after irradiation of **1** or after annealing the matrix. This contrasts with the behavior of cyclopentadienylidene[6] and diphenylcarbene[15] upon oxidation with O_2 under comparable conditions; in these cases, the corresponding carbonyl oxide could be detected by UV or IR spectroscopy. The dependence of the stability of the initially formed carbonyl oxide on the substituents may be based on differing mechanisms of deactivation of the excess energy, leading either to cleavage of the O–O bond or, primarily, to vibrational excitation of the substituents.

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1, 766-91-6; **2**, 3101-08-4; **3**, 100-52-7; **4**, 65-85-0.

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Chelation-Controlled Stereoselective Synthesis of Cyanohydrins**

By *Manfred T. Reetz,* Kurt Kesseler,* and *Alfred Jung*

Dedicated to Professor Karl Dimroth on the occasion of his 75th birthday

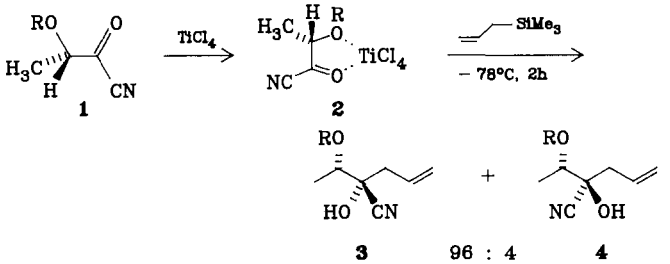
Effective chelation-control in nucleophilic additions to chiral alkoxycarbonyl compounds has become possible in recent years by the use of suitable organometallic compounds.[1] The reagents of choice are often Lewis-acidic titanium compounds of the type $RTiCl_3$ or $TiCl_4$ in combination with soft *C*-nucleophiles such as allylsilanes or silyl

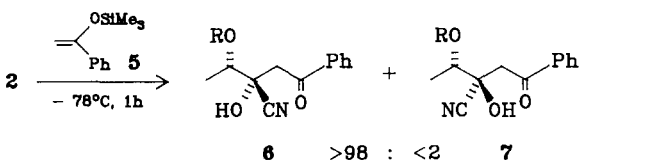
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enol ethers. In the case of α- and β-alkoxyaldehydes, intermediate five- and six-membered chelates are formed, respectively, which are attacked stereoselectively from the sterically less hindered side. Herein, we report a preparatively useful extension of this concept, namely the diastereoselective synthesis of secondary and tertiary cyanohydrins.

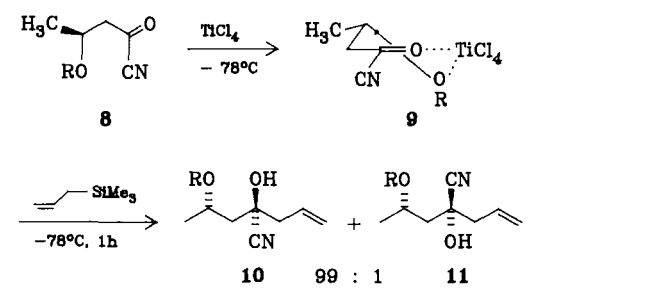
When the chiral acyl cyanide **1**[2] is treated at low temperatures with $TiCl_4$ in CH_2Cl_2, the chelate **2** is presumably formed, since subsequent addition of allyltrimethylsilane affords essentially only adduct **3** (conversion 98%).[3] $SnCl_4$ is not as effective (**3** : **4** = 85 : 15). Aldol addition of the silyl enol ether **5** to **2** takes place with even greater 1,2-asymmetric induction (conversion >90%). The tertiary cyanohydrins **3**, **4**, **6**, and **7** are configurationally stable.[4]





R = CH_2Ph

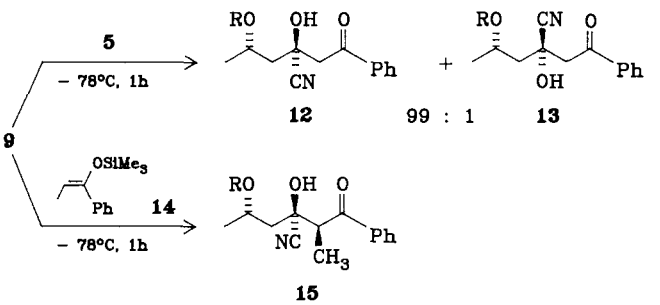
The observed complete 1,3-asymmetric induction in the addition of allylsilane to the β-chiral acyl cyanide **8**[2] (conversion >98%) is also remarkable.[3]



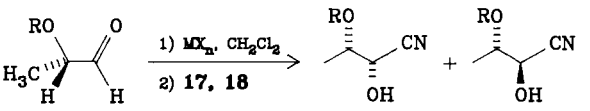
R = CH_2Ph

Furthermore, we found that aldol additions to **9** proceed quantitatively with strict chelation-control to give, e.g., **12**.[3] Reaction of the *E*-configurated prochiral silyl enol ether **14** from propiophenone with **9** leads to the formation of only one (**15**) of four possible diastereomers (ratio 99 : 1).[3] This unusual effect was observed previously in reactions of α- and β-alkoxyaldehydes and can be explained in terms of an open-chain transition state.[1,5]

A different strategy is necessary for the synthesis of secondary cyanohydrins. The compounds can be synthesized stereoselectively by addition of the cyanosilanes **17**[6] or **18**[7] to complexed aldehydes; however, the 1,2- and 1,3-asymmetric induction is not complete (Table 1). In some cases *O*-silylated derivatives are formed. They can be converted into the free cyanohydrins upon acidic work-up



(2 N HCl, tetrahydrofuran, 22°C, 2 h). In order to make configurational assignments, **19** and **20** were converted into the corresponding acetonides and examined by ^{13}C-NMR spectroscopy.



16 **19** **20**

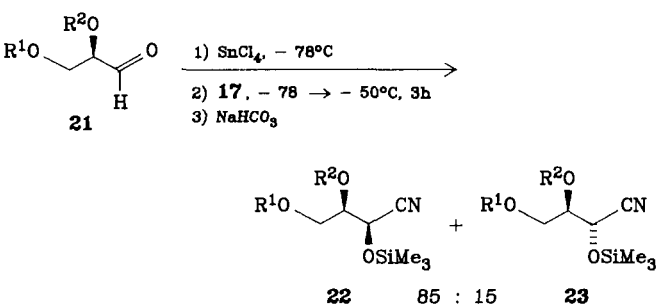
R = CH_2Ph; Me_3SiCN **17**; *t*$BuMe_2SiCN$ **18**

Table 1. Diastereoselective formation of cyanohydrins **19**/**20**.

Cyanating reagent [a]	Lewis acid [a]	*T* [°C]	*t* [h]	Conversion [%] [b]	**19** : **20**
17	$TiCl_4$	–78 → –30	3	63	74 : 26
17 [c]	$TiCl_4$	–78 → –30	3	91	77 : 23
18	$TiCl_4$	–78	1	>98	80 : 20
17	$SnCl_4$	–78	1.5	>98	78 : 22
17	$BF_3 \cdot OEt_2$	–78	2	86	57 : 43
18	$BF_3 \cdot OEt_2$	–78	3	0	—
17	ZnI_2 [d]	0	3	>98	60 : 40
17	ZnI_2 [d]	–30	24	>98	59 : 41
17	$MgBr_2$	–30	24	87	80 : 20

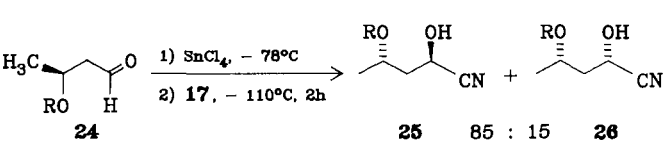
[a] Normally one equivalent. [b] In the case of >90% conversion into **19**/**20** the isolated yield is about 76%. [c] Two equivalents. [d] 0.05 equivalents.

The method can be employed in carbohydrate chemistry, as documented by the reaction of aldehyde **21** obtained from mannitol[8] with formation of **22**/**23** (conversion 95%; unoptimized yield: 62%). Besides **22**/**23**, about 10% of the free cyanohydrins are formed in the same diastereomeric ratio.



R^1 = *t*$BuMe_2Si$; R^2 = CH_2Ph

Finally, we have investigated the 1,3-asymmetric induction in the synthesis of cyanohydrins from the β-alkoxyaldehyde **24** (conversion >90%).[9]



R = CH_2Ph

Since cyanohydrins are useful synthetic building blocks, the importance of a general stereoselective synthesis is obvious. The addition of HCN to L-arabinose described by *Kiliani* and *Fischer* about 100 years ago was one of the first examples of 1,2-asymmetric induction in organic chemistry.[10]

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[3] For work-up, the cold reaction mixture was added to water under acidic conditions. The chromatographic purification of **3/4** (silica gel/petroleum ether 40–60/ether (1:3) gave 69% analytically pure product. The assignment is based on analogy to the $TiCl_4$-controlled allylsilane-addition to aldehydes [1] and was supported by conversion of **3/4** into the acetonides, whose ^{13}C-NMR spectra confirmed the assignment. The assumption of chelation-control [1] in the other reactions seems justified on grounds of plausibility; X-ray structure analyses are presently under way.

[4] Basic conditions should be avoided since the cyanohydrins decompose or undergo configurational equilibration. **6** slowly loses HCN on standing (22 °C).

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[9] Acidic work-up with H_2O [3] (**25**/**26** were isolated in 76% yield).

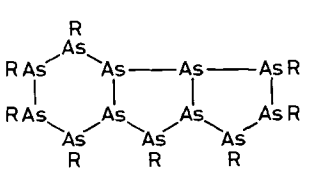
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$As_{12}tBu_8$—a Tricyclo[6.4.0.0^{2,6}]dodecaarsane**

By *Marianne Baudler** and *Stefan Wietfeldt-Haltenhoff*

Dedicated to Professor Max Schmidt on the occasion of his 60th birthday

In contrast to the corresponding phosphanes,[1] polycyclic arsanes are still hardly known. Only in the past few years could the nortricyclene-analogue $As_7(SiMe_3)_3$[2] as well as the *tert*-butylarsanes As_8tBu_6[3] and As_4tBu_2[4] analogous to pentalane and bicyclobutane, respectively, be synthesized as the first representatives[5]. According to more recent findings,[6] arsenic, like phosphorus, is capable of forming polycyclic molecular structures. We have now succeeded in synthesizing octa-*tert*-butyldodecaarsane **1**, the first compound with twelve arsenic atoms in the molecule.



1, R = *t*Bu

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1 is formed on dehalogenation of a mixture of *tert*-butyl(dichloro)arsane and arsenic(III) chloride with magnesium in boiling tetrahydrofuran (THF).

$$8\,tBuAsCl_2 + 4\,AsCl_3 + 14\,Mg \longrightarrow \underset{\mathbf{1}}{As_{12}tBu_8} + 14\,MgCl_2$$

In addition, mainly As_9tBu_7,[6] As_8tBu_6,[3] As_6tBu_4,[6] $As_{16}tBu_{10}$,[6] $(AstBu)_4$,[7] and $(AstBu)_5$[8] are formed together with small amounts of further *tert*-butylarsanes containing up to 20 arsenic atoms in the molecule.[6] The product pattern is strongly dependent on the reaction conditions (molar ratio and concentration of the reactants, reaction rate, duration of additional stirring). Under suitable reaction conditions (optimized by ^1H-NMR spectroscopic monitoring), **1** can be obtained as major product and isolated in analytically pure form.

The dodecaarsane **1** is a bright yellow, crystalline solid (decomposition with browning above 237 °C), which is stable at room temperature in the absence of air and light. It is readily soluble in aliphatic hydrocarbons and THF, moderately soluble in arenes, and only very sparingly soluble in methanol;the solutions are, in contrast to the solid substance, thermally decomposable and extremely sensitive to oxidation and light. The composition of **1** is confirmed by an accurate elemental analysis and by a molecular weight determination (MS). The IR spectrum, unlike those of the other *tert*-butylarsanes, shows an intense band at 348 cm^{-1}.

Since we have so far been unable to obtain single crystals for an X-ray structure analysis, the structure proposed for **1** is based on NMR and mass spectroscopic findings. The ^1H-NMR spectrum[9a] shows eight, partially overlapped signals at $\delta = 1.54$, 1.59, 1.60, 1.61, 1.63, 1.65, 1.69, and 1.75 (in [D_6]benzene, 24 °C), the intensity ratio of which indicates the presence of two configurational isomers[10] with C_1 symmetry in the ratio 5:1. The chemical shifts lie in the region characteristic for *tert*-butyl-substituted five- and six-membered arsenic rings,[3,6] while three- and four-membered rings[6,7,12]—and thus also seven-membered rings—can be ruled out as structural units. This is confirmed by the $^{13}C\{^1H\}$-NMR spectrum[9b], which shows two slightly structured signal humps at $\delta = 32.3$ and 33.5 (in [D_6]benzene, 24 °C) for the primary and tertiary C-atoms, respectively, of the *tert*-butyl groups. Of the possible isomers, whose skeletal frameworks consist only of arsenic five- and/or six-membered rings, only a tricycle of an As_8-skeleton analogous to pentalane with an annelated six-membered ring comes into question for **1** on taking into consideration the steric interactions of the substituents and the observed C_1 symmetry. This is further supported by the mass spectrum (10 eV, 180 °C), in which, aside from the $(M-Bu)^{\oplus}$ ion, primarily five-membered ring/six-membered ring and five-membered ring/five-membered ring fragments of comparably high intensity occur. **1** is thus a 3,4,5,7,9,10,11,12-octa-*tert*-butyltricyclo[6.4.0.0^{2,6}]dodecaarsane.

The configuration and conformation of the structural unit analogous to pentalane should be the same as in As_8tBu_6,[3] with the substituents in the *exo*-coupled six-membered ring arranged predominantly in the *trans* position in both isomers.

Due to its "open" tricyclic As_{12} skeleton, compound **1** decomposes on heating in solution with formation of mono-, bicyclic, and higher annelated polycyclic *tert*-butylarsanes.

According to mass spectroscopic investigations, the element-homologous phosphorus compound $P_{12}tBu_8$ likewise exists; however, because of difficulties encountered in its isolation, the structure of this homologue has not yet been elucidated.[13]

Experimental

A solution of tBuAsCl$_2$, (22.36 g, 0.11 mol) and AsCl$_3$ (13.32 g, 0.073 mol) in THF (95 mL) is added dropwise within 90 min to a vigorously stirred suspension of magnesium turnings (5.36 g, 0.22 mol; previously etched by evaporating a few grains of iodine) in boiling THF (120 mL). The black mixture is refluxed for a further 35 min and then the solvent completely removed at room temperature under reduced pressure. The brown residue is treated with 450 mL of *n*-pentane and the resulting mixture stirred for 3 h. The undissolved material is separated off by suction filtration, washed with 2 × 20 mL of pentane, and the solvent is again removed from the combined filtrates. The remaining yellow solid is dissolved in 15 mL of pentane and chromatographed on Al_2O_3 using pentane at −50 °C with ^{1}H-NMR spectroscopic monitoring [9-cm column, 4.5 cm internal diameter; packing: neutral Al_2O_3 (according to Brockmann), particle size 0.063–0.200 mm, heated in vacuo and gassed with argon; amount of solvent: 4000 mL; duration 5.5 h]. After combination of the fractions containing the largest amounts of **1**, final purification is accomplished by crystallization at −25 °C or by preparative HPLC [11] (Nucleosil-5-C8 column, methanol/*n*-pentane (91.5:8.5); receiver: −78 °C); yield 1.3 g of pure **1** (7% w.r.t. tBuAsCl$_2$; not optimized).

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Decamethyl-7-thiahexasilanorbornane $(CH_3)_{10}Si_6S$**

By *Wiesław Wojnowski, Bogusław Dręczewski, Aleksander Herman, Karl Peters, Eva-Maria Peters,* and *Hans Georg von Schnering**

Dedicated to Professor Max Schmidt on the occasion of his 60th birthday

We have recently investigated intensively the relationships between the structures and properties of silicon-sulfur compounds.[1–3] For this purpose, polysilane-sulfur systems appeared to be particularly attractive, allowing the properties of the polysilanes to be combined with those of the silathianes. Nothing was known about these substances up to now, even though there has been a surge of interest in recent years in acyclic and cyclic polysilanes as well as in Si–S chemistry (3400 and 1850 compounds, respectively, although structure analyses are available for only 40 and 11, respectively[14]).

1,2,2,3,3,4,5,5,6,6-Decamethyl-7-thia-1,2,3,4,5,6-hexasilanorbornane $(CH_3)_{10}Si_6S$ **1**[5] is formed in a surprisingly simple and straightforward reaction from 1,4-dichlorodecamethylcyclohexasilane and H_2S with elimination of HCl. **1** crystallizes as colorless needles, which are very sensitive to moisture and decompose thermally above 240 °C without melting. IR measurements had to be carried out in CS_2 since **1** reacts even with CCl_4.

1 has a very slightly distorted mm2-C_{2v} symmetry. Immediately apparent in the X-ray diffraction structure (Fig. 1) is the size and orientation of the ellipsoids of thermal vibration, which, at first glance, indicate a separate vibration of the Si–S–Si structural unit. The analysis, using the model of a rigid body,[6] shows, however, that the entire molecule behaves like a rigid body, which has important consequences for the analysis of bond lengths. If the vibrations are initially ignored, then the distances and angles shown in Figure 1 are obtained.

The mean Si–S (216.9 pm) and Si–Si bond lengths (234.2 and 234.6 pm) fall in the usual range. This also holds for the Si–C distances (187.4, 187.3, 188.0 pm), which are not significantly influenced by the position of the substituents in the molecule. The notable ellipsoids of all the atoms can be described very well using the model of a rigid body ($R = 0.07$), especially those of the ring atoms ($R = 0.03$). In the crystal, the molecule vibrates about a center on the twofold axis (Fig. 1) that does not coincide with the center of gravity. The maximum values of the librational and

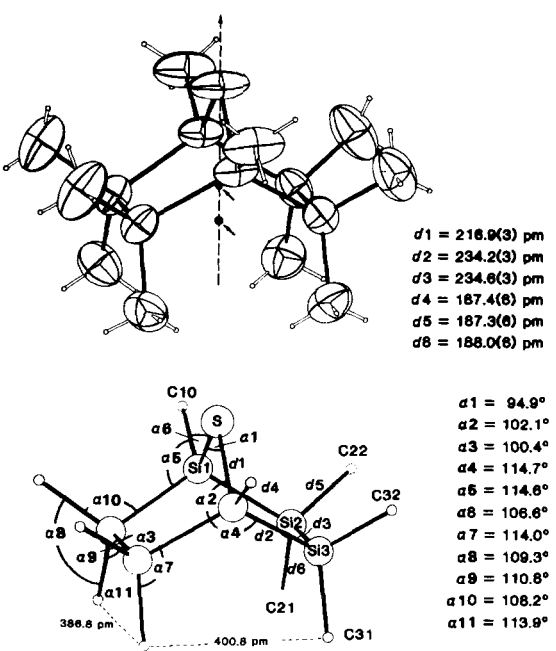


Fig. 1. Crystal structure of **1** with ellipsoids of thermal vibration (above) and the average bond lengths $d1$–$d6$ and bond angles $\alpha1$–$\alpha11$ (below). The position of the twofold axis (dashed line), the center of gravity (•, and the center of vibration (○) are shown (arrow). The position of the H atoms is given in the upper part.

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[**] Contributions to the Chemistry of Silicon-Sulfur Compounds, Part 37.—Part 36: [1].

translational components of the motion are 5.4° and 26 pm. The vibration-corrected bond lengths are about 1 pm longer. $d1^* = 217.8$, $d2^* = 235.6$, $d3^* = 235.5$, and $d^*(\text{Si-C}) = 188.1$–189.0 pm.

The bond angles (Fig. 1) exhibit a noticeable deviation from those of tetrahedral angles. The angle at the S bridge, $\alpha 1 = 94.9°$, is very small, but the other endocyclic angles $\alpha 2$ and $\alpha 3$ at the Si atoms are also strongly reduced. In contrast, $\alpha 4$ and $\alpha 3$ at the Si atoms are also strongly reduced. In contrast, $\alpha 4$, $\alpha 5$, $\alpha 7$, and $\alpha 11$ are considerably expanded. Such deformations should be due, on the one hand, to the topology of the bicyclic ring system and the steric effects between the CH_3 substituents. On the other hand a valence effect must be considered in accounting for $\alpha 1$. If a simple framework molecular model with ideal tetrahedrons as centers and flexible bonds is used as a *S*tructure *M*odel *A*nalogue *C*omputer (SMAC)[7] and the resulting distances between the tetrahedral centers are measured, then surprising values for the angles α^* between the connecting vectors are obtained: $\alpha 1^* \simeq 96$, $\alpha 2^* \simeq 104$, $\alpha 3^* 100$, $\alpha 4^* \simeq \alpha 5^* \simeq 109$, $\alpha 6^* \simeq 115$, and $\alpha 7^*$-$\alpha 11^* = 109.5°$.

The small endocyclic angles $\alpha 1$-$\alpha 3$ are, therefore, a result only of the ring strain of the bicycle. The observed angles $\alpha 4$ and $\alpha 5$ (115°), $\alpha 6$ (107°), $\alpha 7$ and $\alpha 11$ (114°) apparently contain the essential deformations. Accordingly, an increase in $\alpha 4$ and $\alpha 7$ or $\alpha 11$ results in an increase of the van der Waals separations between the methyl groups C21–C31 of 339 to 401 pm and of 360 to 387 pm, respectively. Changes in $\alpha 5$ and $\alpha 6$ result from bending of the methyl group on C10 in the direction of the free space around the S atom.

Experimental procedure:

By reaction of dodecamethylcyclohexasilane $Me_{12}Si_6$ [8] with $SbCl_5$ in CCl_4 [9] in a molar ratio of 1:4, equal amounts of 1,4-dichlorodecamethylcyclohexasilane and monochloroundecamethylcyclohexasilane were formed. 10 g of this mixture was dissolved in 200 mL of pentane containing 3.4 mL of triethylamine, and H_2S was bubbled through the solution. After 6 h, the reaction forming **1** was complete (monitored by gas chromatography). After filtration of Et_3NHCl and evaporation of half of the pentane, **1** crystallized out at 6°C (yield 30%).

Crystallographic data:

Fdd2, $a = 1835.6(12)$, $b = 3231.9(20)$, $c = 727.3(3)$ pm, $Z = 8$. Syntex $P\bar{1}$ diffractometer; $Mo_{K\alpha}$ radiation; 1230 reflections (1178 with $F > 3\sigma(F)$); $R_{iso} = 0.150$; $R_{aniso} = 0.032$. Further details of the crystal structure investigation are available on request from the Fachinformationszentrum Energie, Physik, Mathematik GmbH, D-7514 Eggenstein-Leopoldshafen 2, by quoting the depository number CSD-51523, the names of the authors, and the journal citation.

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New Co and Ni Clusters with Se and PPh_3 as Ligands: $[Co_4(\mu_3\text{-Se})_4(PPh_3)_4]$, $[Co_6(\mu_3\text{-Se})_8(PPh_3)_6]$, $[Co_9(\mu_4\text{-Se})_3(\mu_3\text{-Se})_8(PPh_3)_6]$, and $[Ni_{34}(\mu_5\text{-Se})_2(\mu_4\text{-Se})_{20}(PPh_3)_{10}]$**

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Dedicated to Professor Klaus Krogmann on the occasion of his 60th birthday

We recently described the synthesis of *S*-bridged Co and Ni clusters **1**–**4** in high yields from $[MCl_2(PPh_3)_2]$ (M = Co, Ni) and $S(SiMe_3)_2$.[1]

1 $[Co_7S_6(PPh_3)_5Cl_2]$ $[Co_6S_8(PPh_3)_6]^{\oplus}$ **2**
3 $[Ni_8S_6(PPh_3)_6Cl_2]$ $[Ni_8S_5(PPh_3)_7]$ **4**

We have now carried out analogous reactions with $Se(SiMe_3)_2$.[2] When $[CoCl_2(PPh_3)_2]$ is allowed to react with $Se(SiMe_3)_2$ in toluene; a crystalline, black precipitate consisting of **5** and **6** was obtained within a few minutes; large, black crystals of 7 crystallize from the filtrate.[3] **5** is readily soluble in tetrahydrofuran (THF), thus allowing its separation from the sparingly soluble **6**.

$[Co_4Se_4(PPh_3)_4]$ $[Co_6Se_8(PPh_3)_6]$ $[Co_9Se_{11}(PPh_3)_6]$
5 **6** **7**

5 and **6** are diamagnetic; 7 is paramagnetic. The PPh_3 ligands of **5**–**7** give signals in the ^{31}P-NMR spectrum (in dimethyl sulfoxide) at $\delta = 35.67$ (**5**), 35.8 (**6**), and 36.0 (70.3) (**7**) and in the ^{1}H-NMR spectrum in the region 7.35–7.60 (**5**) 7.13–7.7 (**6**), and 6.95–8.10 (**7**). The IR spectra of **5**–**7** are very similar and differ only below 450 cm^{-1}. These results are in agreement with those of X-ray crystal structure analyses.[4]

The structure of the Co_4Se_4 cluster **5** (Fig. 1) consists of a slightly distorted Co_4 tetrahedron with μ_3-Se ligands

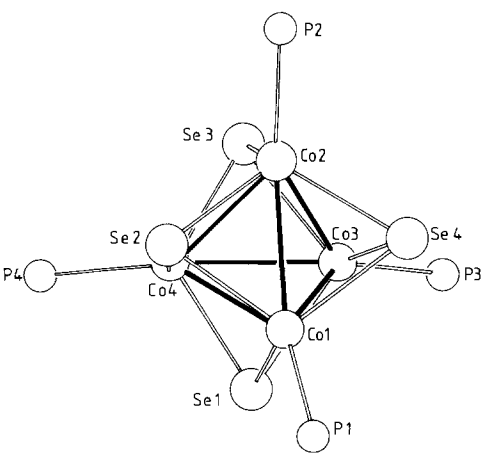


Fig. 1. Crystal structure of **5** (without phenyl groups) [4]. Most important distances (±0.2 pm) and angles (±0.1°): Co-Co 261.6–268.3, Co-Se 233.7–237.5, Co-P 220–224, Se···Se 377–384; Co-Co-Co: 58.6–61.2, Co-Se-Co 67.4–69.4, P-Co-Se 106.5–114.4, Se-Co-Se 105.7–110.1.

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bonded to the faces; the Co atoms are each further coordinated by one PPh_3 ligand. The structure of the 60e Co_4Se_4 cluster resembles that of other heterocubanes, such as $[Fe_4Se_4(NO)_4]$.[5] The Co-Co distances (261.6–268.3 pm) are significantly longer than those in $[Co_4(PPh)_4(PPh_3)_4]$ (257.1–258.6 pm).[6]

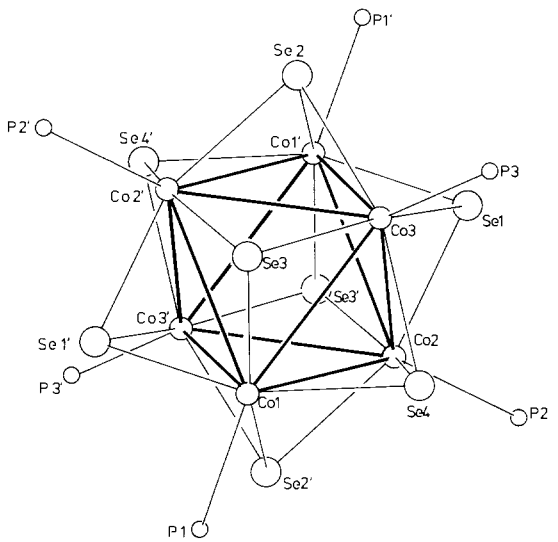


Fig. 2. Crystal structure of **6** (without phenyl groups) [4]. The atomic positions marked with ' are generated by reflection through a center of symmetry. Most important distances (±0.2 pm) and angles (±0.1°): Co-Co 299–302, Co-(μ_3-Se) 233–237, Co-P 216.2–217.5; Co-Co-Co 59.3–60.5, 89.8–90.6, P-Co-(μ_3-Se) 91.2–113.9, Se-Co-Se 87.2–87.8, 154.0–156.2, Co-(μ_3-Se)-Co 79.1–80.9.

The Co_6Se_8 cluster **6** (Fig. 2) has $\bar{1}$ symmetry; the Co_3 faces are each bridged by one μ_3-Se ligand,[4] and each Co atom is coordinated by one PPh_3 ligand. Complexes having the same structure have already been synthesized via a different route, e.g., **2** and $[M_6S_8(PEt_3)_6]^{n\oplus}$ (M = Co, n = 1, 0; M = Fe, n = 2).[7] The Co-Co bonds in **2** (280–282 pm) and in $[Co_6S_8(PEt_3)_6]$ (279–282 pm) are considerably shorter than those in **6** (299–301 pm); the S-S and Se-Se distances are 307–310 pm (**2**) and 324–326 pm (**6**), respectively. Thus, the Se-Se contacts in **6** are significantly shorter than in Mo_3Se_4 (350–374 pm)[8,9] and considerably less than the van der Waals contacts in selenium or $Se_8^{2\ominus}$.[10] This can be explained by the addition of more electrons into antibonding states of the Co_6 cluster in going from E = S to E = Se in $[Co_6E_8(PPh_3)_6]$ and by the increase in the interaction between the Se ligands. Alternatively, **6** could be described as a cubic Se_8 cluster that is coordinated by six $Co(PPh_3)$ groups, the Co atoms lying 49 pm above the faces of the cube. The 98e cluster **6** obeys neither the 18-electron rule nor the Cotton-Haas model.[11]

In the Co_9Se_{11} cluster **7** (Fig. 3), the Co atoms form two face-joined octahedra. Each of Co1,4,9 and Co 6,7,8 is coordinated to a PPh_3 ligand. The faces of the polyhedron are bridged by μ_3-Se (Se 1, 4, and 6–11) and μ_4-Se (Se 2, 3, 5) (Se···Se: 318–346 pm). The Co-(μ_3-Se) and Co-(μ_4-Se) distances, 228–236 and 232–247 pm, respectively, differ. Of the 21 Co-Co bonds (271–298 pm), those of the Co_3 polyhedron faces Co1, 4, 9 and Co6, 7, 8 are 10 pm longer (291–298 pm) than the remaining ones. **7** is formally formed by addition of a Co_3Se_3 group to **6**. This type of structure is known for, e.g., $K_2Mo_9S_{11}$,[12] $In_xMo_{15}Se_{19}$ ($x \leq 3$),[13] $[Rh_9(CO)_{19}]^{3\ominus}$, and $[Ni_9S_9(PEt_3)_6]^{2\oplus}$.[14] The 137e cluster **7** contains 17 and 13 electrons more than are expected on the basis of the 18-electron rule and the topological electron-counting rule,[15] respectively.

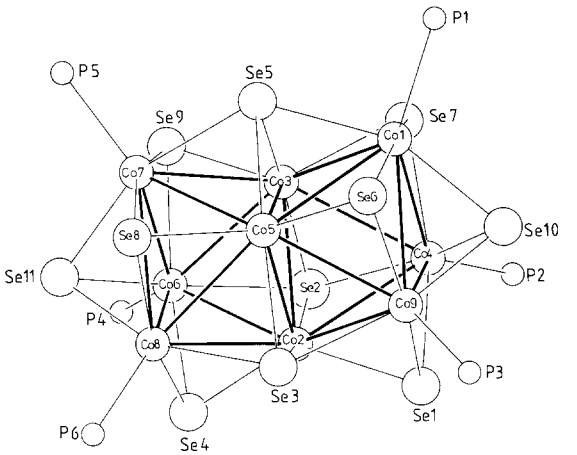


Fig. 3. Crystal structure of **7** (without phenyl groups) [4]. Most important distances (±0.2 pm) and angles (±0.1°): Co-Co 271–298, Co-(μ_3-Se) 228–236, Co-(μ_4-Se) 232–247, Co-P 218–221; Co-Co-Co 56.3–64.8, 88–92.2, 106.2–108.0, 144.6–150.1, Co-(μ_4-Se)-Co 68.2–74.4 and 129.8–132.8, Co-(μ_3-Se)-Co 71.1–78.5.

When $[NiCl_2(PPh_3)_2]$ is allowed to react with $Se(SiMe_3)_2$ in toluene, an insoluble residue of unknown structure is formed in 70% yield (based on Ni). The black $Ni_{34}Se_{22}$ cluster **8** crystallizes from the filtrate (yield 30%).[16] **8** is diamagnetic; in the ^{31}P- and ^1H-NMR spectra, signals are observed at $\delta = 28.0$ (39.8) and at 7.0–7.7, respectively.

$[Ni_{34}Se_{22}(PPh_3)_{10}]$ **8**

In the center of the $Ni_{34}Se_{22}$ cluster **8** (Fig. 4) ($\bar{1}$ symmetry)[17] is a pentagonal Ni_{10} antiprism (black), which is

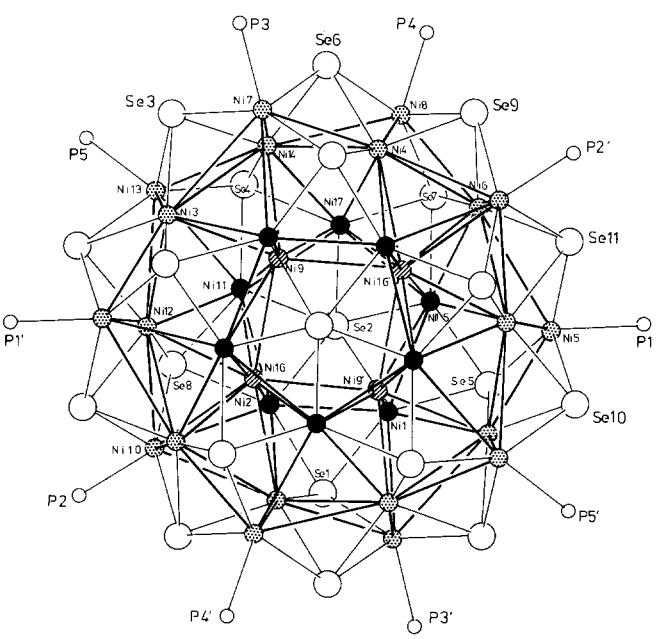


Fig. 4. Crystal structure of **8** (without phenyl groups) [17]. The atomic positions marked with ' are generated by inversion through a center of symmetry. Ni-Ni bond lengths are given when the Ni-Ni distance is ≤312 pm. Most important distances (±0.2 pm) and angles (±0.1°): Ni-Ni distances to the atoms Ni1 236–282, Ni2 239–275, Ni3 260–302, Ni4 260–310, Ni5 252–307, Ni6 241–310, Ni7 256–307, Ni8 260–301, Ni9 236–312, Ni10 260–293, Ni11 247–286, Ni12 256–312, Ni13 257–297, Ni14 258–313, Ni15 250–313, Ni16 242–293, Ni17 247–277. Ni-P 221–222, Ni-(μ_4-Se) 226–246, Ni-(μ_5-Se) 236–246; Ni-(μ_4-Se)-Ni 63–93, 114–129, Ni-(μ_5-Se)-Ni 62–63, 114–116.

coordinated by a μ_5-Se ligand at each of the terminal faces (Ni-(μ_5-Se): 236–246 pm). Between the two Ni_5 faces (distance: 448–456 pm) lies an intervening Ni_4 face (hatched); Ni9 is disordered. **8** formally arises by addition of five Ni_4 clusters to the pentagonal antiprism. Five distorted, connected Ni_8 cubes are thereby formed, the polyhedron faces of which are occupied by μ_4-Se ligands (Ni-(μ_4-Se): 226–246 pm). With the exception of Ni9, 9′, 16, and 16′, the Ni atoms are each bonded to three μ_4-Se ligands. Furthermore, a PPh_3 ligand is coordinated to each of ten Ni atoms (Ni 5, 7, 8, 10, 13 and the positions generated by reflection through an inversion center) (Ni-P: 221 pm).

The differing Ni-Ni distances (236–312 pm) complicate a description of the bonding situation. The *P*-coordinated Ni atoms are bonded to four other Ni atoms (distance: 252–307 pm). On the other hand, the remaining Ni atoms on the periphery of the cluster each exhibit four short (252–272 pm) and three long (297–313 pm) contacts. The Ni-Ni distances in the pentagonal antiprism vary from 236 to 275 pm and from 280 to 312 pm. **8** contains 448 valence electrons, a value that is in good agreement with the number of electrons calculated for M_n clusters ($n > 13$) using the electron-counting concept based on the Hume-Rothery rules.[18]

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[3] *Experimental procedure:* $[CoCl_2PPh_3)_2]$ (15.13 g, 0.023 mol) was suspended in 100 mL of toluene and treated with 5.25 g (0.023 mol) of $Se(SiMe_3)_2$. The blue solution immediately turned black. After 4 d, the mixture of **5** and **6** was filtered off (yield 6.0 g). When the residue was treated with THF, **5** was dissolved. Addition of a layer of pentane afforded crystalline **5** (2.8 g, 30% yield). By dissolving the residue in dichloroethane and adding a layer of pentane, crystalline **6** was obtained in the form of black crystals (yield: 2.0 g, 20%). From the filtrate of the reaction solution, 7 precipitated as large, black rhomb-shaped crystals (yield: 1.8 g, 25%).

[4] **5** (from THF), space group $P2_1/n$, lattice constants (180 K): $a = 1347.2(6)$, $b = 2560.1(11)$, $c = 1908.6(9)$ pm; $\beta = 100.40(3)°$, $Z = 4$, $\mu(Mo_{K\alpha}) = 33.9$ cm^{-1}, empirical absorption correction. Syntex R3, $2\theta \leq 55°$, 12264 reflections, 7472 with $I > 2\sigma(I)$. Patterson methods, Co, P, Se, C anisotropic, H positions calculated and isotropically refined. $R_1 = 0.078$, $R_2 = 0.069$.—**6** (from $C_2H_4Cl_2$), **6** crystallizes with four molecules of $C_2H_4Cl_2$, space group $P2_1/n$, lattice constants (180 K): $a = 1422.9(11)$, $b = 2000.0(20)$, $c = 1926.4(14)$ pm; $\beta = 102.29(4)$, $Z = 2$, $\mu(Mo_{K\alpha}) = 41.0$ cm^{-1}, empirical absorption correction. Syntex R3, $2\theta \leq 55°$, 11415 reflections, 7448 with $I > 2\sigma(I)$. Patterson methods, Co, Se, P, C anisotropic, H positions calculated and isotropically refined. $R_1 = 0.076$, $R_2 = 0.068$.—**7** (from toluene), **7** crystallizes with one molecule of toluene, space group $P\bar{1}$, lattice constants (180 K): $a = 1763.9(21)$, $b = 1820.6(13)$, $c = 2034.4(13)$ pm; $\alpha = 94.10(5)$, $\beta = 105.70(6)$, $\gamma = 107.11(5)°$, $Z = 2$, $\mu(Mo_{K\alpha}) = 46.9$ cm^{-1}, empirical absorption correction. Syntex R3, $2\theta \leq 50°$, 23096 reflections, 15230 with $I > 2\sigma(I)$. Patterson methods, Co, P, Se anisotropic, C isotropically refined, $R_1 = 0.067$, $R_2 = 0.063$.—Further details of the crystal structure investigation are available on request from the Fachinformationszentrum Energie, Physik, Mathematik GmbH, D-7514 Eggenstein-Leopoldshafen 2, by quoting the depository number CSD 51564, the names of the authors, and the journal citation.

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[16] *Experimental procedure:* $[NiCl_2(PPh_3)_2]$ (15.03 g, 0.023 mol) was suspended in 100 mL of toluene and treated with $Se(SiMe_3)_2$ (10.5 g, 0.046 mol). The blue solution immediately turned black. After 4 d, the residue was filtered off. From the filtrate, crystalline **8** separated after several days (yield: 1.3 g, 30%).

[17] **8** (from toluene), **8** crystallizes with six molecules of toluene, space group $P\bar{1}$, lattice constants (180 K): $a = 1676.4(5)$, $b = 1987.8(8)$, $c = 2027.7(8)$ pm; $\alpha = 91.79(3)$, $\beta = 112.30(2)$, $\gamma = 107.24(2)°$, $Z = 1$, $\mu(Mo_{K\alpha}) = 61.5$ cm^{-1}, empirical absorption correction. Syntex R3, $2\theta \leq 50°$, 18987 reflections, 12076 with $I > 2\sigma(I)$. Patterson methods, Ni, P, Se anisotropic, C isotropic. $R_1 = 0.076$, $R_2 = 0.070$.

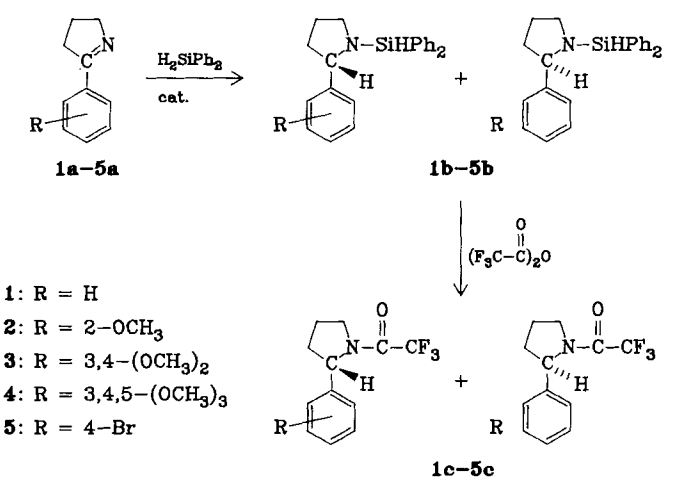
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Enantioselective Hydrosilylation of Prochiral 3,4-Dihydro-2*H*-pyrrole Derivatives**

By *Richard Becker, Henri Brunner,* Siavosh Mahboobi,* and *Wolfgang Wiegrebe**

Dedicated to Professor Hellmut Hartmann on the occasion of his 90th birthday

Pyrrolidine alkaloids, a class of compounds to which nicotine belongs, contain an asymmetric center (C-2 of the five membered ring). We report here on the Rh-catalyzed enantioselective hydrosilylation of the five-membered ring imines **1a**–**5a** with up to 64% optical induction, whereby a new acylating work-up procedure enables isolation of the products **1c**–**5c** in yields between 80 and 90%. In the cata-



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[**] Asymmetric Catalyses, Part 28. This work was supported by the Deutsche Forschungsgemeinschaft, the Fonds der Chemischen Industrie, and BASF AG.—Part 27: H. Brunner, A. Knott, R. Benn, A. Rufińska, *J. Organomet. Chem.*, in press.

Table 1. Hydrosilylation of imines **1a**–**5a** (2 mmol) in toluene (2 mL) with diphenylsilane (0.8 mL, 4 mmol) and the in situ catalyst $[Rh(cod)Cl]_2$/(−)-diop.

No.	Imine	Rh : Substrate	Rh : (−)-diop	Substrate : Ph_2SiH_2	*t* [h]	*T* [°C]	Yield [%]	*ee* [%] [d]
1	**1a**	1 : 50	1 : 1.1	1 : 2	32	0→20	85	59 (*R*)
2	**1a**	1 : 50	1 : 1.3	1 : 2	32	0→20	83	59 (*R*)
3	**1a**	1 : 50	1 : 1.1	1 : 2	69	−6	84	61 (*R*)
4 [a]	**1a**	1 : 100	1 : 1.1	1 : 2	30	0→20	84	64 (*R*)
5 [a]	**2a**	1 : 50	1 : 1.0	1 : 2	48	0→20	85	31 (*R*)
6	**3a**	1 : 50	1 : 1.12	1 : 2	48	0→20	87	33 (*R*)
7 [b]	**3a**	1 : 50	1 : 1.12	1 : 2	20	0→20	89	33 (*S*)
8 [c]	**4a**	1 : 50	1 : 1.0	1 : 2	72	0→20	81	31 (*R*)
9 [c]	**5a**	1 : 50	1 : 1.0	1 : 2	24	0→20	82	60 (*R*)

[a] Without solvent. [b] Catalyst: $[Rh(cod)Cl]_2$/(+)-diop. [c] 1 mmol imine employed. [d] Reproducibility ± 1.5% *ee*.

lytic hydrosilylation of the six-membered ring imine 3,4-dihydropapaverine an enantiomeric excess (*ee*) of 39% with only low chemical yields was achieved.[1]

The 3,4-dihydro-2*H*-pyrrole derivatives **1a**–**5a** were prepared from acetophenone and its derivatives via Mannich reaction with formaldehyde/dimethylamine.[2] The Mannich base was allowed to react with KCN; the resulting nitrile[3] was then hydrogenated with Raney nickel, whereupon cyclization to give **1a**–**5a** took place.[4, 5] The substrates **1a**–**5a** were dissolved in toluene together with the in-situ-catalysts prepared from $[Rh(cod)Cl]_2$/(−)-diop.[6] After 10 min stirring at room temperature the mixture was cooled (Table 1) and the reaction initiated by addition of diphenylsilane. The reaction was then allowed to continue with steady warming to room temperature. One of the Si–H bonds of the diphenylsilane adds to the C=N bond of the imines **1a**–**5a** with formation of the silylamines **1b**–**5b**. Isolation of the secondary amines could not be accomplished by hydrolysis with aqueous hydrochloric acid. The trifluoroacetamides **1c**–**5c** formed upon reaction of the silylamines **1b**–**5b** with trifluoroacetic anhydride, however, can, after neutralization with $NaHCO_3$, be extracted with ether and separated by distillation.[7]

The optical purity of the trifluoroacetamides **1c**–**5c** was determined by capillary gas-chromatography on Chirasil-L-Val®,[8] while the configuration was deduced from the retention behavior, according to which the *R*-enantiomers have shorter retention times.[9] When (−)-diop is employed as cocatalyst, the preferred configuration for all compounds **1c**–**5c** is uniformly *R* configuration.

The optical induction of the imine **1a** unsubstituted in the phenyl moiety can be increased from 59 to 61% *ee* if the reaction is carried out at −6 °C instead of at room temperature (Table 1, Entries 1–3). The best result (64% *ee*) is achieved when the reaction is carried out in the absence of solvent; the solid imine **1a** and the catalyst slowly dissolve in the diphenylsilane which is added at 0 °C (Entry 4). In the hydrosilylation of **2a**, whose *o*-methoxy group could coordinate intramolecularly to Rh, the optical induction drops to 31% *ee* (Entry 5). Since the optical inductions for the imines **3a** and **4a**, whose *m*- and *p*-methoxy groups cannot react intramolecularly with the rhodium, are likewise only 33 and 31% *ee*, respectively (Entries 6–8), an intermolecular effect, favored by the 50- to 100-fold excess of the substrate, must be responsible for such a drop in induction; this is even more pronounced in the hydrosilylation of the *p*-Br derivative **5a**, where 60% *ee* with the same enantiomeric yield as in the case of the unsubstituted imine **1a** is achieved (Entries 1, 2, 9), so that electronic effects cannot play any significant role. Catalyses with (+)-diop as cocatalyst preferably yield the *S*-enantiomer with the same optical purity as (−)-diop the (*R*)-isomer (Entries 6, 7).

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1a, 700-91-4; *R*-**1b**, 98421-38-6; *S*-**1b**, 98421-39-7; *R*-**1c**, 98421-40-0; *S*-**1c**, 98421-41-1; **2a**, 98464-65-4; *R*-**2b**, 98421-42-2; *S*-**2b**, 98421-43-3; *R*-**2c**, 98421-44-4; *S*-**2c**, 98421-45-5; **3a**, 91640-98-1; *R*-**3b**, 98421-46-6; *S*-**3b**, 98421-47-7; *R*-**3c**, 98421-48-8; *S*-**3c**, 98421-49-9; **4a**, 98421-50-2; *R*-**4b**, 98421-51-3; *S*-**4b**, 98421-52-4; *R*-**4c**, 98421-53-5; *S*-**4c**, 98421-54-6; **5a**, 22217-79-4; *R*-**5b**, 98421-55-7; *S*-**5b**, 98421-56-8; *R*-**5c**, 98421-57-9; *S*-**5c**, 98421-58-0

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[3] The 3-oxo-3-phenylbutyronitriles can also be prepared analogously to the method of *Leete* et al. from α-(4-morpholinyl)phenylacetonitriles and acrylonitrile: E. Leete, M. R. Chedekel, G. B. Bodem, *J. Org. Chem. 26* (1972) 4465.
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[6] cod = 1,5-cyclooctadiene; (−)-diop = (*R,R*)-(−)-*P,P'*-[2,2-dimethyl-1,3-dioxolane-4,5-diylbis(methylene)]bis[diphenylphosphane].
[7] For work-up, the mixture was cooled in an ice-bath, treated with tetrahydrofuran (2 mL), stirred for 5 min, and finally treated with 0.6 mL of trifluoroacetic anhydride. After 10 min stirring at room temperature the pH was adjusted to 8–9 with aqueous $NaHCO_3$ solution and the mixture extracted three times with 15 mL ether. The combined organic phases were dried over $MgSO_4$. After removal of solvent, the residue was distilled under vacuum in a Kugelrohr.
[8] About 30 mg of the product (**1c**–**5c**) was in each case dissolved in dichloromethane (0.5 mL) and measured gas-chromatographically on a 25-m Chirasil-L-Val® glass capillary column; injector temperature 250 °C; column temperature 100 °C (**1c**), 125 °C (**2c**), 135 °C (**3c**, **5c**), 170 °C (**4c**).
[9] H. Frank, G. J. Nicholson, E. Bayer, *J. Chromatogr. 146* (1978) 197.

Stereo- and Enantioselective Synthesis of Both *cis*-Chrysanthemic Acid Methyl Esters in High Optical Purity**

By *Michel Franck-Neumann,* Madjid Sedrati, Jean-Paul Vigneron,* and *Vincente Bloy*

Pyrethroids, in particular esters of the chrysanthemic acids (cf. **8**) or the side-chain modified *cis*-chrysanthemic

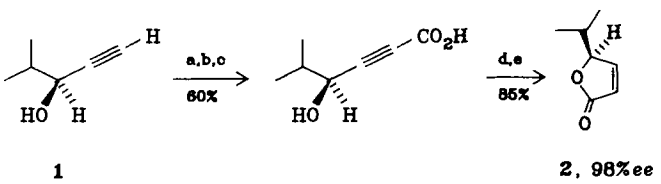
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[**] Pyrethroids, Part 5.—Part 4: M. Franck-Neumann, M. Miesch, *Bull. Soc. Chim. Fr. II 1984*, 362.

acids, are highly effective insecticides.[1] The physiological activity of such esters strongly depends on the absolute configuration, so that stereospecific and, if possible, enantioselective syntheses are necessary, especially in the *cis*-series.

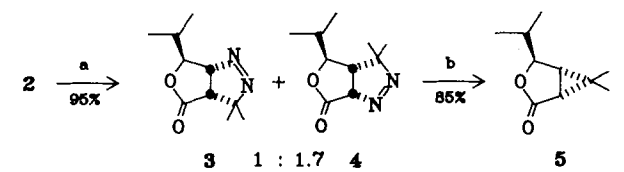
We report herein on a stereo- and enantioselective synthesis of both enantiomeric *cis*-chrysanthemic acid methyl esters: these compounds, which serve also as very important precursors for the synthesis of caronaldehyde acid esters,[2] are obtained in high yields and almost optically pure by stereospecific cyclopropanation of the corresponding chiral butenolides (cf. **2**). The key step of our synthesis is the 1,3-dipolar cycloaddition of 2-diazopropane with subsequent photolysis of the adducts (cf. **5**).[3]

The unsaturated, optically active lactone **2** was synthesized according to the method described for the preparation of similar chiral lactones[4] from the chiral alcohol **1**[5,6] (Scheme 1).



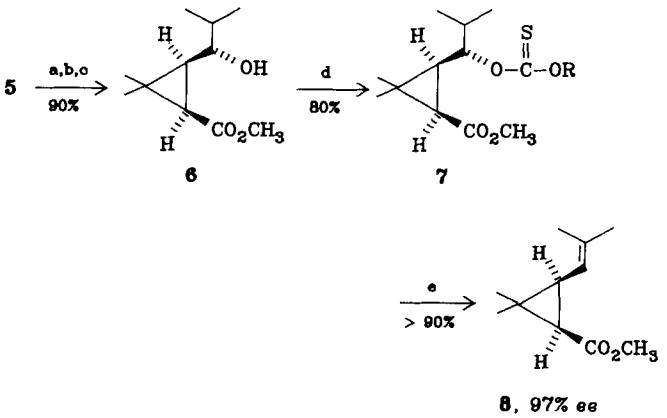
Scheme 1. a) *n*BuLi (2 equiv.), tetrahydrofuran (THF), −78°C; b) CO_2, −78 to +20°C; c) HCl, two recrystallizations from benzene; d) H_2/Lindlar catalyst (Pd/$BaSO_4$/quinoline), MeOH; e) HCl, ether.

The 1,3-dipolar addition of 2-diazopropane to **2**, which does not proceed regiospecifically but completely stereospecifically, furnishes the diastereomerically free 4,5-dihydro-1*H*-pyrazoles **3** and **4** (overall yield 95%)[7] (Scheme 2).



Scheme 2. a) $(CH_3)_2CN_2$ (2 equiv.), ether/ethylbenzene, −10°C [8]; b) *hv*, $(C_6H_5)_2CO$, benzene.

In contrast to **3**, the thermolysis of **4**, as expected, does not lead to a three-membered ring, despite loss of nitrogen. However, this does take place upon photolysis, preferably in the presence of a triplet-sensitizer such as benzophenone.[9] The cyclopropanated lactone **5** can be obtained directly in pure form and in at least 85% yield by irradiation of the mixture of **3** and **4**.[10] Hydrolysis of **5** under mild conditions and subsequent esterification with diazomethane finally afford the *cis*-cyclopropanecarboxylic acid methyl ester **6** (>90%), which could not however be dehydrated under mild conditions. Under drastic conditions, mainly opening of the three-membered ring was observed. Thermal elimination according to the method of *Gerlach* and *Müller*[13] proceeds quite differently when performed in 1,2,4-trichlorobenzene. **6** was first esterified to the thiocarbonate **7**, whose thermolysis in 1,2,4-trichlorobenzene led exclusively to the *cis*-chrysanthemic acid methyl ester **8** (Scheme 3).



Scheme 3. R = *p*-tolyl. a) KOH in EtOH/H_2O (2 : 1), 20°C, 12 h; b) HCl 5%; c) CH_2N_2, ether; d) R-OC(S)Cl, pyridine, CH_2Cl_2, 0°C, 48 h; e) 1,2,4-trichlorobenzene, 140°C, 15 min.

The pure *cis* ester **8** is separated from the sparingly volatile solvent by filtration through silica gel. Its optical purity is at least 97%, determined by direct comparison of the optical rotation with that of the authentic (1*R*,3*S*)-*cis*-ester.[14] The (1*R*,3*S*)-(+)-chrysanthemic acid methyl ester **8** depicted here, which leads to the physiologically most effective *cis* analogues, is formed from the (*S*)-(+)-butenolide **2**, which is obtained via the (*S*)-(−)-hydroxy acid from the (*S*)-(−)-alcohol **1**. This enantioselective total synthesis is also applicable to the (1*S*,3*R*)-*cis*-ester *ent*-**8**.

Microbiological or enzymatic reactions or resolution and separation of diastereomers are thus not necessary; this synthesis requires only cheap optically active auxiliary substances that can be readily recovered.

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[1] Review: D. Arlt, M. Jautelat, R. Lantzsch, *Angew. Chem. 93* (1981) 719; *Angew. Chem. Int. Ed. Engl. 20* (1981) 703.

[2] J. Martel, DOS 1935320 (1970), 1935321 (1970), 1935386 (1970), 1966839 (1969), Roussel-Uclaf.

[3] a) M. Franck-Neumann, *Angew. Chem. 80* (1968) 42; *Angew. Chem. Int. Ed. Engl. 7* (1968) 65; b) asymmetric cycloadditions of 2-diazopropane to optically active three-membered rings: H. M. Walborsky, T. Sugita, M. Ohno, Y. Inouye, *J. Am. Chem. Soc. 82* (1960) 5255; M. Franck-Neumann, D. Martina, M. P. Heitz, *Tetrahedron Lett. 23* (1982) 3493; c) almost enantiospecific cyclopropanation with isopropylidene(triphenyl)phosphorane in the *trans*-series: J. Mulzer, M. Kappert, *Angew. Chem. 95* (1983) 60; *Angew. Chem. Int. Ed. Engl. 22* (1983) 63; *Angew. Chem. Suppl. 1983*, 23.

[4] J. P. Vigneron, J. M. Blanchard, *Tetrahedron Lett. 21* (1980) 1739.

[5] The enantiomeric alcohols (*S*)-(−)-**1** and (*R*)-(+)-**1** (≡*ent*-1) are obtained in 86% optical purity from 4-methyl-1-pentyn-3-one by asymmetric reduction with $LiAlH_4$, (+)- or (−)-*N*-methylephedrine, respectively, and 3,5-dimethylphenol (molar ratio 1 : 1 : 2): J. P. Vigneron, V. Bloy, *Tetrahedron Lett. 1979*, 2683.

[6] The enantiomeric γ-isopropylbutenolides **2** and *ent*-**2** (b.p. 78–79°C/10^{-1} torr; $[\alpha]_D^{21} = \pm 121$ ($c = 2$ in dioxane) are obtained almost optically pure (no splitting in the high-resolution ^{1}H-NMR spectrum upon addition of chiral Eu-complex) in 50% yield (after two recrystallizations of the intermediary hydroxy acids from benzene, m.p. 80°C; constant rotation $[\alpha]_D^{25} = \pm 10.6$ ($c = 2$ in dioxane)).

[7] Separation by rapid column chromatography on silica gel Si60 (hexane/ether 4 : 1).

[8] C. Dietrich-Buchecker, M. Franck-Neumann, *Tetrahedron 33* (1977) 745.

[9] A mixture of the 1% solution of **3** and **4** in benzene and double the amount of benzophenone is irradiated in a pyrex apparatus with a Hg high-pressure lamp (Philips HPK 125).

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[10] Separation of benzophenone by distillation or rapid column chromatography on silica gel (hexane/ether 4:1). **5**, b.p. 47–48 °C/5 × 10^{-2} torr; $[\alpha]_D^{20} = \pm 80$ ($c = 1.2$ in $CHCl_3$). IR and NMR spectra are identical to those of the racemic lactone [11].
[11] M. Majewski, V. Snieckus, *J. Org. Chem. 49* (1984) 2682, and references cited therein.
[12] Even the reagents used by *Burgess* and *Martin* (see [11]) met without success in this case.
[13] H. Gerlach, W. Müller, *Helv. Chim. Acta 55* (1972) 2277.
[14] **8**, $[\alpha]_D^{20} = +66.4$ ($c = 1.5$, benzene); *ent*-**8**, $[\alpha]_D^{20} = -66.8$ ($c = 1.5$, benzene). Optically pure reference compound (Roussel Uclaf): $[\alpha]_D^{20} = +67.5$ ($c = 1.8$, benzene).

Hydroboration and Hydrozirconation of *tert*-Butylimino-2,2,6,6-tetramethylpiperidinoborane

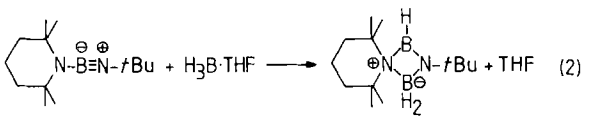
By *Detlef Männig, Heinrich Nöth,* Manfred Schwartz, Siegfried Weber,* and *Ulrich Wietelmann*

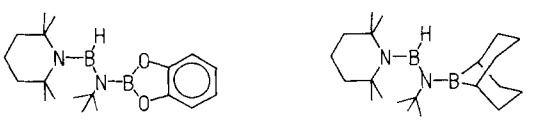
Dedicated to Professor Max Schmidt on the occasion of his 60th birthday

In many respects the chemistry of the iminoboranes[1–3] is similar to that of the isoelectronic alkynes: they oligomerize or polymerize,[2] add HX,[3] and form complexes with transition metals.[4] However, the polarity of the BN bonds confers enhanced reactivity on iminoboranes. This is exemplified by their rapid organoboronation to diborylamines according to Eq. (1).[1]

$$R-\overset{\ominus}{B}\equiv\overset{\oplus}{N}-R' + BR_3'' \longrightarrow RR''B-NR'-BR_2'' \qquad (1)$$

Alkynes undergo a *cis*-hydrometalation.[5] We have now investigated the hydrometalation of iminoboranes using *tert*-butylimino-2,2,6,6-tetramethylpiperidinoborane **1** as an example.[6] If $H_3B\cdot THF$ (THF = tetrahydrofuran) is used, the reaction at −65 °C and high dilution proceeds according to Eq. (2) to give the four-membered ring diborylamine **2** as the main product.[8] In contrast to this, hydroboration with 1,3,2-benzodioxaborole and with 9-borabicyclo[3.3.1]nonane leads to the BN chain compounds **3**[9] and **4**,[10] respectively, since electronic and (particularly) steric effects prevent ring closure.

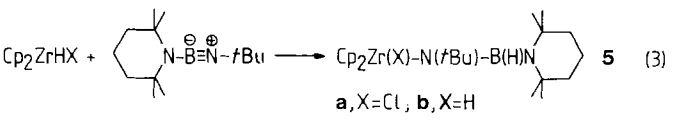


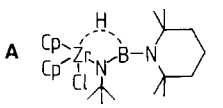


Whether the hydroboration of **1**, like that of the alkynes, proceeds stereospecifically by *cis*-addition, could not be confirmed in the above three examples by monitoring the reactions NMR spectroscopically at low temperatures. The reason for this is that the rotation barrier of the CC double bond is markedly higher than that of the BN bond of aminoboranes (40–100 kJ/mol).[11] For formation of **2**, a rotation about the central BN bond of a *cis*-hydroboration product is necessary.

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Whereas the NMR data of **2**–**4** are consistent with the proposed structures, the two hydrozirconation products **5a**, **b** obtained according to Eq. (3) (Cp = cyclopentadienyl)[12] showed ^{11}B-NMR signals which are not reconcilable with an *N*-metalated bis(amino)borane (**5a**: $\delta = 21.5$; **5b**: $\delta = 16.8$; $HB(NR_2)_2$: $\delta = 26$–28; $RN(NR_2)NRLi$: $\delta = 25$). The IR spectra do not contain any stretching modes of terminal BH-bonds. Medium strength bands in the region 1865–1910 cm^{-1} suggest the presence of hydride bridges. The proposed structure **A** is based on this finding (for **5b**: Cl replaced by H).





An X-ray structure analysis of **5a** confirms this postulate (cf. Fig. 1). The zirconium atom is coordinated in a distorted trigonal-bipyramidal fashion if one takes into consideration the centroids C_x and C_y of the η^5-bonded Cp ligands and the atoms H1, Cl, and N1. Each Cp ring shows two longer and three shorter CC bond distances. The thermal parameters of the C(F)–C(K) ring suggest disorder; its CC bonds are on average shorter (1.352(9) Å) and subject to larger standard deviations than the CC bonds of the Cp ring C(A)–C(E) (1.395(4) Å).

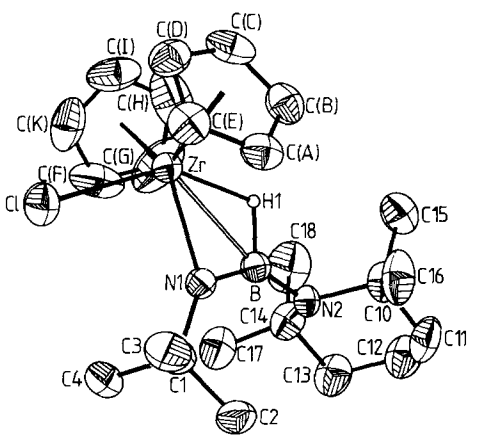


Fig. 1. ORTEP plot of the molecular structure of **5a** [13]. For clarity, C-bonded hydrogen atoms have been omitted. Selected bond lengths and angles ([Å] and [°], standard deviations in brackets): Zr-Cl 2.551(1), Zr-N1 2.211(2), Zr-H1 1.96(2), Zr-B 2.627(2), B-N1 1.360(3), B-N2 1.459(4), B-H1 1.25(2), N1-C1 1.497(3), N2-C10 1.499(4), N2-C14 1.493(4); Cl-Zr-H1 146.3(6), Cl-Zr-B 119.4(2), Cl-Zr-N1 88.7(1), Zr-N1-B 91.5(2), Zr-N1-C1 137.8(2), C1-N1-B 130.5(2), N1-B-N2 140.3(3), N1-B-H1 102.3(9), N2-B-H 117.4(9), B-N2-C10 115.9(2), B-N2-C14 120.1(3), C10-N2-C14 117.7(2), B-H1-Zr 107.7(12); C_x-Zr-Cl 99.8, C_y-Zr-Cl 98.3, C_x-Zr-C_y 122.3, C_x-Zr-N1 114.1, C_y-Zr-N1 120.6 (C_x, C_y: centroids of the Cp rings).

Characteristic for **5a** is a ZrHBN four-membered ring system. A short BN bond of only 1.360 Å is present which may be regarded as a double bond (1.37 Å in $(CH_3)_2NBCl_2$,[14] 1.33 Å in $(R_2N)_2B^{\oplus}$[15]). The ZrN bond is only slightly longer than in compounds of Zr^{IV} with sp^2 hybridized N atoms (2.070 Å in $ClZr[N(SiR_3)_2]_3$ (R = CH_3),[16] 2.167 Å in $Cp_2Zr(NC_4H_4)_2$, and 2.198 Å in

$[Zr(NC_4H_4)_6]^{2-}$[17]). Both the BH as well as the ZrH distances are consistent with H-bridges (1.25 and 1.35 Å in μ-aminodiboranes[18] and 1.73–1.88 Å in H-bridged Cp_2Zr-compounds[19]). The tetramethylpiperidino group is strongly twisted towards the four-membered ring plane: the C10–N2–C14 plane is inclined at an angle of 77° to the plane of the four-membered ring. Consistent with this is the relatively long BN2 bond (1.459 Å), indicating single bonding.[20]

The ZrB distance is only 0.18 Å longer than would be expected for a covalent ZrB bond (2.45 Å). This finding is compatible with a Zr–H–B multicenter bonding, and the resulting ZrB interaction could be responsible for the good shielding of the boron atoms in the NMR experiment.

5a thus contains a novel bonding system reminiscent of that of a μ-H-metallaborane. However, it differs from the latter in that the boron atom is only three-coordinated. Thus, *N*-metalated aminoboranes, whose structural chemistry promises new and interesting aspects of bonding, are accessible by hydrometalation of **1** (and presumably also of other iminoboranes).

Experimental

Bis(η^5-cyclopentadienyl)-μ-hydridozirconium-*tert*-butyl(2,2,6,6-tetramethylpiperidinoboryl)amide chloride **5a**: A stirred suspension of Cp_2ZrHCl (0.52 g) in toluene (5 mL) was treated dropwise with a solution of **1** (0.44 g) *in toluene (4.4 mL) in the absence of light.* After 24 h the clear solution showed ^{11}B-NMR signals at $\delta = 30.2$, 21.1, and 18.4 in the ratio 15 : 70 : 15. The toluene was removed by distillation and the residue was dissolved in a small amount of dichloromethane. Hexane was then added to the resulting solution until it turned turbid. The Cp_2ZrHCl which crystallized out on cooling to −15 °C was removed by filtration and the solution concentrated to a third of its volume by evaporation. Subsequent cooling to −78 °C afforded 0.4 g of **5a** (42%).

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[7] **1** can also be hydrosilylated, hydrostannated, and hydroaluminated.

[8] B.p. 57–58 °C/10^{-3} torr; NMR (C_6D_6): $\delta(^1H) = 1.52$–1.08 (6H), 1.38 (6H), 1.29 (6H), 1.27 (9H), 4.40 (BH), 3.47 (BH_2); $\delta(^{11}B) = 28.8$ (d), 4.4 (t) (1 : 1); $\delta(^{13}C) = 56.6$, 49.6, 37.5, 30.8, 30.1, 25.8, 17.2; IR: 2510 (ν(BH)), 2362, 2350 (ν(BH_2)), 1580 cm^{-1} (ν(BN)). Also formed are $(R_3CNBH)_{2,3}$ ($\delta(^{11}B) = 37.2$), tmpH·BH_3 ($\delta(^{11}B)$: −20.3, Q) μ-tmpB_2H_5 ($\delta(^{11}B) = 26.2$, doublet of triplets); R = CH_3, tmp = tetramethylpiperidino moiety). **2** cannot be completely separated from byproducts by distillation.

[9] M.p. 72–73 °C; NMR (C_6D_6): $\delta(^1H) = 7.1$–6.6 (m, 4H), 1.46 (s, 9H), 1.42 (s, 12H), 1.6–1.3 (m, 6H); $\delta(^{11}B) = 34.7$ (HBN_2), $h(1/2) = 430$ Hz; 24.4 (NBO_2), $h(1/2) = 280$ Hz (1 : 1); $\delta(^{13}C) = 15.76$, 31.26, 33.63, 37.03, 52.97, 55.48, 111.42, 121.66, 149.13; IR: 2482 cm^{-1} (ν(BH_t)).

[10] M.p. 65–67 °C; NMR (C_6D_6): $\delta(^1H) = 1.05$ (2H), 1.37 (12H), 1.50 (9H), 1.91 (12H); $\delta(^{11}B) = 48.8$ (NBC_2), 35.3 (HBN_2) with $^1J(^{11}B^1H) = 82$ Hz; $\delta(^{13}C) = 15.86$, 23.46, 26.45, 32.25, 33.03, 33.17, 33.87, 37.23, 53.57, 55.91; IR: 2475 cm^{-1} (ν(BH_t)).

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[12] **5a**: m.p. 135 °C (Zers.); NMR (C_6D_6): $\delta(^1H) = 5.96$ (10H), 1.57 (9H), 1.6–1.2 (6H), 1.20 (6H), 1.16 (6H); $\delta(^{11}B) = 21.5$, $h(1/2) = 250$ Hz (decoupled), 330 Hz (coupled); $\delta(^{13}C) = 18.24$, 26.39, 32.34, 35.17, 40.73, 51.66, 56.72, 112.59; IR: 1909 (sh, w), 1887 (m), 1865 (w); 1597 (w), 1498 cm^{-1} (s).—**5b**: m.p. 180–188 °C (decomp.); NMR (C_6D_6): $\delta(^1H) = 5.68$ (10H), 1.36 (9H), 1.5–1.0 (18H); $\delta(^{11}B) = 16.8$, $h(1/2) = 190$ Hz (decoupled), 240 Hz (coupled); $\delta(^{13}C) = 18.65$, 24.9, 31.57, 32.5, 40.90, 51.46, 53.90, 104.14; IR: ν = 1875 cm^{-1} (br).

[13] Single crystals from hexane; $a = 8.201(2)$, $b = 32.11(12)$, $c = 9.531(2)$ Å, $\beta = 108.30(2)°$, $V = 2383(1)$ Å^3, $Z = 4$, $\rho_{calc} = 1.34$ g/cm^3, $P2_1/n$, crystal dimensions: 0.2 × 0.3 × 0.5 mm, ω scan, scan rate 3–29.3°/min, range of measurement 2θ: 2–50°, ±h, k, ±l, 7815 measured intensities, 3789 symmetry-independent with $I > 3\sigma(I)$; anisotropic temperature factors for non-hydrogen atoms; one methyl group refined as rigid group. $R = 0.043$, $R_w = 0.034$ with $1/w = \sigma(F) + 0.0001(F)^2$. Number of refined parameters: 396. Further details of the crystal structure investigation are available on request from the Fachinformationszentrum Energie, Physik, Mathematik GmbH, 7514 Eggenstein-Leopoldshafen 2, on quoting the depository number CSD-51403, the names of the authors, and the full citation of the journal.

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Synthesis and Structure of a Diaza-λ^2-phosphanylia-λ^5-stannatacyclobutane

By *Manuela Bürklin, Elisabeth Hanecker, Heinrich Nöth,* and Wolfgang Storch**

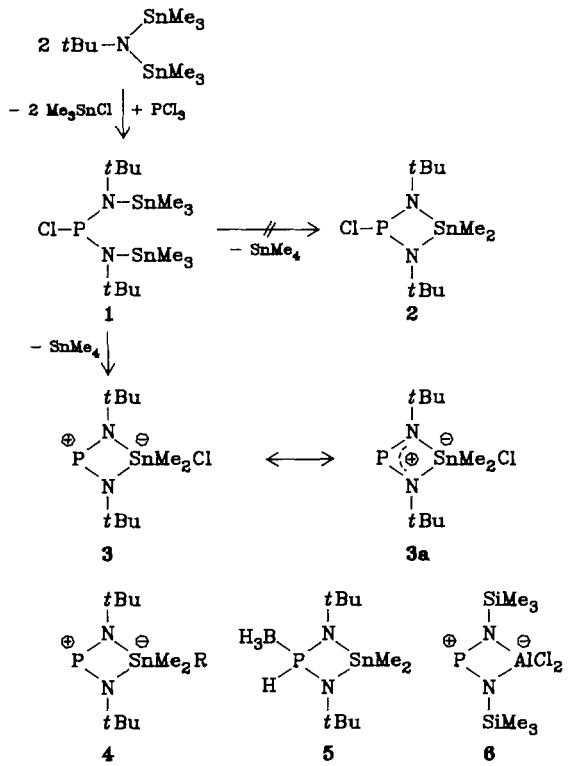
Stannazanes are attracting increasing interest as versatile synthons for main group element-nitrogen compounds,[1] e.g., for the synthesis of phosphazanes.[2,3] They are also suitable, as reported here, for the synthesis of a novel ring system.

Phosphorus trichloride reacts with the stannazane *tert*-butylbis(trimethylstannyl)amine in the molar ratio 1 : 2 to give the diaminochlorophosphane **1**, which has only been detected NMR-spectroscopically; **1** decomposes slowly below 0 °C and quantitatively within 5 h at room temperature. Cyclocondensation, which surprisingly involves formation of tetramethyltin, does not, however, lead to the diazaphosphastannetidine **2** but to the zwitterion diaza-λ^2-phosphanylia-λ^5-stannatacyclobutane **3**. In contrast, the *N*-silylated diaminophosphane $ClP(NCR_3SiR_3)_2$, a homologue of **1**, decomposes with elimination of Me_3SiCl.[4,5] Compound **3** undergoes substitution at the Sn-bonded chlorine atom on reaction with organolithium compounds: The zwitterionic derivatives **4** are formed. By way of contrast, the reaction of **3** with $LiBH_4$ in ether leads to formation of **5**. Apparently a positively charged λ^3-phosphorus center is unstable; its expectedly pronounced electrophilicity therefore favors a hydride migration from the tin atom to the phosphorus atom.[6]

The structures of **3**–**5** follow from the NMR spectra.[7] Thus, the ^{119}Sn chemical shifts confirm pentacoordination[8] in **3** and **4a** and tetracoordination of the tin atom in **5**, whose BH_3 group, according to the BP coupling, is bound to the P atom. The ^{14}N-nuclei in **5** are better shielded ($\Delta\delta(^{14}N) = 130$) as compared to those in **3** and **4a**. This is not only an indication of trigonal planar coordinated N atoms but is also a strong argument for pro-

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a, R = Ph; **b**, R = Bu; **c**, R = Me

nounced (pp)π interactions between the phosphorus center and the amino nitrogen atoms,[9] leading to stabilization of the positive charge (cf. **3a**). The $\delta(^{31}P)$ values lend support to the phosphanylia-character of **3** and **4**.[10] The two *tert*-butylamino groups in **3** and **4** should be magnetically non-equivalent, since one nitrogen atom is expected to be bonded equatorially and one axially to the pentacoordinate Sn atom. However, they cannot be differentiated by NMR spectroscopy; no signal splitting is observed, even at −60°C. This suggests fluctional behavior, which is favored by pentacoordination.

An X-ray structure analysis of **3** confirms the constitution derived from NMR data.[11] Figure 1 shows the pentacoordination at the tin atom and the dicoordination at the phosphorus atom. The PN_2Sn four-membered ring lies on a crystallographic mirror plane and is thus planar. Its N atoms show angle sums of 360°. As a result, the tertiary C atoms of the *tert*-butyl groups also lie in the ring plane. In this respect **3** resembles the zwitterion **6**.[12] The apical positions are occupied by the Cl atom and one N atom,[13] while two methyl C-atoms and one nitrogen atom are found in the equatorial positions. The trigonal bipyramidal coordination polyhedron is somewhat distorted. The apical SnN bond is about 0.20 Å longer than the equatorial one. As a consequence, two PN distances are observed: The PN bond to the equatorial N atom is longer than that to the axial N atom. They are short compared to other PN distances,[12] so that (pp)π bonding, which is to be expected from the ^{14}N-NMR spectra, is also supported by the X-ray structure analysis. Finally, also the relatively short transannular SnP distance (2.983 Å), which lies well below the sum of the van der Waals radii, corresponds with the large value for $^2J(^{119}Sn^{31}P)$.

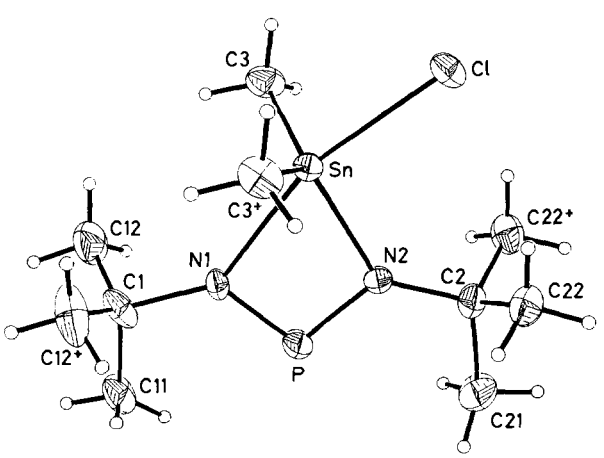


Fig. 1. ORTEP plot of the crystal structure of **3**. Selected atomic distances [Å] and bond angles [°] (with standard deviations): PN1 1.586(9), PN2 1.643(7), SnN1 2.359(6), SnN2 2.156(7), SnCl 2.489(3), SnC3 2.114(8); N1PN2 96.6(4), N1SnN2 64.4(3), PN1Sn 96.3(3), PN2Sn 102.7(4), N2SnCl 97.5(2), N1SnCl 161.8(2), C3SnC3$^+$ 128.6(5).

Experimental

1,3-Di(*tert*-butyl)-4-chloro-4,4-dimethyl-1,3,2λ^2,4λ^5-diazaphosphanyliastannatacyclobutane **3**: A solution of PCl_3 (2.9 mL) in CH_2Cl_2 (12 mL) was added dropwise at −78°C to a stirred solution of *tert*-butyl-bis(trimethylstannyl)amine (20 mL) in 60 mL CH_2Cl_2. After allowing the solution to warm up to 25°C, stirring for 12 hours, and refluxing for an additional hour, $(CH_3)_3SnCl$ and CH_2Cl_2 were removed from the light-brown solution by condensation into a trap cooled to −78°C. 11.7 g (97%) of **3**, mp. 84°C, was obtained by sublimation of the residue at 90°C/10^{-2} torr.

1,3-Di(*tert*-butyl)-4,4-dimethyl-4-phenyl-1,3,2λ^2,4λ^5-diazaphosphanyliastannatacyclobutane **4a**: A 2 M solution of PhLi in benzene (3.1 mL) diluted with ether (3 mL) was added dropwise at −78°C to a stirred solution of **3** (2.2 g, 6.15 mmol) in 50 mL of a 1:1 ether-pentane mixture. After the suspension had slowly acquired ambient temperature and after 24 hours' stirring at room temperature, the insoluble material was removed by filtration (G4 frit). The solvent was then removed from the filtrate at 25°C/10^{-2} torr and the viscous residue was fractionally distilled. 2.1 g (85%) of **4a** was obtained as a slightly yellow liquid, b.p. 108–109°C/10^{-2} torr.

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[6] We assume that R^- and BH_4^- attack nucleophilically and with electrophilic help by Li^+ at the Sn atom with substitution of Cl^-. BH_3, liberated by hydride-abstraction from BH_4^-, subsequently coordinates at the P atom.

[7] The ^{1}H- and ^{13}C-NMR spectra were recorded in CH_2Cl_2 and C_6D_6/$CDCl_3$ solutions, respectively, with a JEOL FX90 apparatus, all the remaining ones in C_6D_6 with a Bruker WP 200 apparatus. Standards: TMS int. (^{1}H, ^{13}C), $BF_3 \cdot O(Et)_2$ ext. (^{11}B), NO_3^- saturated solution (^{14}N), $SnMe_4$ ext. (^{119}Sn), 85% H_3PO_4 ext. (^{31}P). **3**: ^{1}H NMR: δ = 0.96 ($^2J(^{119}Sn^1H)$ = 70.1 Hz, SnMe); 1.39 (d, $^4J(^{31}P^1H)$ = 1.6 Hz, *t*Bu). ^{13}C NMR: δ = 11.1 (d, $^1J(^{119}Sn^{13}C)$ = 621 Hz, SnMe); 33.8 (d, $^1J(^{119}Sn^{13}C)$ = 7.0, $^3J(^{31}P^{13}C)$ = 11.4 Hz, $C(CH_3)_3$); 55.9 (d, $^2J(^{119}Sn^{13}C)$ = 5.0, $^2J(^{31}P^{13}C)$ = 10.3 Hz, $C(CH_3)_3$. ^{14}N NMR: δ = −151. ^{31}P NMR: δ = 260.2 (CH_2Cl_2), 276.2 (C_6D_6). ^{119}Sn NMR: δ = −80.2 (d, $^2J(^{119}Sn^{31}P)$ = 35.1 Hz).—**4a**: ^{1}H NMR: δ = 1.40 (s, $^2J(^{119}Sn^1H)$ = 33.7 Hz, SnMe); 1.99 (d, $^4J(^{31}P^1H)$ = 2.0 Hz, *t*Bu); 7.93–8.32 (m, SnPh); ^{13}C NMR: δ = 1.80 (d, $^1J(^{119}Sn^{13}C)$ = 457.2 Hz, SnMe); 34.65 (d, $^3J(^{31}P^{13}C)$ = 15.1 Hz, $C(CH_3)_3$); 55.4 (d, $^2J(^{31}P^{13}C)$ = 10.1 Hz, $C(CH_3)_3$); 136.1 ($^1J(^{119}Sn^{13}C)$ = 41.4 Hz, *ipso*-C); 128.3 (*o*/*p*-C), 120.2 (*m*-C). ^{14}N NMR: δ = −142. ^{31}P NMR: δ = +274.1 (CH_2Cl_2); +259.2 (C_6D_6). ^{119}Sn NMR: δ = −70.2 (d, $^2J(^{119}Sn^{31}P)$ = 39.5 Hz).—**5**: ^{1}H NMR: δ = 0.55 (s, $^2J(^{119}Sn^1H)$ = 62.1 Hz, SnMe); 1.19 (d, $^4J(^{31}P^1H)$ = 0.7 Hz, *t*Bu). ^{13}C NMR: δ = 1.05 (s, SnMe); 31.61 (d, $^3J(^{31}P^{13}C)$ = 4.1 Hz, $C(CH_3)_3$); 52.45 (d, $^2J(^{31}P^{13}C)$ = 4.6 Hz, $C(CH_3)_3$). ^{14}N NMR: δ = −274. ^{31}P NMR: δ = +31.6 (q, $^1J(^{31}P^{11}B)$ = 73.4 Hz). ^{119}Sn NMR: δ = +107. ^{11}B NMR (in CH_2Cl_2): δ = −35.5 ($^1J(^{31}P^{11}B)$ = 76.9, $^1J(^{11}B^1H)$ = 79.1 Hz).

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[11] C2/m, $a = 15.239(10)$, $b = 10.849(4)$, $c = 10.177(3)$ Å, $\beta = 103.0(4)°$, $V = 1639.5(13)$ Å^3, $\mu = 18.04$ cm^{-1}, $\rho_{calc} = 1.45$ g/cm^{-3}. $Mo_{K\alpha}$ radiation, $2 < \theta < 50°$ in $\pm h$, $\pm k$, $\pm l$; 6481 measured intensities, 1580 symmetry-independent, absorption-corrected intensities with $I > 6\sigma(I)$. Structure solution by the heavy atom method and difference Fourier syntheses. Non-hydrogen atoms refined with anisotropic temperature factors; H atom positions calculated and considered as rigid groups with fixed U_i in the final refinement (97 parameters). $R = 0.056$, $R_w = 0.064$. Further details of the crystal structure investigation are available from the Fachinformationszentrum Energie, Physik, Mathematik GmbH, D-7514 Eggenstein-Leopoldshafen 2, on quoting the depository number CSD-51543, the names of the authors, and the full citation of the journal.
[12] S. Pohl, *Chem. Ber. 112* (1979) 3159. The longer PN-bond in the cation is as long as that in 6 (1.614(6) Å) and $P(NiPr_2)_2^{\oplus}$ (1.613(4) Å) [10c]). The NPN bond angle is comparable to that in **6** (97.4(4)°), whereas it is opened to 114.8° in the PN_2 cation.
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Novel Polymerization of α-Olefins with the Catalyst System Nickel/Aminobis(imino)phosphorane

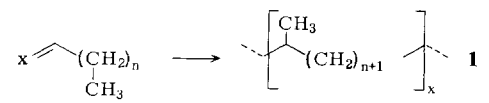
By *Volker Michael Möhring* and *Gerhard Fink**

Polymerization of ethene with the catalyst system nickel(0) compound[1]/bis(trimethylsilyl)aminobis(trimethylsilylimino)phosphorane[3] leads, according to *Keim* et al.[4] to short-chain, branched polymers. We have found that this system polymerizes α-olefins: surprisingly the structure of the products is consistent not with the usual 1,2 coupling of the monomers to give a comb-like branched product but with a 2,ω-coupling.

With the homogeneous catalyst system nickel(0) compound/aminobis(imino)phosphorane, linear α-olefins (experimentally tested range: C_3 to C_{20}) and singly branched α-olefins can be polymerized, but not α-olefins with quaternary C-atoms in the chain or olefins with vinylene or vinylidene groups. Besides α-olefin homopolymers, copolymers with ethene or other α-olefins can be prepared, whereby random copolymers or block copolymers are obtained, depending on the method employed. The catalyst components—preferably in equimolar ratio—are employed in situ in the pure liquid monomer or in aromatic solvents. The nature of the ligand of the Ni^0 compound (see[11]) has no influence on the structure of the α-olefin polymer.

This finding and results of kinetic investigations[5] suggest that the rate-determining step in the formation of the polymerization-active species is the release of the ligand from Ni^0.[5]

The structure of the poly-α-olefins is unusual. When a linear α-olefin is polymerized, the polymer (see **1**) contains only methyl branches, regularly spaced along the chain with a separation corresponding to the chain length of the monomer.



1

Thus, in the polymer of a linear α-olefin with n CH_2 groups the distance between two methyl branches is (n+1) CH_2 groups. Because their structure is well defined and can be predetermined by selection of the appropriate α-olefin, these products are suitable as model substances for physical investigations. Thus, for example, the structure of the polymer synthesized from 1-pentene corresponds to that of a rigidly alternating copolymer of ethylene and propylene.

The structure of the products was confirmed ^{13}C-NMR spectroscopically (for examples, see Figs. 1 and 2). The assignment of the signals was carried out with the help of the increment rules of *Lindemann* and *Adams*.[6] All the signals to be expected for 2,ω-linked α-olefin polymers were found in the spectra in the corresponding intensity ratios. The additional signals arise from the difference between the beginning and the end of the polymer chains: at the beginning there are not (n+1) but (n+3) CH_2 groups between the first two methyl branches (Fig. 1).

Analysis of the ^{13}C-NMR spectra of polymers of deuterated α-olefins revealed that the growing chain is bound to the next α-olefin via $C_\omega \rightarrow C^2$ linking; C^1 forms the later methyl branch in the polymer.

The average molecular weight and the molecular weight distribution are strongly dependent on the reaction temperature. Below ca. 273 K characteristic features of a "living polymer" are observed; that is, the molecular weight can be regulated by the ratio of monomer to catalyst-concentration, and the molecular weight distribution remains narrow. Above ca. 273 K the average molecular weight decreases with increased polymerization activity; at the same time the molecular weight distribution becomes broader and the double bonding in the polymer (vinylene, vinyl, vinylidene groups) is increased. This finding indicates that transfer reactions to the monomer take place via β-H elimination.

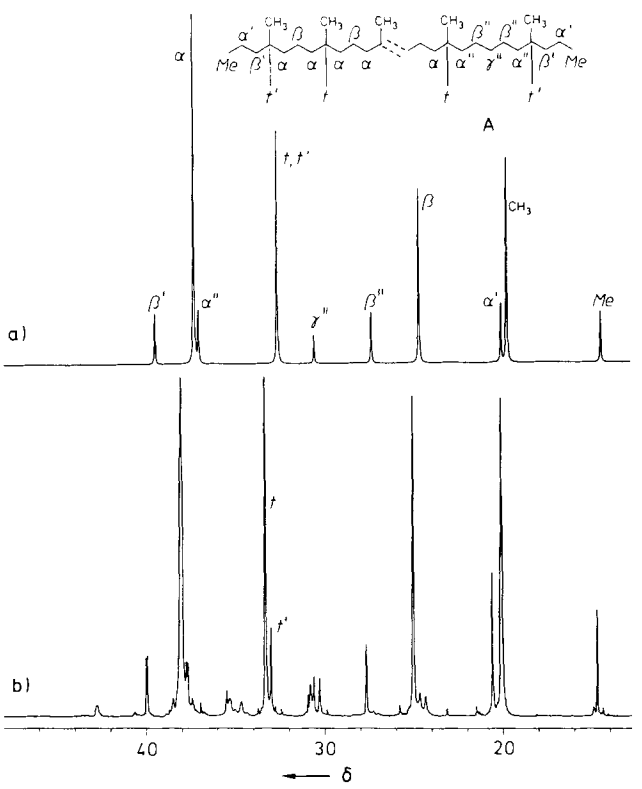


Fig. 1. a) Simulated $^{13}C\{^1H\}$-NMR spectrum of a polymer with the given structure obtained from 1-pentene (with A beginning of the chain); b) $^{13}C\{^1H\}$-NMR spectrum of poly-2,5-(1-pentene)[poly(1-methyltetramethylene)] (75.5 MHz, [D_6]benzene 30°C).

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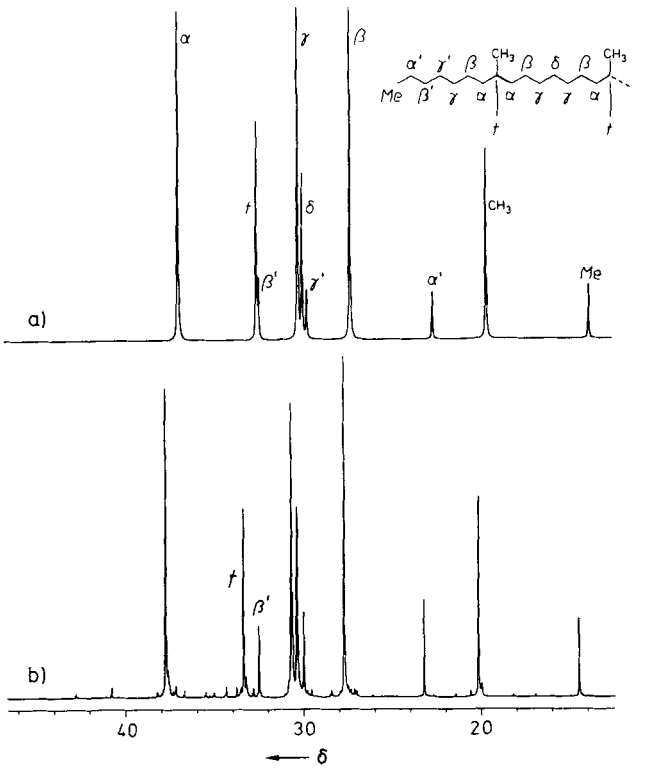


Fig. 2. Simulated $^{13}C\{^1H\}$-NMR spectrum of a polymer of the given structure (with chain ends) obtained from 1-nonene; b) $^{13}C\{^1H\}$-NMR spectrum of poly-2,9-(1-nonene)[poly(1-methyloctamethylene)] (75.5 MHz, [D_6]benzene, 30°C).

In addition, it emerges that, under otherwise equal reaction conditions, the average molecular weight always has the same value independent of the C-number of the monomer (e.g. at 298 K: ca. 1000 g/mol[7]). The degree of polymerization decreases linearly with increasing chain length of the α-olefin.

Taking all the results into account, a reaction scheme was developed with which the origin of the special structure of the poly-α-olefin can be explained (Fig. 3). The main points of the scheme are:

- The monomer can only insert into a CH_2–Ni bond at the end of the growing chain;
- the insertion is regioselective; only $C_\omega \rightarrow C^2$ coupling of the growing chain with the next monomer takes place;
- the nickel-catalyst complex "migrates" along the polymer chain between two insertions. During this "migration" transfer reactions to the monomer can occur, but not insertions.

These processes are represented schematically in Figure 3 for the polymerization of the 1-butene. The "migration" can be explained in terms of an addition-elimination mechanism via allylnickel/nickel hydride species with 1,2-hydride shift. The nickel hydride could also function as a transferring species, whereby the various types of detectable double bonds would be formed via β-H elimination corresponding to the momentary position of the nickel-catalyst complex in the chain.

If each step of the "migration" is reversible, then statistically the nickel-catalyst complex not only moves forward to the "correct" end of the chain but also back in the direction to the beginning of the formed polymer chain. The ever increasingly longer chain being formed in the polymerization is so structured that the "migrating" nickel-catalyst complex always finds a similar chemical environment after a certain chain length. That is, any possible influence of the chain end will progressively get smaller, so that there is equal probability of migration in both directions. The dependence of the degree of polymerization on the length of the linear α-olefin could be explained in terms of a limiting chain length after which the probability of formation of a Ni–CH_2 grouping at the end of the chain, and thus the possibility of insertion of a further monomer, tends to zero under the particular reaction conditions.

The formation of all structural features (short- and long chain branches) which are detectable in polyethylene prepared with this catalyst system can likewise be explained in terms of an extended "migration mechanism".[8]

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CAS Registry numbers:
Poly(1-pentene) (homopolymer), 25587-79-5; poly(1-nonene) (homopolymer), 29254-71-5; 1-butene 106-98-9; poly(1-methyloctamethylene) (SRU), 33825-82-0; nickel, 7440-02-0.

[1] Examples: bis(1,5-cyclooctadiene)nickel, (1,5,9-cyclododecatriene)nickel, or (cyclooctatetraene)nickel [2].

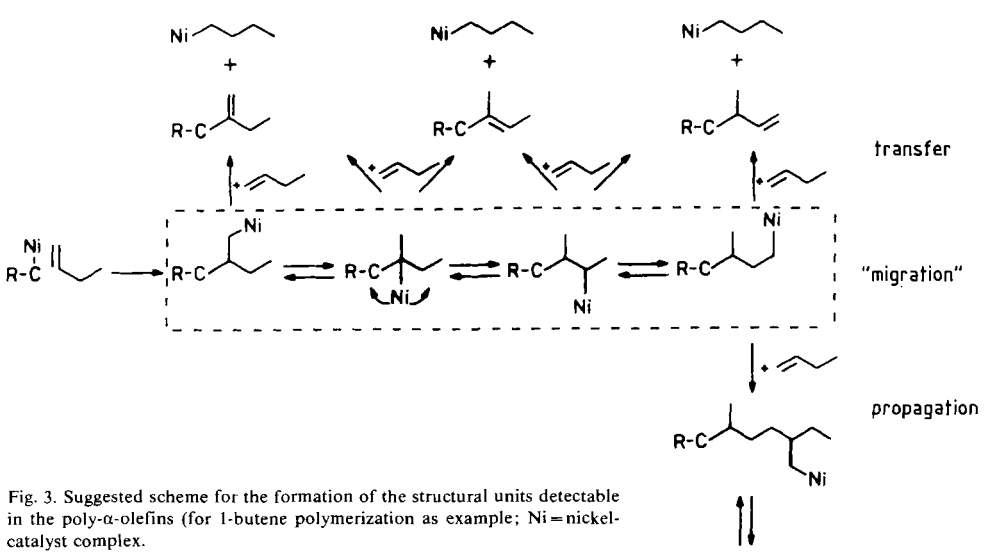


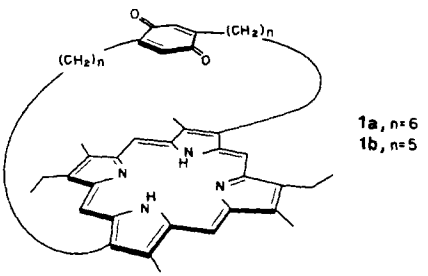
Fig. 3. Suggested scheme for the formation of the structural units detectable in the poly-α-olefins (for 1-butene polymerization as example; Ni = nickel-catalyst complex.

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The Synthesis of Porphyrins Doubly Linked to Quinones by Hydrocarbon Chains**

By *Brian Morgan* and *David Dolphin**

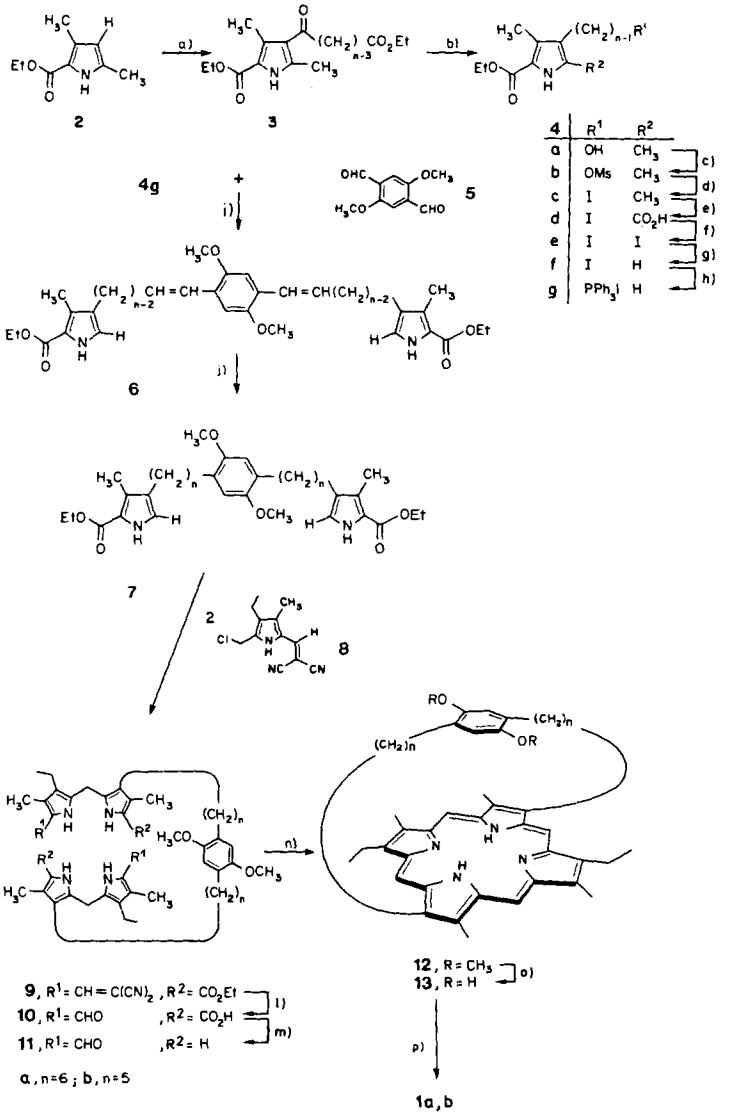
Electron transfer from an excited ((bacterio)chlorophyll through a series of intermediate compounds (bacterio)pheophytin, Fe-S clusters) to a quinone acceptor (ubiquinone, plastoquinone) is a key step in bacterial and plant photosynthesis.[1] Not surprisingly, attempts have been made to mimic this light-induced separation of charge using various model complexes in which a quinone is covalently attached to the periphery of a porphyrin macrocycle.[2] However, meaningful results depend on a knowledge of the relative orientation and separation of the two reaction centers. For those complexes in which the porphyrin electron donor and the quinone acceptor are linked by a *single*, flexible chain, observation of intramolecular charge transfer may be obscured by intermolecular reaction.



1a, n=6
1b, n=5

We report here on a general route for the synthesis of porphyrin-*p*-benzoquinone systems such as **1a**, **b** in which the quinone ring is held in position above one face of the porphyrin by *two* oligomethylene straps. *Staab* et al. recently described the synthesis of a porphyrin related to **1** which is doubly capped by *p*-benzoquinone.[3] Postponement of the porphyrin ring-forming reaction until the final stages of the synthesis of **1** (Scheme 1) ensures good yields of the product even for relatively short straps. The compounds **1a** and **1b** prepared by us contain two hexa- and pentamethylene straps, respectively, and it is anticipated that also variants of **1** with $n \geq 4$ can be obtained in this way.

The key step of the synthesis is the double Wittig reaction of the pyrrolephosphonium salt **4g** and the dialdehyde **5**,[4] both compounds being easily prepared from readily available starting materials, the β-free pyrrole **2**



Scheme 1. Synthesis of the capped porphyrins **1a** and **1b**. The yields [%] are given in parentheses. (a) $SnCl_4$, CH_2Cl_2, 0°C, $ClOC(CH_2)_{n-3}CO_2Et$ (n = 6 and 5, resp.) (84, 73); (b) $BF_3 \cdot Et_2O$, $NaBH_4$, tetrahydrofuran (85, 72); (c) CH_3SO_2Cl, Et_3N, CH_2Cl_2, 0°C (92, 88); (d) NaI, acetone, reflux (92, 88); (e) SO_2Cl_2, CH_2Cl_2, Et_2O; H_2O, acetone, reflux (83, 91); (f) $NaHCO_3$, KI, I_2, $ClCH_2CH_2Cl$, reflux (84, 86); (g) HI, EtOH (88, 43); (h) PPh_3, $C_6H_5CH_3$, reflux (97, 86); (i) $K_2CO_3 \cdot 1.5\,H_2O$, dioxane, reflux; (j) 10% Pd/C, cyclohexene, EtOH, reflux, (two steps: 83, 42); (k) ACOH, 80°C (88, 90); (l) KOH, PrOH, H_2O, reflux; (m) dimethylformamide, reflux; (n) TosOH, high dilution (three steps: 49, 39); (o) BBr_3, −78°C → room temperature; (p) PbO_2, CH_2Cl_2 (two steps: 60, 70).

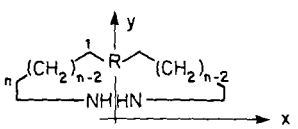
and 1,4-dimethoxybenzene, respectively. Phase transfer reaction[5] of **4g** and **5** in refluxing dioxane in the presence of potassium carbonate yielded the diolefin **6**, which was reduced to the oligomethylene-bridged bis(pyrrole) **7**.[6] This was then condensed with two equivalents of the α-chloromethylpyrrole **8** to provide the highly substituted bis(dipyrromethane) **9**. Base hydrolysis and thermal decarboxylation gave the unstable α-free, α′-formyl chain-linked bis(dipyrromethane) **11**. Acid-catalyzed cyclization of **11** was carried out under high dilution conditions to encourage intramolecular condensation, and the strapped porphyrin **12** was isolated chromatographically (**12a**, 20–60%; **12b**, 40%). Compounds **12a** and **12b** were recrystallized from CH_2Cl_2/hexane (m.p. 271–274°C and 264–267°C, resp.) and characterized by elemental analysis, high resolution mass spectrometry (*m/z* 724.4695 (M^+) and 696.4365 (M^+), resp.), and ^1H- and ^{13}C-NMR spectroscopy.

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The methoxy functions could be removed under mild conditions by treating **12** with excess boron tribromide in CH_2Cl_2 at $-78°C$, and then warming to room temperature. The crude porphyrin-hydroquinone **13** was then oxidized to **1** by stirring with lead dioxide in CH_2Cl_2. Chromatography (neutral Al_2O_3) furnished the desired porphyrin in excellent yield (**1a**, 82%; **1b**, 96%). The structures of **1a**, **b**, like those of **12a**, **b** were confirmed by elemental analysis, high resolution mass spectrometry (*m/z* 694.4249 (M^+) and 666.3984 (M^+), resp.), and ^{1}H- and ^{13}C-NMR spectroscopy.

That the dimethoxybenzene or quinone rings are held in place above the porphyrin was dramatically illustrated in the ^{1}H-NMR spectra. All protons of the two oligomethylene straps experience the effect of the porphyrin ring current and since this effect decreases along both x- and y-axes (Scheme 2), the chemical shifts of the strap protons depend on the length and conformation of the strap. For example, protons directed into the cavity bounded by the strap and the porphyrin ring experience large upfield shifts. The internal shift reagent effects a spread in the chemical shifts over a wide range, thus allowing identification of each resonance by simple decoupling experiments.



Scheme 2.

Table 1. ^{1}H-NMR data of **12** and **1** (δ values, $CDCl_3$).

Group	12a	12b	1a	1b
10,20 Methine H's	9.98	9.93	10.02	10.05
5,15 Methine H's	10.00	9.97	10.03	
CH_2CH_3	4.12 4.04	4.17 4.07	4.12	4.08–4.24
Phenyl 3,6-H	3.91	3.80	—	—
CH_3	3.60 3.59	3.62 3.54	3.68 3.60	3.70 3.57
Quinone 3,6-H	—	—	2.76	2.94
CH_2CH_3	1.87	1.88	1.89	1.93
Phenyl OCH_3	1.58	1.91	—	—
N-H	−3.99	−3.90	−4.00	−3.91
Chain 1-CH_2	0.70 0.21	0.53 0.96	0.27 −0.70	0.65 0.0
Chain 2-CH_2	−0.10 0.11	−1.13 −0.31	0.05–0.15 —	−1.29 −0.32
Chain 3-CH_2	0.82 —	0.88 1.07	0.95 1.11	1.14 1.25
Chain 4-CH_2	1.22 1.50	1.91 2.22	1.51 1.73	1.93 2.33
Chain 5-CH_2	2.32 —	3.93 4.25	2.51 —	3.97 4.30
Chain 6-CH_2	3.72 4.43	—	3.63–3.75 4.40	—

The larger upfield shift of the quinone protons in **1a** ($\delta = 2.76$) compared to that in **1b** ($\delta = 2.95$) suggests that the longer, more flexible oligomethylene chain can accommodate a shorter porphyrin-quinone distance, and this was reinforced by examination of space-filling models. A similar situation was observed by *Baldwin* in his "cap" and "homo-cap" porphyrins,[7] and also by *Sanders* et al.[2i] The situation is less clear for the porphyrin-dimethoxybenzene complexes **12**, with the shifts of the phenyl and the methoxy protons offering conflicting estimates of the separation of the porphyrin and phenyl rings. However, when the ^{1}H- and ^{13}C-NMR spectra of **12a** are recorded in trifluoroacetic acid (10%)/$CDCl_3$ a broadening or disappearance of the phenyl protons and some of the strap protons is observed. It would appear that for the free base form of **12a** the straps can rotate freely among a number of conformations, resulting in sharp signals for the average conformation. On protonation this rotation is restricted and the signals for the phenyl ring and some of those of the straps are broadened. Observation of all resonances for **12b**, both in the free base and the protonated forms, suggests that again the longer, more flexible chain in **12a** accommodates a shorter separation between the phenyl and the porphyrin rings.

Metalation and electron-transfer studies on complexes **1** and the corresponding hydroquinones **13** are presently in progress. The extension of this synthetic route to the preparation of other porphyrins bearing bulky groups and potential ligands in the strap will be subsequently communicated.

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A great, and still rapidly increasing, number of heterocyclic compounds is known; this makes it progressively more difficult to obtain a survey of particular aspects of this field, which is so important in synthesis, in biochemistry and in its many practical applications. Attempts at orientation in this mass of material by means of textbooks often founder on account of the selective or even uninterested coverage given to heterocycles. As far as specialized literature goes, "Elderfield", which largely stems from the 1950's, can only be conditionally considered and even the 60+ volumes of "Weissberger-Taylor" are not all up to date. The present monumental work sets out to fill an obvious gap in the market. Formally, it complements the series "Comprehensive Organic Chemistry" and "Comprehensive Organometallic Chemistry" (cf. *Angew. Chem. Int. Ed. Engl. 22* (1983) 797). Heterocyclic chemistry is dealt with here in more than 6000 pages by over 120 authors, predominantly from English speaking countries. From the FRG *K. Dimroth, W. Flitsch, W. Friedrichsen, H. Gotthardt, H. Neunhoeffer, W. Pfleiderer, I. Ugi*, and *H. Wamhoff* have contributed and from the GDR *G. W. Fischer, E. Schmitz*, and *T. Zimmermann*.

The numerous applications and biological aspects of heterocycles are prominent in the first volume. Observations on the toxicity of chlorinated dibenzodioxins (p. 118) provide an indication of how up to date the work is. Beside this there is a section on nomenclature (36 pages), a literature survey of heterocyclic chemistry (34 pages) and a very informative chapter on the synthesis of non-heterocycles from heterocycles (79 pages). The volume concludes by treating boron containing rings (35 pages), rings containing higher elements of groups 4 or 5 (phosphorus: 45 pages, arsenic, antimony, bismuth: 23 pages), rings containing halogens (10 pages) and rings containing a transition metal (8 pages).

The mass of material on heterocycles containing nitrogen or a group 6 element requires clear arrangement of the content. As is usual, ring size, together with the number and type of heteroatoms, serves as the general criterion of organization. To emphasise common properties, however, annelated systems are discussed with the corresponding monocycle. Parts 2 to 5 (Vols. 2 to 7) are each introduced by a general chapter which gives a condensed survey and, above all, draws out relationships between the ring systems to be dealt with. Then follow extensive sections on the individual ring systems. Whenever possible, general and specialized chapters are subdivided as follows:

- structure, especially molecular structure, as well as spectroscopic data and problems of tautomerism
- reactivity of ring positions and substituents of aromatic compounds as well as non-aromatic derivatives
- synthesis from non-heterocycles, arranged according to the number of newly formed bonds, or from heterocyclic precursors
- applications.

In the second volume pyridine and benzo-annelated pyridines are dealt with according to this general plan (95 pages survey and 422 pages specialized material). The volume is completed by short sections on quinolizinium ions (55 pages) and pyrido-pyridines (46 pages).

The third volume is a compilation, in 17 chapters, of the chemistry of 6-rings with at least two nitrogen atoms or with oxygen or sulphur. Apart from (benzo)pyridazines (57 pages), -pyrimidines (98 pages), and -pyrazines (41 pages), amongst others pteridines (64 pages), (benzo)triazines (altogether 160 pages), pyranes (306 pages) and thiopyranes (58 pages) are dealt with in depth.

The fourth volume begins with a general introduction to 5-rings with one heteroatom (153 pages). Amongst others (benzo)pyrroles (221 pages), -furans (181 pages), -thiophenes (219 pages) and -selenophenes (36 pages) are handled in individual chapters. Porphyrins, corrins and phthalocyanins (66 pages) belong in this volume too.

In volumes 5 and 6 the treatment of 5-rings is extended to those with at least two heteroatoms. After the introduction (162 pages), the following receive substantial sections of their own: (benzo)pyrazoles (135 pages), -imidazoles (153 pages), purines (105 pages), (benz)isoxazoles (130 pages) and (benzo)thiazoles (95 pages).

The seventh volume contains 15 contributions on heterocyclic 3- and 4-rings and 7 sections on rings with at least seven members. Individual chapters are devoted to penicillins (41 pages), cephalosporins (14 pages), crown ethers and cryptands (32 pages) and heterophanes (18 pages).

Without reference to the organizational structure, the entire work is accessible via the four indexes of volume 8. A "physical data index" contains sources of quantitative information on more than 4000 heterocycles, e.g. for "furan, tetrahydro" information is supplied on the dipole moment, ^{1}H-, ^{13}C-, ^{17}O-NMR spectra, microwave spectrum, pK_a value and the photoelectron spectrum. The subject index contains 40,000 entries; the author index lists 30,000 names in 35,000 references. A ring index, analogous to the "Chemical Abstracts" register, names 4000 ring systems.

A striking characteristic of the work is that literature references are given as an alphanumeric code derived from the year of publication, an abbreviated designation of the journal and the page number. Thus the reference [*Angew. Chem. 95* (1983) 819] would appear as ⟨83AG819⟩. This method enables the reader to identify the most recent reference directly in the text and, after a little practice, to find the original straightaway. The complete references are given at the end of each volume, arranged by year of publication. The literature references reach up to 1982; in places publications from 1983 are also included.

All in all this is a successful work; the external appearance is pleasing and every page is strewn with useful information. The rigorous arrangement of the individual volumes enables quick orientation, even without recourse to the index, and means that cross references can largely be dispensed with. The numerous clear formula diagrams and informative tables are very helpful. Preparative chemists will particularly welcome the tabular grouping of the "best methods of synthesis".

The production of this work must have been a Herculean task for authors and editors alike. This deserves recognition and makes detailed criticism mere niggling. Spot tests indicate that printing errors have been carefully expunged and that transcription errors do not exceed the sadly inevitable limits. One striking example of this is the citation of two different (by 1.98 eV) ionization potentials for oxetane on the same page (Vol. 7, p. 368). It is unfortunate that "oxete", the correct name for the unsaturated 4-ring ether, is replaced even in a chapter heading by "oxetene" (Vol. 7, p. 363). In a few cases the chapters have turned out to be pretty eclectic, as, for example, when 1,2- and 1,3-dioxolanes as well as 1,2- and 1,3-oxathiolanes are discussed in tandem, although they are cyclic derivatives of quite different classes of compounds (Vol. 6, p. 749ff).

The selection of material by authors and editors is naturally subjective and some readers will find particular aspects missing or inadequately dealt with. Obviously, however, exhaustive treatment cannot be expected even in 42 cm of shelf space. Even so a survey of the subject and an entry into further literature are provided. The general chapters enable interested students to find their bearings and could also serve as the basis for a lecture; for this reason this work should enable heterocyclic chemistry to find a place in the curriculum that corresponds to its importance. The specialized chapters are available to meet the demand for more detailed information. Even experts—in universities or industry—will find useful references here. Interested parties from neighboring disciplines will appreciate the extensive sections on applications and biochemical aspects. Quite apart from searching for particular information, the book is interesting territory for the browser; even in the age of machine readable data this "semi-systematic" access to information is indispensable and will ensure a large readership for "Comprehensive Heterocyclic Chemistry".

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Gene und Klone. Eine Einführung in die Gentechnologie. By *E.-L. Winnacker*. Verlag Chemie, Weinheim 1984. xii, 454 pp., bound, DM 70.00.—ISBN 3-527-26061-7

Textbooks dealing with topics in molecular biology have a very short half-life and become rapidly outdated. Courage and the ability to foresee future developments are therefore required when one sets out to write a detailed introduction into the concepts and techniques of gene technology. *Ernst-Ludwig Winnacker*, with his book "Gene und Klone", has succeeded in making a contribution that will not only be of value to novices in the field of molecular biology. In didactically exemplary fashion, the fundamental principles of molecular biology are combined with the concepts and techniques of gene technology. The sequence of chapters reflects the experimental procedures routinely followed in cloning experiments. Research in molecular biology always involves genuine craftsmanship that has to be mastered and modified daily on the basis of the most recent developments. This practical aspect has also been adequately dealt with by *Ernst-Ludwig Winnacker*'s presentation. The combination of theoretical considerations and practical instructions renders the book readable for newcomers; accuracy in detail and the author's efforts to cover current findings make the book useful and worthwhile reading for advanced students as well. Essentials for daily work are readily available by the inclusion of numerous, clearly drawn illustrations presenting genetic and structural maps. In the appendix, the guidelines of the "Zentrale Kommission für die Biologische Sicherheit" are also included. The reader should, however, be aware of the fact that these guidelines are currently being revised.

Shortly before writing this book review, I wanted to leaf through "Gene und Klone" again. I had to search for my two copies in the laboratory. Only after days of questioning, however, was I able to find them. One copy had been extensively used and showed it. Apparently, the book has been consulted frequently by my younger colleagues. This observation is perhaps the best recommendation for the book.

In Munich, it must be difficult to compete with the "Schönheitengalerie" of the first Ludwig.[*] Although the gallery of molecular biologists presented by the Ludwig who writes about genes and clones may render the cold scientific facts more likeable, its attraction is in general far inferior to the collection of the first Ludwig.

This book is highly recommended above all to students in the field. I hope that the book goes through many, carefully rewritten editions and will be translated into English after having been brought up-to-date.

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Hydrazine and its Derivatives. Preparation, Properties, Applications. By *E. W. Schmidt*. Wiley, Chichester 1984. xxv, 1059 pp., bound, £ 87.00.—ISBN 0-471-89170-3

The major sections of this book are: the production of hydrazine (including the anhydrous compound), together with details of the capacities of and processes employed by western manufactures; physical properties; chemical properties of hydrazine and its salts with a detailed section on hydrazine analysis; the handling of hydrazine with a very important subsection on its toxicology; the decomposition of hydrazine; utilization of hydrazine, especially its use as a rocket propellant whose description occupies more than 100 pages.

Organic derivatives are described only very briefly and, essentially, only insofar as they are of importance to the field of rocket propellants.

As the author, who is a senior staff scientist of the Rocket Research Corporation and obtained his doctorate in Tübingen, correctly states, this is the first comprehensive survey of hydrazine in an occidental language for the last 30 years. For all who are doing work in the field of hydrazine the absence of such a book has been a significant handicap.

Here too, as in many other fields, the literature has exploded. The reference list contains more than 4400 citations on 194 pages. The references are listed "lexically", that is alphabetically according to the name of the first author, so that the list fulfills some of the functions of an author index.

[*] Ludwig I., King of Bavaria (1825–1848), had portraits of the most beautiful Munich women painted for his "Schönheitengalerie", which is now exhibited in Schloss Nymphenburg. Go and see it.

Because of the professional activities of the author, the emphasis of the book is on the chapters concerned with the application of hydrazine as a rocket propellant. A new technology has been developed here that is rarely reviewed in the normal chemical literature. Who, for example, is aware that the anhydrous hydrazine employed for the Viking landing on Mars had to be freed from organic impurities by fractional crystallization because of apprehensions that hydrazine cyanide, occurring in the exhaust gases, might interfere with the biological experiments?

In the important section on the toxic properties of hydrazine and its compounds the author points out that investigations are still in progress and that there is no lack of contradictory results.

The reviewer has several reservations in spite of the many positive aspects of this book. For instance, the almost 60 lines per page and the relatively small type make reading difficult. However, the following objections are of more importance: Today, three processes are employed for the production of hydrazine on an industrial scale, whereas one process was formerly employed, the urea process. Each of these processes are, of course, described (flow diagrams are also provided) but one also finds a host of irrelevant details from the patent literature. Some statements are even incorrect. In the Bayer process their is no hydrazine formed which is intercepted as the ketazine. Diaziridine is a feature of the (not practised) Bergbau process and not of the Bayer process. Since these processes are to be found under the heading "Bergbau-Bayer-Whiffen Process" this section can only confuse readers who are unfamiliar with the matter. It is also questionable if a ketone imine is an intermediate in the PCUK process.

In the discussion of the large number of processes that are not employed for the synthesis of hydrazine on an industrial scale, e.g. the fixation of nitrogen in complexes with subsequent reduction or electrochemical methods, one misses a short account as to why these interesting variants are not employed industrially. The description of the application of hydrazine in fuel cells is a positive example where it is clearly stated that technical application is not to be expected (and why).

In all, a necessary book for all who have anything to do with hydrazine; but care must be taken by those searching in the chemistry part of the book for rapid up todate information concerning the present state of the art in this field.

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Selenium in Natural Products Synthesis. By *K. C. Nicolaou* and *N. A. Petasis*. CIS Inc., Philadelphia 1984, 300 pp., bound, $ 39.50.—ISBN 0-914891-00-6

It is well-known that the usefulness of novel synthetic methods depends on their application to the synthesis of complex natural products. In the last 15 years the efforts of several groups with organoselenium compounds have led to the development of many preparative methods. This book documents the fact that these have found frequent use up till now in the synthesis of natural products and evaluates this, rightly, as evidence for the breadth of application of selenium chemistry.

The introductory chapter reports very briefly on the particularities of organoselenium compounds; then the most important reagents are listed in tabular form, together with the comment that many are now commercially available. Details of the preparation of the non-commercially available substances would have been desirable here.

The following chapters describe, according to reaction type, a wide range of natural product syntheses with selenium reagents. In the second chapter entitled "Selenium-mediated oxygenations" the reader finds alongside allylic oxidation with selenium dioxide also examples of the modern variations of this well-known reaction which have been introduced especially by *Sharpless* and *Barton*. In Chapters 3 and 4, which deal with dehydrogenations, a—somewhat arbitrary—distinction is made between "Selenium-mediated Dehydrogenations" (= Dehydrogenations without the isolation of an intermediate) and "Organoselenium-mediated Olefinations". By this the authors understand the synthesis of olefins by the preparation of selenium oxides followed by elimination, a method which has become known under the names of *Sharpless* and *Reich*. Chapter 5 briefly covers reductions with selenium reagents. Chapter 6 is concerned with selenium-stabilized carbanions which were first described by *Seebach* at the end of the 1960s and have since found extensive application by *Krief* and *Reich*. Unfortunately the expression "synthetic equivalent" is employed in the review at the commencement of the chapter when "synthon" was what was meant. The electrophilic addition of selenium reagents to CC double bonds and their subsequent cyclization by intramolecular reaction of the selenium ion (e.g. "selonlactonization") is described in the seventh chapter with many examples including some from *Nicolaou* himself. Finally, a potpourri of reactions, some of which have not (yet) been employed in natural product synthesis, is included under the title "Miscellaneous Applications of Selenium Compounds".

Before going into the numerous examples of applications, the key reactions are presented in generalized form in the individual chapters by means of clear formula graphics. The target molecules range from terpenes via steroids and alkaloids to prostaglandins and macrolides. In accordance with the intensions of the book only the relevant steps of multistep syntheses are reported. Unfortunately the yields of the individual steps are not always included in the clearly presented reaction schemes.

The authors have been able to provide a comprehensive insight into the potential of selenium reagents which is, nevertheless, understandable even to the advanced student. A successful book in spite of the flaws mentioned.

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Non-Benzenoid Conjugated Carbocyclic Compounds. By *D. Lloyd*. Elsevier, Amsterdam 1984. xvi, 431 pp., bound, HFl. 260.00—ISBN 0-444-42346-X

This book communicates a feeling of the fascination which has brought synthetic chemists, spectroscopists and theoreticians together in a unique manner. The chemistry of non-benzenoid conjugated carbocycles has years of hectic development behind it; this is reason enough for the stock-taking that *Lloyd* planned. The author has also succeeded in representing the continuous, the living force of his subject which transcends the ups and downs of fashion, particularly by the inclusion of original work up to 1983.

The concept of aromaticity and its unchanging importance is dealt with in an introductory chapter. This section impresses with its historical completeness; it has a strongly narrative character, but suffers from the absence of a dis-

cussion of, for instance, the theory of the fixation of double bonds. The following chapters are devoted to cyclopentadienes and cyclopentadienide ions (2.), cycloheptatrienes and tropylium ions (3.), cyclopropenes and cyclopropenium ions (4.), cyclobutadienes (5.), cyclooctatetraenes and cyclononatetraenes (6.), annulenes (7.), and bicyclic and polycyclic compounds (8.). The descriptions of the results are always comprehensive; thus, in the case of the seven-membered ring compounds, the coverage ranges from tropylium ions to tropones, tropolones, heptafulvenes up as far as the cycloheptatrienylidenes and cycloheptatrienide ions. The description of the individual substance types is always under the headings "Synthesis", "Spectra and Structure" and "Chemical Reactions".

The book is convincing in the care and specialist knowledge with which the relevant literature has been collected and pithily reviewed. The sympathetic "devotion to the literature" which is the real strength of the book becomes an unintentional disadvantage in instances were a criticism of the original work or a discussion of discrepant results is called for. The text also remains a little conventional because the beginnings of newer developments within the chemistry of conjugated carbocycles such as, for example, "aromaticity and electrical conductivity" or "multilayered π systems and properties of stacks" remain unmentioned. Taking this into account it remains a resumee which will be of great value to every interested chemist who makes use of the material collected in it.

The publishers must be excluded from the recognition awarded to the author. The author deserved better support in the large quantities of graphics. The print and graphics have an improvised appearance and are at great variance with the exaggerated price.

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New Books

The following books have been received by the editor. All the publications listed are available through W & P Buchversand für Wissenschaft und Praxis, Boschstrasse 12, D-6940 Weinheim (Federal Republic of Germany). Tel. (06201) 606-0, Telex 465516 vchwh d, Telefax (06201) 602328.

Ellis Horwood Series in ANALYTICAL CHEMISTRY. Handbook of Chemical Equilibria in Analytical Chemistry. By *S. Kotrly* and *L. Sucha*. Ellis Horwood, Chichester 1985. 414 pp., bound, £ 45.00—ISBN 0-85312-107-9

Reactive Intermediates. A Serial Publication. Vol. 3. By *M. Jones, Jr.* and *R. A. Moss*. John Wiley, Chichester 1985. ix, 435 pp., bound, £ 96.00.—ISBN 0-471-01893-7

Encyclopedia of Polymer Science and Engineering. 2nd Edition. **Vol. 1: A—Amorphous Polymers.** Edited by *H. F. Mark, N. M. Bikales, C. G. Overberger, G. Menges,* and *J. I. Kroschwitz*. John Wiley, Chichester 1985. lxii, 843 pp., bound, subscription price: £ 175.00, individual volume: £ 210.00.—ISBN 0-471-89540-7; 19 further volumes, a supplement, and an index volume are scheduled to appear before June 1989.

Laborbücher Chemie. Praxis der Hochleistungs-Flüssigkeitschromatographie. 3rd Edition. By *V. Meyer*. Diesterweg Salle Sauerländer, Frankfurt 1985. x, 245 pp., paperback, DM 54.00.—ISBN 3-425-05452-X

Analytical Measurement and Information. Advances in the Information Theoretic Approach to Chemical Analyses. By *K. Eckschlager* and *V. Stepanek*. Research Studies Press, Letchworth (Herthfordshire, England) 1985. xii, 140 pp., bound, £ 25.00.—ISBN 0-86380-021-1

IUPAC Chemical Data Series No. 31. Chlorine. International Thermodynamic Tables of the Fluid State—8. Tentative Tables. By *S. Angus, B. Armstrong,* and *K. M. de Reuck*. Pergamon Press, Oxford 1985. xviii, 162 pp., bound, £ 30.00.—ISBN 0-08-030713-2

Wissenschaftliche Taschenbücher WTB Biologie. Molekulare Wirkungsmechanismen von Pharmaka. Eine Einführung in die Molekularpharmakologie. By *P. Nuhn* and *H.-J. Hofmann*. Akademie-Verlag, Berlin 1985. 188 pp., paperback, DM 16.00.—Order-No. 763-312-0 (7294)

Specialist Periodical Reports. Photochemistry. Vol. 15. Edited by *D. Bryce Smith*. The Royal Society of Chemistry, London 1985. xx, 555 pp., bound, £ 110.00.—ISBN 0-85186-135-0

Special Publication No. 52. Recent Advances in the Chemistry of β-Lactam Antibiotics. Third International Symposium, Cambridge (England) 2-4 July 1984. Edited by *A. G. Brown* and *S. M. Roberts*. The Royal Society of Chemistry, London 1985. viii, 391 pp., paperback, £ 26.50.—ISBN 0-85186-955-6

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Molecular Mechanism of Action of the Antibiotic Rifampicin

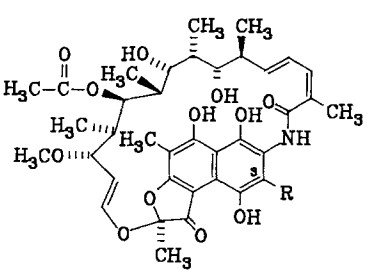
By Guido R. Hartmann,* Peter Heinrich, Margit C. Kollenda, Bernhard Skrobranek, Maximilian Tropschug, and Wolfgang Weiß

Dedicated to Professor Wolfram Zillig on the occasion of his 60th birthday

The lipophilic antibiotic rifampicin is successfully used in the treatment of tuberculosis. On the molecular level it interferes with the metabolism of Eubacteria by blocking RNA synthesis. This effect is the consequence of the tight binding of the drug to a single and highly specific binding site on the DNA-dependent RNA polymerase. The enzyme-bound drug strongly inhibits RNA chain initiation and chain elongation. This inhibition can be explained by the influence of enzyme-bound rifampicin on binding sites for the reaction products diphosphate and RNA. In order to reach its target the antibiotic must penetrate into the cytoplasm of the bacteria. Mutants have been discovered which are resistant to rifampicin because its uptake from the medium is significantly reduced. The gene responsible for this effect has been cloned. It confers on bacterial cells with highly sensitive RNA polymerases a remarkable resistance to the drug.

1. Introduction

Rifampicin, an antibiotic with a wide antibacterial spectrum, has proved particularly effective in the treatment of tuberculosis. Chemically, it is a semisynthetic member of the class of rifamycins, which are produced by the bacterium *Nocardia mediterranei*. The productive strain was discovered in a sample of soil collected by *Hermes Pagani*, a technician of the pharmaceutical company Lepetit in Milan, from a pine arboretum close to the seaside resort of Saint Raphaël in southern France where he had spent his vacation. The antibiotic was named after "Rififi," the title of a well-known movie.[1,2] *Sensi*, *Oppolzer*, and *Prelog*[2,3] elucidated the chemical structures of the rifamycins and showed that they are naturally occurring ansa compounds.[4] Many derivatives of the parent compound, rifamycin SV, have been prepared semisynthetically. Most of them are effective only after parenteral application. The



R = CH=N–N⟨⟩N–CH$_3$: Rifampicin
R = H : Rifamycin SV

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derivative rifampicin, also known under the trade names rifa, rifampin, or rimactan, is fully effective after oral application and is therefore the commercially most successful form of the rifamycins.[5] The drug is well tolerated because the metabolism of human cells is not disturbed at antibiotically effective concentrations whereas the metabolism of Eubacteria such as *Mycobacterium tuberculosis*, the causative agent of tuberculosis, is drastically impaired.[6]

2. RNA Polymerase as Target

Of the metabolic processes in bacteria, RNA synthesis is most strongly inhibited by rifampicin, even at very low concentrations (0.5 μg/mL in cell culture).[7] Protein synthesis ceases as a consequence of this inhibition, resulting in the termination of bacterial replication.[8] Termination of RNA synthesis is caused by the inhibition of the enzyme that catalyzes DNA-directed RNA synthesis, namely, DNA-dependent RNA polymerase (EC 2.7.7.6).[9] Only the eubacterial enzyme and not the corresponding RNA polymerase from eukaryotic cells contains a single and specific binding site for the antibiotic. It binds rifampicin even at concentrations as low as 8 μg/L.[4] These observations explain the excellent toleration of the drug at low concentrations by human cells. The drug is very hydrophobic and at 1000-fold higher concentrations also binds to many other proteins, causing various side effects.[4,10-12] The primary effect of rifampicin can therefore be investigated only if higher concentrations are strictly avoided.

Since DNA-dependent RNA polymerase has not been crystallized, the X-ray crystallographic analysis of the antibiotic-enzyme complex has not yet been carried out. Therefore, we do not know which part of the drug molecule is directly involved in the binding. With the exception of residues in position 3 of the naphthohydroquinone ring system, not much can be altered in the structure of the drug without concomitant loss of the tight binding to the eubacterial enzyme.[4] In vitro the enzyme-rifampicin complex dissociates immediately in the presence of agents such as guanidinium chloride that disrupt the three-dimensional structure of proteins.[13] Accordingly, the drug does not bind covalently to the protein.

Bacterial strains resistant to rifampicin as a consequence of a mutation have been known for a long time.[14] Two classes of mutants have been characterized. In the first class, all mutations occur in the bacterial gene that codes for the β subunit of RNA polymerase.[15,16] This is independent evidence for RNA polymerase being the immediate target of rifampicin since, otherwise, such mutations would not lead both to the loss of the tight binding between the drug and the enzyme and, simultaneously, to the loss of rifampicin sensitivity of the bacterial cells.[4] The DNA-dependent RNA polymerase from Eubacteria is a large protein with a relative molecular weight of about 0.5 million. The enzyme from the intestinal bacterium *Escherichia coli* has been studied most thoroughly. It consists of four different polypeptide chains, α, β, β′, and σ, of known amino acid sequence which form a stable complex with the stoichiometric composition $\alpha_2\beta\beta'\sigma$. Most mutations of the first class that lead to rifampicin resistance are located in a single region of the gene. This region codes for a sequence of about 50 amino acids[17,18] close to the center of the β polypeptide chain, which is 1342 amino acids in length.[19] Presumably, this region of the β subunit forms an essential part of the rifampicin binding site. This assumption is supported by observations from our laboratory which demonstrate that this region of the β subunit is protected against proteolytic cleavage by bound rifampicin.[20]

3. Inhibition of RNA Synthesis

E. coli RNA polymerase catalyzes the stepwise chemical condensation of ribonucleoside triphosphates to form RNA using DNA as a template. The formation of a phosphodiester bond is accompanied by the release of a molecule of diphosphate (Scheme 1). The sequence of bases in the RNA synthesized is complementary to the transcribed strand of the DNA template as required by the base-pairing rule. A careful analysis of the individual steps of the reaction has shown that the substrates associate in an ordered sequence on the enzyme-DNA complex.[21,22] If a template coding for an RNA with the sequence ApUpCp... is used, then the first substrate that binds to the enzyme-DNA complex is ATP (≡pppA), which acts as a primer. Binding of UTP (≡pppU) follows (Fig. 1).

In the next step, the first phosphodiester bond is formed and the intermediate dinucleoside tetraphosphate pppApU is produced. If the next nucleotide is absent from the reaction mixture, this product is released and diphosphate dis-

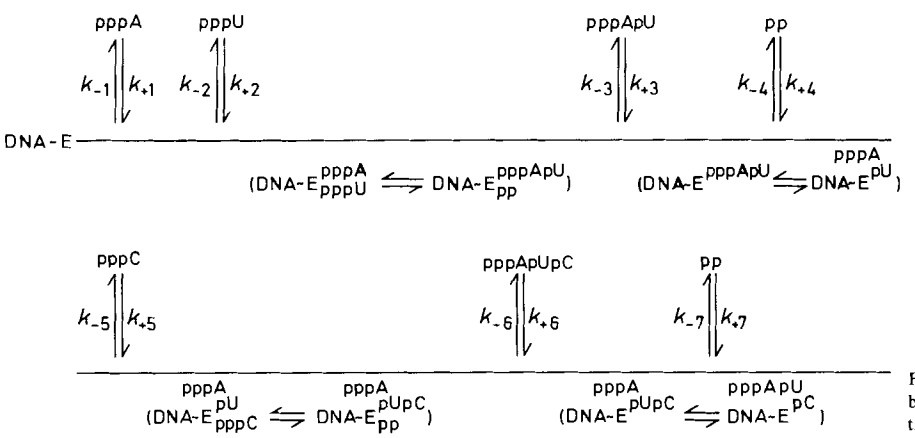
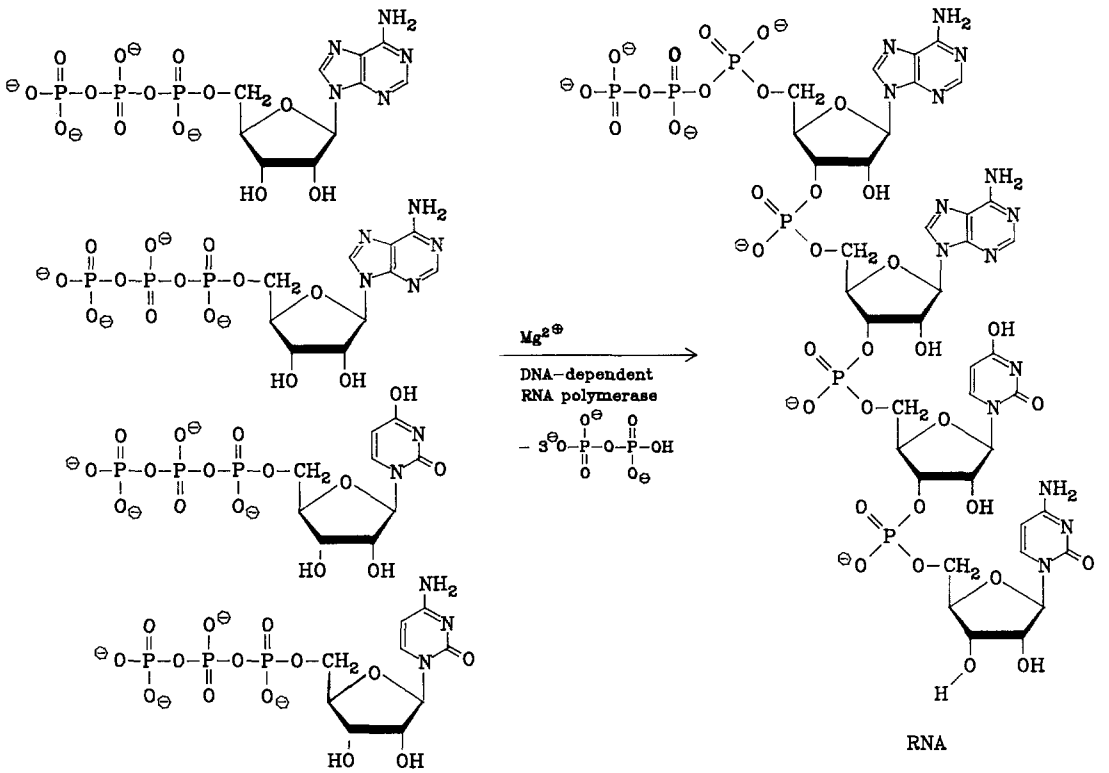


Fig. 1. Mechanism of initiation of RNA synthesis by *E. coli* RNA polymerase (see text). DNA~E is the DNA-enzyme complex.



Scheme 1.

sociates from the enzyme.[22] In this case, termed abortive initiation,[23] the initiation is continuously repeated, leading to the accumulation of pppApU.

If suitable nucleotides are available for further reactions, the dinucleoside tetraphosphate undergoes translocation. The uridine moiety of pppApU then occupies the binding site formerly occupied by the adenosine residue of the priming ATP. Simultaneously, the enzyme must move by one base along the template strand. The former binding site of UTP is free to accept the next substrate molecule, CTP(≡pppC), and the second phosphodiester bond is formed. Continuous repetition of these steps leads to the synthesis of long-chain RNA. This scheme describes a minimal mechanism for the catalytic process, all details of which are not yet known. However, its essential points suffice for the discussion of the effects of the association of rifampicin on the enzyme.

If antibiotic is added to the enzyme in vitro followed by addition of template and a complete set of ribonucleoside triphosphates, the rate of RNA synthesis rapidly decreases with increasing concentration of the antibiotic (Fig. 2). At a concentration of 0.06 μg/mL (0.1 μM), an inhibition of 50% is already observed. At a tenfold higher concentration, RNA synthesis is barely detectable. Simultaneously with the decrease in the rate of RNA synthesis, an increase in the rate of formation of the dinucleoside tetraphosphate pppApU is observed.[24] Half of the maximum rate is obtained at the same drug concentration that depresses RNA synthesis by 50%. Thus, the enzyme–rifampicin complex can still catalyze the synthesis of pppApU but not that of long-chain RNA.[23] In this context it is important to note that rifampicin does not alter the apparent Michaelis constant for the reaction of the substrates ATP and UTP on the enzyme.[25]

The inhibition of RNA synthesis may be explained by several different hypotheses. The simplest one assumes steric blocking of that part of the product binding site required for binding intermediate products longer than di- or trinucleotides.[26,27] Another hypothesis postulates an increase in the rate constant k_{-3} for dissociation of the intermediate dinucleotide (Fig. 1). This assumption is based on results obtained mainly with the synthetic template poly[d(A-T)].[28]

Both hypotheses assume that the drug does not inhibit the formation of dinucleotides. This can be tested experimentally. Abortive initiation is possible with a large num-

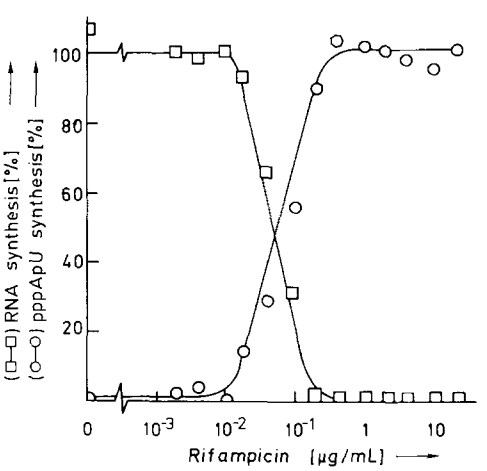


Fig. 2. Influence of rifampicin on the RNA or pppApU synthesis catalyzed by *E. coli* RNA polymerase. The experiments were carried out at 25°C with bacteriophage T4 DNA as template [36]. 100% pppApU synthesis (○—○) in the presence of 2 μg/mL rifampicin corresponds to an incorporation of 1830 cpm per hour of incubation. 100% RNA synthesis (□—□) in the absence of rifampicin corresponds to an incorporation of 2380 cpm per hour of incubation.

ber of adenosine derivatives (e.g., adenosine, 5′-AMP, 5′-ADP, ATP) as priming substrates[21,26,29] [Eq. (1)]. The rate

$$R-A + pppU \rightleftharpoons R-ApU + pp \quad (1)$$
$$R = HO, p, pp, ppp$$

of synthesis depends on and varies with the priming substrate. At 25 °C it is highest with 5′-AMP, followed by ATP and ADP. Adenosine is the poorest substrate (Table 1). Similar results have been obtained with RNA polymerase from the gram-negative *E. coli* and the gram-positive *Micrococcus luteus*. Low concentrations of rifampicin have noticeable effects on these reactions at 25 °C. The synthesis of the dinucleoside monophosphate ApU is inhibited by 85%. The synthesis of pApU and ppApU is also strongly reduced. Such an inhibition violates the assumptions of the hypotheses mentioned above. Different effects of rifampicin on dinucleotide synthesis catalyzed by the enzymes from *E. coli* and *M. luteus* are only observed when the highly charged, anionic pppApU is the product. Whereas its synthesis by the enzyme from *M. luteus* is inhibited by 27%, the rate observed with the *E. coli* enzyme is increased by 27% under identical conditions (Table 1).[30] This surprising effect is not only observed when the enzyme is preincubated with the antibiotic in order to form the complex but also when rifampicin is added during abortive initiation (Fig. 3). Similar results have been obtained with different templates. At temperatures above 30 °C, the rate of pppApU synthesis is also inhibited when the *E. coli* enzyme is used.[26,30]

Table 1. Relative rate (v_{rel}) of dinucleotide synthesis at 25 °C in the presence and absence of 2μM rifampicin. Abortive initiation was carried out with 1.5 mM primer and [α-^{32}P]UTP on bacteriophage T7 D111 DNA as template with RNA polymerase from *E. Coli.* or *M. luteus* as described in [36].

Primer	Product	v_{rel}		v_{rel} (2μM rifampicin)	
		E. coli [%]	*M. luteus* [%]	*E. coli* [%] [a]	*M. luteus* [%] [a]
5′-ATP	pppApU	100	100	127	73
5′-ADP	ppApU	60	79	47	34
5′-AMP	pApU	124	124	42	18
Adenosine	ApU	51	32	15	15

[a] 100% = rate in the absence of rifampicin (columns 3 and 4).

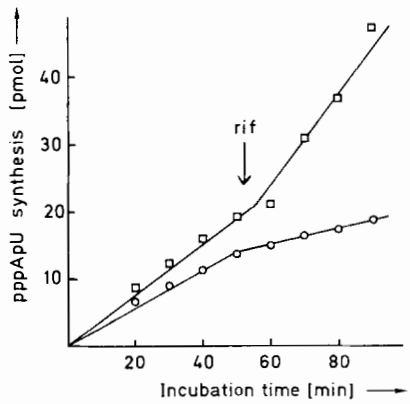


Fig. 3. Influence of rifampicin at 26 °C on pppApU synthesis catalyzed by the RNA polymerase from *E. coli* (□—□) and *M. luteus* (○—○) on bacteriophage lambda DNA. After 52 min of incubation, 2 μg/mL rifampicin (rif) was added.

The inhibitory effect of rifampicin apparently decreases with the increasing overall charge of the dinucleotide formed. However, it is still observed even if pppApU or pppppApU are formed.[26] Therefore, the drug cannot inhibit RNA synthesis in general by increasing the rate of dissociation of the intermediate dinucleotide or by blocking the product binding site for longer intermediate products. Since the RNA polymerase from *E. coli* and *M. luteus* differ in several details of their structure,[31] it is not surprising that the action of rifampicin differs slightly for these two enzymes.

4. Competition between Diphosphate and Rifampicin

So far, the influence of the enzyme-bound rifampicin has been discussed only for the forward reaction [Equation (1)]. Is the backward reaction inhibited similarly? In order to determine the rate of diphosphorolysis, radioactively labeled diphosphate was added to an incubation mixture containing enzyme, template, ATP, UTP, and Mg^{2+}. The rate of the backward reaction was determined by measuring the formation of radioactively labeled UTP, which was separated from the labeled diphosphate by adsorption on charcoal.[31] The backward reaction is strongly inhibited by rifampicin. This effect is independent of the number of phosphate groups at the 5′ end of the dinucleotide. At a diphosphate concentration of 0.34 mM, 50% inhibition is observed with 0.08 μM rifampicin. The rate of diphosphorolysis is strongly dependent on the concentration of diphosphate (Fig. 4). Interestingly, rifampicin changes the

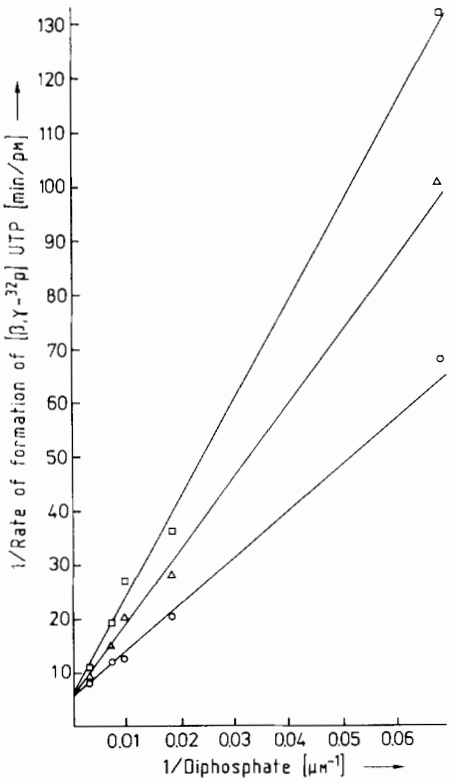


Fig. 4. Influence of rifampicin and diphosphate on the enzyme-catalyzed diphosphorolysis of pppApU on bacteriophage T7 D111 DNA as template (Lineweaver-Burk plot). Diphosphorolysis was measured at 25 °C similarly to the procedure in [32] in the absence (○—○) or presence of 0.05 (△—△) and 0.10 (□—□) μg/mL rifampicin.

rate of reaction competitively to diphosphate as is evident from the Lineweaver-Burk plot of the data (Fig. 4). This suggests that the binding of diphosphate to the enzyme-DNA complex is altered by the drug and vice versa. An increase of the diphosphate concentration should therefore decrease the binding of rifampicin to the enzyme-template complex.[33] This is indeed the case (Fig. 5). In the presence of the template, the influence of the diphosphate concentration is more pronounced. The binding site of diphosphate is apparently altered by the association of the enzyme with the template. The rate of the backward reaction does not change with the concentration of pppApU in the range of 0.03 nM–10 μM and is independent of the presence of the antibiotic. An inhibition is only observed at higher concentrations and is probably due to the formation of a kinetic dead-end complex.[22]

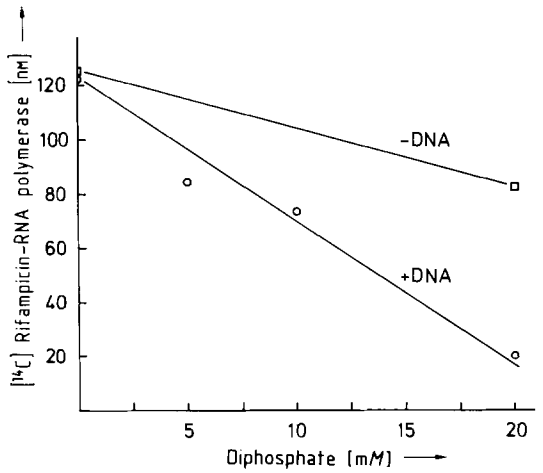


Fig. 5. Influence of diphosphate on the binding of [^{14}C] rifampicin to *E. coli* RNA polymerase at 37 °C in the absence (□—□) and presence (○—○) of 70 pmole/mL bacteriophage T7 D111 DNA. The enzyme-bound [^{14}C] rifampicin was determined similarly to the procedure in [33].

5. Competition between RNA and Rifampicin

RNA strongly inhibits the catalytic activity of the enzyme when added prior to the template.[34,35] Interestingly, the inhibition of pppApU formation by RNA is strongly reduced if the enzyme is preincubated with 0.1 μM rifampicin before the addition of RNA.[36] This protecting effect of the drug may be explained by a competitive effect of the antibiotic on the binding of RNA and vice versa, similar to the observations reported for diphosphate. Indeed, it is well known that RNA strongly inhibits binding of rifampicin to RNA polymerase.[37] It is more difficult to demonstrate the inhibitory effect of the drug on the binding of RNA since the enzyme contains two binding sites for nucleic acids, namely, one for the product and one for the template. For further analysis, therefore, it is necessary to physically separate these two sites. The subunits of RNA polymerase form several complexes with each other: $\alpha_2\beta\beta'\sigma$ (holoenzyme), $\alpha_2\beta\beta'$ (core enzyme), α_2 (dimer), and the subassembly $\alpha_2\beta$. Fortunately, $\alpha_2\beta$ is able to bind both RNA[20] and rifampicin[38,39] with rather high affinity,[40] while DNA is only loosely bound.[20] Rifampicin inhibits the binding of RNA to the subassembly[20] and, vice versa, RNA that of rifampicin.[36] These observations strongly support the notion that the drug and RNA compete for binding to RNA polymerase. This would explain why RNA polymerase does not bind rifampicin during RNA synthesis.[13,41] For the same reason, the antibiotic cannot terminate RNA chain elongation if added to the reaction mixture after initiation. It prevents, however, the start of RNA synthesis if added to the enzyme before the substrate.[42] Originally, these observations led to the hypothesis of rifampicin being a specific inhibitor of RNA chain initiation, which has been widely propagated even in textbooks.[43] This hypothesis, however, explains the plethora of observations concerning the molecular effects of rifampicin much less convincingly than the hypothesis of an indirect interference of the bound drug with the binding of the reaction products.

6. Penetration of Rifampicin into Bacteria

The activity of rifampicin on the metabolism of bacteria must also be discussed with respect to the process of penetration of the drug into the bacterial cell, which allows it to reach its target in the cytoplasm. It has been postulated that rifampicin does not require a special mechanism of penetration since it is so lipophilic. Rifampicin is thought to dissolve readily in the lipid-rich cell wall and membranes of bacteria and therefore to reach the cytoplasm via an equilibrium distribution.[44] In fact, *M. tuberculosis*, the causative agent of tuberculosis, contains very high amounts of complex lipids in its cell wall, which should facilitate the solubilization and penetration of rifampicin. However, recent observations indicate that the penetration of the drug is controlled by additional factors.[45] After mutagenesis of *E. coli* AB1157[46] with *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine, clones that contain an RNA polymerase highly sensitive to the drug but that are able to grow in its presence were isolated by an appropriate selection procedure. No evidence for the degradation of the drug by the mutants was found. The rate of rifampicin uptake in the mutant cells is extremely reduced (Fig. 6). These mutants are only resistant to rifamycins, while their sensitivity to other toxins, such as phenol, acriflavin, malachite green, neomycin, tetracycline, or chloramphenicol, remains unchanged.

The mutated gene can be transduced into sensitive strains with bacteriophage P1kc. Mapping of the mutation with the help of bacteriophage mu[47] has shown that the gene is located between the loci cysB (28 min) and aroD$_6$ (37 min) of the *E. coli* standard gene map far away from the gene loci of the RNA polymerase subunits. The mutated gene has been cloned in pBR322. *E. coli* DH1 or HB101 cells harboring this plasmid are resistant to up to 200 μg/mL of rifampicin in the growth medium, whereas the RNA polymerase activity is as sensitive to the drug as in the plasmid-free host. In vitro expression of the cloned gene[48,49] resulted in the appearance of a protein with a relative molecular weight of 49000 in dodecylsulfate-containing polyacrylamide gels. The cloned DNA fragment

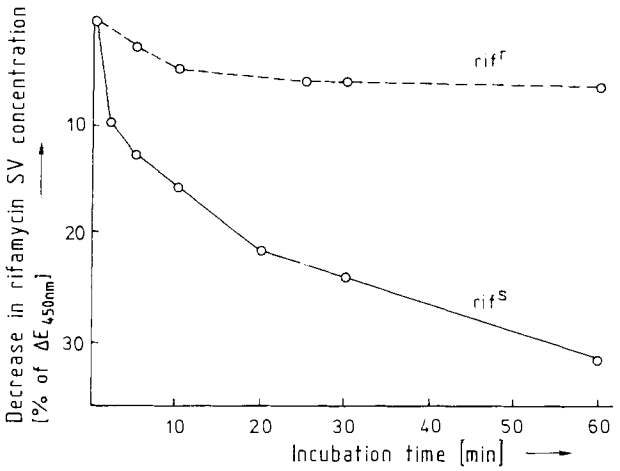


Fig. 6. Uptake of rifamycin SV by *E. coli* CR 34 thy ("rif") and by the rifampicin-resistant rif 41 ("rif") mutant at 37°C. The decrease of the rifamycin concentration in the supernatant was determined spectrophotometrically [44].

with a length of 2145 base pairs has been sequenced. It contains two open reading frames starting with a methionine codon close to a Shine-Dalgarno-like sequence. The larger one has a coding capacity for a protein of 452 amino acids length until to the next stop codon. It may code for the protein observed upon in vitro gene expression. More work will be required to elucidate the function of these gene products in the uptake of such a lipophilic compound as rifampicin by *E. coli* cells.

7. Outlook

Thanks to improved hygiene and healthier nutrition, better methods of early detection, and—last but not least—more effective drugs such as rifampicin, the formerly widespread disease tuberculosis has today become, at least in the industrialized countries, a seldom and specifically treatable illness. The times are forgotten when every seventh human being died of tuberculosis. Transients and drug addicts, that is, those social groups that are difficult to treat therapeutically, are still afflicted by the disease. Furthermore, there is the ever-present danger that bacterial strains will appear that are resistant toward antibiotics such as rifampicin. It was surprising to discover that such resistance can also arise from the blocking of the uptake of a hydrophobic drug, which ought to be able to penetrate easily the lipophilic membranes of microorganisms. The natural function of the gene that determines this behavior is still unknown. Further research is necessary to elucidate the specificity and extent of this kind of resistance.

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Error Rates of the Replication and Expression of Genetic Information

By Uwe Englisch,* Dieter Gauss, Wolfgang Freist, Sabine Englisch, Hans Sternbach, and Friedrich von der Haar

Dedicated to Professor Friedrich Cramer

Biological evolution is based on continual changes in the genomes of cells. If stable organisms are to develop nonetheless in the course of this process, low error rates (high accuracy) in both the replication of genes and their transcription and translation into proteins have to be assured. The overall error rates of these processes are measurable and can be estimated: they result from the error rates of the individual enzyme-catalyzed steps. In many cases, for example in the discrimination of the amino acids valine and isoleucine during protein biosynthesis, it is not possible to achieve a sufficient accuracy only on the basis of the difference of the free energies of binding of the correct and incorrect substrates (the two amino acids differ only in a CH_2 group). The necessary low error rate is maintained by an additional proofreading step, which is carried out by the enzymes involved after formation of the enzyme-substrate complex, either during catalysis or before product release. In this step, an incorrect intermediate or product is hydrolyzed. The energy input necessary for the synthesis of the incorrect intermediate or product, which is provided by hydrolysis of adenosine or guanosine triphosphate, is the price paid for the low error rates. In this article, the proofreading mechanisms of several enzymes—mainly those involved in DNA replication and the aminoacylation of transfer RNA during protein biosynthesis—are discussed.

1. Introduction[**]

The specificity of enzymes has fascinated chemists and biologists since the early days of bioorganic chemistry. *Emil Fischer*'s "lock and key" theory of enzyme-substrate recognition was the first mechanistic model of this interaction.[1] The rapid development of biochemistry in the last few decades has resulted in increasingly detailed models of enzymatic reactions,[2-4] such as the "induced fit" theory (fitting of the active site of an enzyme to the substrate) and the "strain" theory (activation of the substrate by the enzyme). At the same time the principles of enzymatic catalysis have been evaluated using low-molecular-weight organic compounds.[5,6] The elucidation of the basic molecular mechanisms of heredity and the formation of phenotypes has stimulated the search for enzyme systems responsible for DNA replication and protein biosynthesis[7,8] (see Fig. 1). Shortly after their discovery it was demonstrated that these enzymes exhibit greater specificity[9,10] than most of the known enzymes of such important metabolic pathways as the Calvin, citrate, or urea cycles.

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In 1963 *Loftfield* investigated the accuracy of ovalbumin biosynthesis in hen oviduct tissue[11] and showed that the misincorporation of valine in place of isoleucine occurred with a frequency of $\approx 1:3000$. This overall error rate includes all possible errors in protein biosynthesis, from the transcription of DNA through the esterification of amino acids to transfer RNAs up to peptide bond formation at the ribosome.

The error rates of DNA replication in prokaryotic and eukaryotic cells, on the other hand, are orders of magnitude lower, as indicated by the rates of spontaneous mutation.[12,13] They occur in the range of one mutation per $\approx 10^8$ to 10^{12} incorporated nucleotides, which reflects the extreme accuracy with which the genetic code is conserved. However, this error rate does not only include the errors of the DNA polymerase, but also all other changes of the DNA sequence[14-17] that are not corrected by repair enzymes before replication starts.[18] Such changes can be caused, for example, by UV radiation (dimerization of neighboring thymidines to form a cyclobutane derivative) or by mutagenic compounds (alkylation, deamination of nucleosides.

The extremely low error rate of DNA replication, however, need not be achieved in gene expression, since in replication each nucleic acid strand is replicated only *once*, whereas in gene expression one gene is transcribed to give many copies of messenger RNA, which, in turn, serve as templates for the synthesis of many protein molecules. Both the messenger RNAs and the proteins are degraded after a short lifetime. Moreover, proteins with a wrong amino acid sequence often have a different tertiary structure which favors fast proteolytic cleavage.[19]

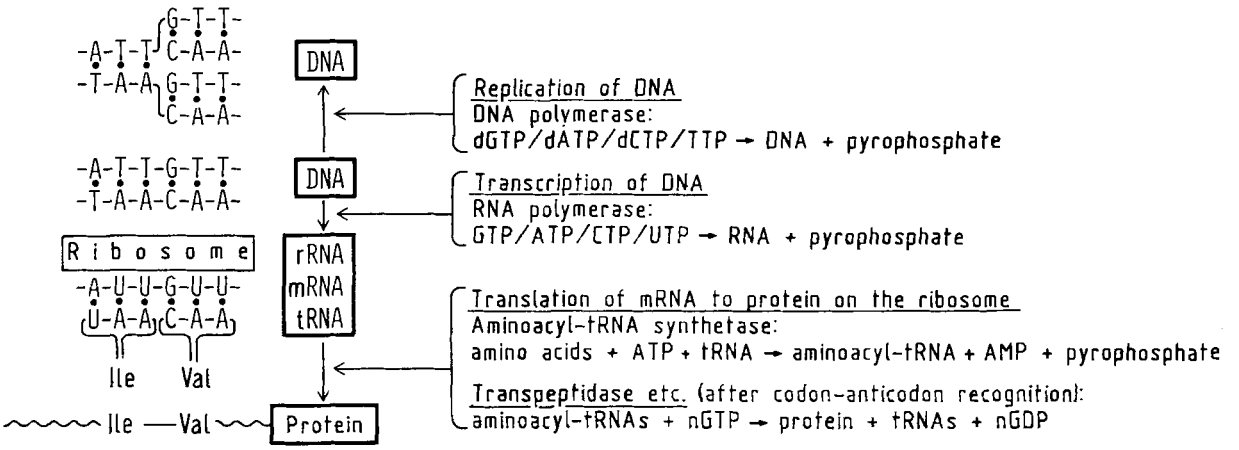


Fig. 1. Scheme of replication, transcription, and translation; some key enzymes and their reactions with energy-rich substrates are given with the reaction steps.

The expression of the genetic information is a multistep system optimized for economy and efficiency. Accordingly, the error rates of the single steps are always expected to be slightly lower than the overall error rate, which is obtained (to a first approximation) by the addition of the single error rates. However, if the accuracy of any one step is improved by a proofreading mechanism, the resulting error rate (again to a first approximation) is the product of the initial discrimination of the substrates and a proofreading factor, which is the inverse ratio of the number of errors before and after the proofreading.

2. Relevance of Error Rates in the Replication and Expression of Genetic Information

High error rates during DNA replication and protein biosynthesis would have two important consequences. First, a high (but not lethal) exchange rate for single nucleotides during DNA synthesis would generate many different mutants. This would enable organisms to adapt faster to changing environmental conditions, assuming a sufficient number of cell divisions occur. Second, the stability of the genome would be impaired and useful mutations would not be conserved. In gene expression high error rates would lead to large amounts of heterogeneous, nonspecific, functionally impaired, or even nonfunctional proteins. The consequences would range from metabolic disturbances to possible breakdown of the cell metabolism.

The accuracy of DNA replication and protein biosynthesis are coupled to each other. On the one hand, error-prone DNA replication results in a direct change of the genotype, leading to defective proteins, even if the protein biosynthesis is free of errors. On the other hand, error-prone protein biosynthesis results in DNA polymerases and other proteins that interact with DNA with low specificity. The necessity of maintaining intact replication units and simultaneously permitting a certain level of mutations led in the course of evolution to an optimized range of mutation rates. Slow and fast mutating species of one organism are known[20-23] in which the mutation rate is genetically determined or in which a specific regulation mechanism is responsible for an increased rate of mutation in a rapidly changing environment.[24]

A low accuracy in protein biosynthesis plays a major role in one of the theories of biological aging, the "error catastrophe theory" of *Orgel*.[25] Since all reaction steps of the protein biosynthesis are catalyzed by enzymes, errors in the synthesis of these enzymes lead to the biosynthesis of increasingly defective proteins, resulting finally in cell death. The error catastrophe is definitely not the only source of cell aging, but a decrease in enzyme activities and specificities might play an important role in this process.[26-31]

The severe effect of *one* point mutation in a large genome is exemplified in sickle cell anemia:[32] persons carrying homozygotic chromosomes have a shorter lifetime due to a change in the shape of their erythrocytes. This phenomenon is the result of an amino acid exchange in position 6 of the β-chain of hemoglobin, where a valine is inserted in place of a glutamic acid. The sequence CTC in the gene, which is transcribed into GAG in mRNA, codes for glutamic acid.[33] Since valine is coded for by GUG in mRNA, the corresponding sequence in the gene is CAC, indicating a T→A exchange.

Recent studies on tumor cell lines show a connection between point mutations and tumor induction: in cell lines of human bladder carcinoma, one uncorrected point mutation changes a silent proto-oncogene into an active oncogene. This one mismatch produces a glycine/valine exchange in the expression product,[34-37] which is a key factor for the transformation of the cell.

3. Error Rates of DNA Replication

The synthesis of a daughter strand of the DNA double helix is catalyzed by DNA polymerase with the assistance of many other proteins. The polymerase uses the deoxynucleotides dATP, dCTP, dGTP, and TTP as substrates, while the mother strand serves as template (Fig. 1). The enzyme does not recognize single deoxynucleotides, only base pairs formed with the pyrimidine and purine residues of the template.[38] The accuracy of this selection process is

not perfect, as the shapes and properties of the correct base pairs can be mimicked. *Watson* and *Crick*[39] suggested that amino/imino and keto/enol tautomerism of the nucleobases can reduce the specificity of DNA polymerases. The imino form of cytosine can establish the same hydrogen bonding pattern as thymine and the enol form of thymine that of cytosine, resulting in A : C(imino) and G : T(enol) base pairs. Additionally, the interatomic distances in these mismatch base pairs are the same as in the correct A : T and G : C base pairs (Fig. 2).

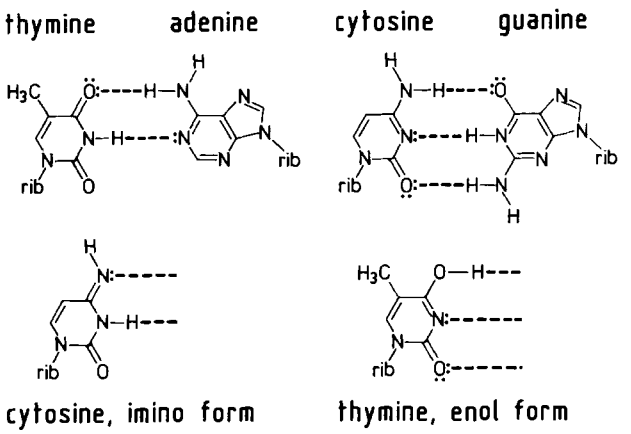


Fig. 2. Structures of thymine·adenine and cytosine·guanine base pairs in comparison with the imino form of cytosine and the enol form of thymine, which are suitable for mispairing. rib = ribosyl.

This mispairing occurs with a frequency of $\approx 1:10^4$ to $1:10^5$.[40,41] This rate is by 3 to 6 orders of magnitude higher than the frequency of in-vivo mutation of *E. coli* ($\approx 1:10^8$ to $1:10^{10}$).[42] The mutation rate in eukaryotic cells is thought to be even lower by a factor of about 100. The slower rate of replication (30 nucleotides/s versus 1000 nucleotides/s in *E. coli*) may be an indication that eukaryotic cells use more sophisticated proofreading steps before a nucleotide is finally incorporated into the daughter strand.[43,44]

3.1. Mechanism of Proofreading in DNA Replication

To maintain a low error rate of DNA replication, prokaryotic DNA polymerases have an exonuclease activity in addition to their polymerizing activity. In the case of a recognized mismatch, excision of the incorrect nucleotide takes place. Only after this proofreading step and, if necessary, incorporation of the correct nucleotide does replication continue.[44–46] The connection between polymerase and exonuclease activities was demonstrated for the first time when fast- and slow-mutating species of bacteriophage T4 ("mutator" and "antimutator" strains) were examined.[47] The exonuclease activity of DNA polymerase isolated from "mutator" phages is much lower than its polymerase activity. Therefore, the proofreading activity of this enzyme is low in comparison with that of the wild-type enzyme. Exactly the opposite phenomenon was observed with the "antimutator" phages. In further studies with DNA polymerase III from a mutator *E. coli* strain it could be shown that a mutation in the gene of the ε-subunit of the enzyme, which seems to control the exonuclease activity, is responsible for the observed high rates of mutation.[48,49]

The quantitative measurement of error rates in DNA replication—using as templates either synthetic polynucleotides in in-vitro biochemical assays[45] or DNA in in-vivo molecular genetics assays[50,51]—has shown that the error rate is reduced by a proofreading system to one mistake per $\approx 10^6$ to 10^9 polymerized nucleotides.[51–56] The proofreading system of prokaryotic DNA polymerases therefore decreases the error rate by a factor of $\approx 10^2$ to 10^4 compared with the rate of mispairing but this is still not sufficient to explain the observed rates of spontaneous mutations. A further reduction is achieved by the action of a second system, the post-replicative proofreading.

Until recently, it was thought that error correction could only occur before the incorporation of the next nucleotide because the proofreading enzyme cannot distinguish afterwards which nucleotide in the mismatch base pair was the original correct one. However, it has been shown in the meantime that specific methylation of the DNA strand, which occurs in all cell systems examined so far,[57] provides a recognition signal to differentiate between mother and daughter strands. The methylation of adenine (N^6 atom) in the sequences G-A-T-C of *E. coli* (Fig. 3) lags behind replication,[58] such that newly synthesized strands are transiently unmethylated or undermethylated. The mismatch repair system moves along the undermodified daughter strand, removes the mismatches, and replaces them with the correct nucleotides.[59–61] This mismatch repair system reduces the error rate of replication by a factor of ≈ 100 to 10000, resulting in an overall error rate of one mistake in $\approx 10^9$ to 10^{11} polymerized nucleotides.

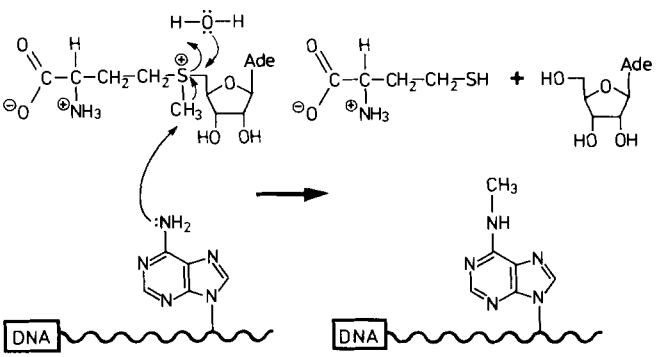


Fig. 3. Enzymatic methylation of DNA; this reaction allows the template DNA strand to be discriminated from the newly synthesized strand.

4. Error Rates of Transcription

The transcription of the genetic information from DNA into mRNA by DNA-dependent RNA polymerase does not appear to involve a proofreading system.[62–64] The observed in-vitro error frequencies with synthetic polynucleotides are in the range of one mistake per $\approx 10^3$ to 10^5 polymerized ribonucleotides;[62] for example, in an in-vivo *E. coli* system the transcriptional error of a nonsense muta-

tion is one mistake per 10^4 polymerized ribonucleotides.[64] This error frequency is the same as that predicted from the intrinsic tautomerism of the heterocyclic bases, and thus no evidence for a proofreading mechanism is detectable.

5. Error Rates of Aminoacylation of Transfer RNA

The main task of the enzymes involved in replication and transcription is to assure the correct base-pairing of nucleotides. In protein biosynthesis, on the other hand, three nucleotides (triplet or codon) of the messenger RNA (mRNA) have to be correlated to one amino acid (cf. Fig. 1). The links between these two systems are the transfer RNAs (tRNAs),[65-67] which consist of 50 to 100 ribonucleotides. In Figure 4 (bottom left), the schematic structure of phenylalanine tRNA is shown. The binding of the tRNA to the mRNA occurs by base-pairing of the three nucleotides of the anticodon with the codon of the mRNA; the corresponding amino acid is esterified to the 3′-terminal adenosine of the tRNA (cf. Fig. 1 and Fig. 4). The aminoacylation of each tRNA species is catalyzed by a specific aminoacyl-tRNA synthetase.[68-72] In this reaction, the following two selection problems arise for each of the twenty enzymes: the accurate selection of the correct tRNA from a population of at least 20—but usually ca. 70—species, and the accurate selection of the correct amino acid from 20 possibilities.[73]

The aminoacylation takes place via two successive steps known as activation and transfer (Fig. 4). The intermediate after activation of the amino acid by ATP, the aminoacyl adenylate, is a mixed anhydride. Thermodynamic considerations show that the free energy of hydrolysis of the α,β-phosphoric acid anhydride bond of ATP is largely conserved in the free energy of hydrolysis of the aminoacyl-tRNA.[71] This large amount of energy[74,75] may be necessary for the subsequent transformation of the ester linkage into a peptide linkage at the ribosome. Although the exact details of this process are still unknown, energy might be necessary for providing the correct stereochemical orientation of the macromolecules, and for assuring the high rate of elongation of the peptide (≈ten aminoacyl residues per second).

5.1. Selection of Transfer RNA

Each aminoacyl-tRNA synthetase has to select its cognate tRNA, carrying the amino-acid-specific anticodon. However, the anticodon does not seem to be the recognition site—at least not the only one—of the tRNA for the synthetase. Although many studies have been carried out, e.g., aminoacylations of chemically or enzymatically modified tRNAs, the addition of cross-linking reagents to aminoacylation reactions, the misaminoacylation of tRNAs, or the comparison of the ca. 1000 known tRNA sequences,[76] no specific recognition site on the tRNA (Fig. 4) has been unambigously identified.[65,67,68,73,77] This clearly demonstrates the complexity of the selection process, which probably changes in terms of both the recognition site and the selection mechanism from tRNA to tRNA and from organism to organism. The enzyme (consisting of 500 to 1000 amino acids) and the tRNA (50 to 100 nucleotides) offer a large number of possibilities for recognition. Taking into consideration the informational content of an anticodon or codon, a recognition sequence of six steps is reasonable if, for each of the three base pairs, two questions must be posed: Is the opposite base a purine or a pyrimidine? In the former case, is it A or G, and in the latter, U or C? Accordingly, six questions arise for a sequence of three base pairs. The results of biochemical experiments[78-80] and theoretical studies[81,69] suggest that a similar number of steps are involved in the recognition process. Probably, step by step, the cognate tRNA docks more and more tightly to the enzyme.[78-80] An important role—at least in some systems—is played by the terminal adenosine of the

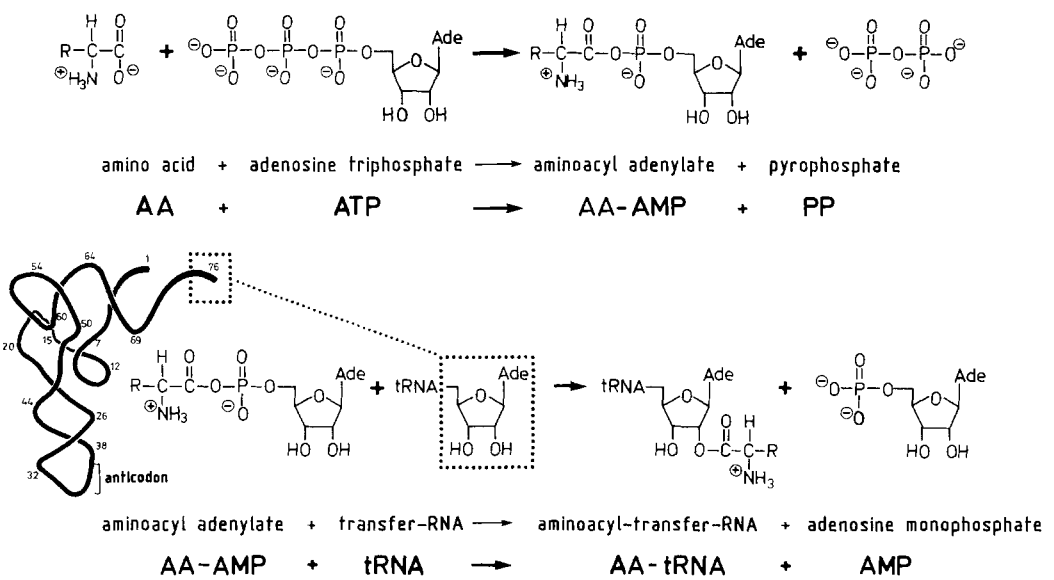


Fig. 4. The coupling of tRNAs with amino acids (aminoacylation), catalyzed by aminoacyl-tRNA synthetases, is a two-step process: the formation of an aminoacyl adenylate from an amino acid is called activation (upper reaction); aminoacyl-tRNA formation is called transfer (lower reaction). Bottom left: sugar-phosphate backbone of yeast $tRNA^{Phe}$ (76 nucleotides).

tRNA and its 2′- or 3′-hydroxyl groups,[82,83] to which the aminoacyl residue is transferred.[84-87] In most cases, this transfer specifically involves one of these hydroxyl groups; the other one—at least in several cases (see Section 5.2)—is important for the error rate of the aminoacylation. In most experiments, an error rate of one mistake per $\approx 10^4$ to 10^5 tRNA-enzyme recognitions is observed, which is in the range of the other steps of gene expression and therefore does not seem to require a proofreading step. As early as 1972/1973, however, it was demonstrated that phenylalanyl-tRNA synthetase from *E. coli* could hydrolyze misaminoacylated Ile-tRNA^{Phe}, the product of a misaminoacylation reaction using isoleucyl-tRNA synthetase;[88,89] this hydrolysis was called "verification." Detailed examination of the recognition process in the system isoleucyl-tRNA synthetase + tRNA^{Ile} + tRNA^{Val} from yeast (the close relationship of the two tRNAs is quantified by the number and kind of the ribonucleotides) recently showed that the initial discrimination of the tRNA is only $\approx 1:10$ and that an additional proofreading step is necessary to decrease the error to $\approx 1:100$.[90] In vivo the error is then diminished to $\approx 1:10^4$ to 10^5 by the presence of the tRNA^{Val}-complexing valyl-tRNA synthetase. Nothing is known yet about the mechanism of this proofreading.

5.2. Selection of the Amino Acid

In comparison to tRNAs, amino acids are very small cell constituents. In addition to their small size, some of them, e.g., glycine and alanine, phenylalanine and tyrosine, or isoleucine and valine (Fig. 5), are very similar. Therefore, it may be especially difficult for the enzyme to differentiate very accurately between the closely related amino acids.

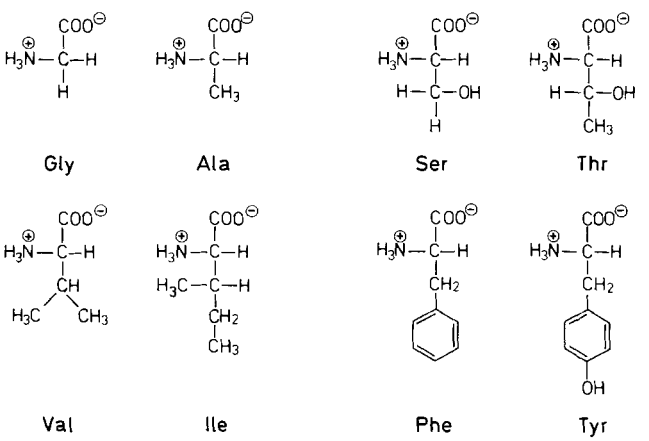


Fig. 5. Satisfactory discrimination of some amino acids by aminoacyl-tRNA synthetases requires proofreading steps. Structures of some related amino acids: glycine and alanine, serine and threonine, valine and isoleucine, phenylalanine and tyrosine.

The decisive parameter determining the ability of an enzyme to discriminate between two substrates (A and B) is the difference in the free energy of binding of the two substrates in the transition state. Under the assumption that the reaction steps involved are energetically the same for both substrates, this parameter can be calculated from relatively easily measurable kinetic parameters:[3,91]

$$(k_{cat}/K_m)_A/(k_{cat}/K_m)_B = \exp(-\Delta\Delta G/RT)$$

where k_{cat} and K_m are the turnover numbers and the Michaelis constants, respectively, of the substrates and $\Delta\Delta G$ is the difference between their free energies of binding in the transition state. According to calculations based on the London theory of electronic dispersion forces and on measurement of energy differences in binding of chemically related compounds to antibodies, *Pauling*[92,93] demonstrated in the 1950s that the free energy for the hydrophobic interaction of a methylene group with a molecule is about 4 kJ/mol. Using this result, he calculated, years before the discovery of the molecular mechanism of protein biosynthesis, that the error rate for the incorporation of glycine instead of alanine, or valine instead of isoleucine, must be about 1 : 10.[93] Although another calculation in the 1970s gave a lower error rate,[94] these numbers are very far from the error rates necessary in protein biosynthesis.

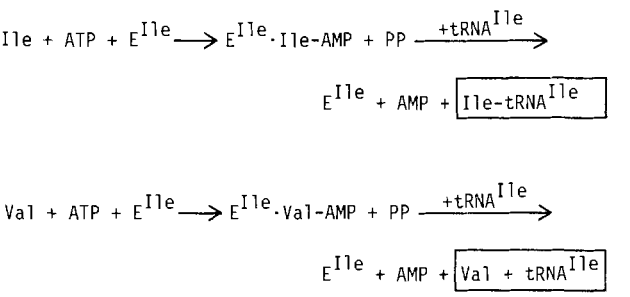


Fig. 6. Aminoacylation of tRNA^{Ile} with isoleucine by isoleucyl-tRNA synthetase (E^{Ile}, above) and misactivation of valine by the same enzyme (followed by hydrolysis to valine and tRNA^{Ile})

The difficulties predicted by *Pauling* for the discrimination between isoleucine and valine by the isoleucyl-tRNA synthetase of *E. coli* were confirmed experimentally some years later: valine is actually misactivated by the enzyme to give enzyme-bound valyl adenylate[95,96] (Fig. 6, cf. Fig. 4, top). *Berg* et al.[9,95,97,98] showed that, despite this activation, no Val-tRNA^{Ile} is obtained in the presence of tRNA^{Ile} (Fig. 6). In 1972, however, Val-tRNA^{Ile} was demonstrated to be the probable intermediate.[99] The mechanism of this reaction remained unclear for some time. The product is apparently proofread by the enzyme, and a misactivated amino acid is eliminated by hydrolysis and not released as aminoacyl-tRNA from the enzyme. The cost of this proofreading is the hydrolysis of one ATP molecule to AMP per misactivation (Fig. 6).

5.2.1. *Proofreading Mechanism of Aminoacylation*

Numerous experimental results and theoretical arguments on the mechanism of proofreading by aminoacyl-tRNA synthetases have led to different models for this phenomenon. Each of these, however, was only developed for one or a few of the aminoacyl-tRNA synthetases and, therefore, should not be regarded as general or valid in all cases. In 1974, *Hopfield* et al.[100,101] proposed a correction mechanism, called "kinetic proofreading." The main principle of this mechanism is that the discrimination between two competing substrates, according to Michaelis-Menten

kinetics, can be repeated on the level of the intermediates, resulting in an error rate that is the product of the error rates of the two steps. This argument is only valid if there is an irreversible step between the Michaelis-Menten complex and the intermediate (Fig. 7, step 2) and if this intermediate can in principal be processed in two different ways (Fig. 7, step 3 or 3'). In the aminoacylation reaction, the hydrolysis of ATP (and the subsequent hydrolysis of pyrophosphate) is regarded as an irreversible step (Fig. 7, step 2), and the enzyme-aminoacyl adenylate complex can either react to give product (Fig. 7, step 3) or dissociate from the complex and undergo hydrolysis in solution (Fig. 7, step 3'). This model is very convincing and is supported by the experimental fact that significantly increased ATP consumption is observed in aminoacylation of tRNAs with noncognate amino acids. For instance, 270 molecules of ATP are hydrolyzed before one molecule of Val-tRNA^{Ile} *(E. coli)* is formed, whereas the formation of the cognate Ile-tRNA^{Ile} only requires 1.5 ATP molecules.[100, 102–104] So far, the most persuasive experimental support for such a model is the discrimination between tyrosine and phenylalanine by phenylalanyl-tRNA synthetase.[105] This mechanism of selection is probably also of importance for other amino acids (cf. Section 5.2.2). The obvious weakness of the model is that it only deals with a proofreading mechanism on the level of the aminoacyl adenylate and does not explain what happens on the level of enzyme-bound transient misaminoacylated tRNAs, which have been detected by several groups.[99, 103, 106–108]

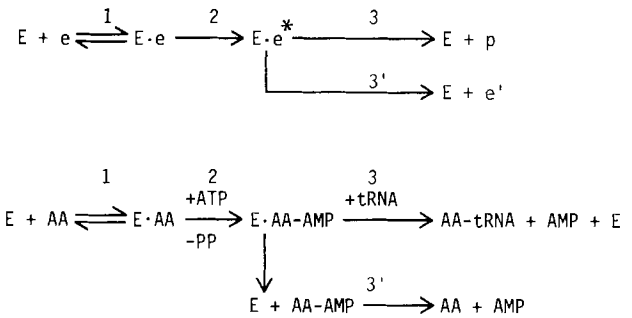


Fig. 7. A reaction scheme suitable for "kinetic proofreading" (above, taken from *Hopfield*) and aminoacylation according to this scheme (below, E = aminoacyl-tRNA synthetase).

Two other proofreading models do take into consideration these species. The double sieve model of *Fersht* et al.[109–112] is a two-step mechanical model, in which the active site acts twice as a sieve for the selection of the correct amino acid. The first sieve, the binding pocket, which perfectly accomodates the amino acid, blocks the binding of more voluminous amino acids by steric repulsion. However, smaller or isosteric amino acids are bound (albeit with lower affinity) and can react to give the aminoacyl adenylate. The second sieve acts in the following way: after transfer of the aminoacyl residue to the accepting hydroxyl group of the terminal adenosine of tRNA (cf. Section 5.1 and Fig. 4), isomerization to the nonaccepting hydroxyl group (which is close to a hydrolytic site of the enzyme) occurs if the aminoacyl residue is smaller than the correct one. The cognate aminoacyl residue cannot reach this site for stereochemical reasons and remains bound to the tRNA. The double sieve model is the result of experiments[113, 114] in which fast kinetics were used to detect the intermediates. Proofreading could be found with methionyl-,[110] valyl-,[109, 111, 115] and isoleucyl-tRNA synthetases[104, 107] from *E. coli* and *Bacillus stearothermophilus*. The authors concluded that, in the case of isoleucine,[111] threonine,[109] and α-aminobutyric acid,[115] the proofreading mechanism acts mainly after transfer of the aminoacyl residue to the tRNA, whereas valyl adenylate is hydrolyzed before the transfer step. The model could not explain, however, the activation, transfer to tRNA^{Val}, and final hydrolysis of the valine-isosteric threonine by the valyl-tRNA synthetase without further assumptions. The discrimination of more voluminous amino acids in the first sieve has been cast in doubt by the observation of a misactivation of cysteine by alanyl-tRNA synthetase.[116]

Using chemically modified tRNAs, in which either the 2'- or 3'-hydroxyl group was missing or replaced by an amino group,[117, 118] *Cramer, von der Haar,* et al.[119–121] were able to show that, at least in yeast, both hydroxyl groups act together in the proofreading.[122, 123] Besides the esterification of isoleucine with tRNA^{Ile} to Ile-tRNA^{Ile}-C-C-A (Fig. 8a), isoleucyl-tRNA synthetase also catalyzes the formation of misaminoacylated Val-tRNA^{Ile}-C-C-3'dA, which is likewise released from the enzyme. In contrast, Val-tRNA^{Ile}-C-C-A is hydrolyzed by the enzyme before release can occur.[103, 124] The model of chemical proofreading explains the hydrolysis of Val-tRNA^{Ile}-C-C-A by the assumption that the nonaccepting 3'-hydroxyl group and a water molecule—which replaces the missing methylene group—together with a nucleophilic group of the enzyme are responsible for the hydrolysis of Val-tRNA^{Ile}-C-C-A (Fig. 8b). Although the fact that one ester is hydrolyzed and the other is not can be explained quite simply for this specific case, this model cannot be easily generalized to other systems. Investigations of the valine system (Fig. 8c) showed that the hydrolysis of a mistransferred threonyl residue by valyl-tRNA synthetase (Fig. 8d) is not directly mediated by the 3'-hydroxyl group of the terminal adenosine of the tRNA.[106, 109] A possible explanation for this phenomenon would be the transient lactonization of threonine (Fig. 8d), but since the four-membered lactone product is unstable, no direct chemical proof is possible. Although a stable five-membered lactone could be formed from γ-hydroxyvaline (which is roughly the same size as isoleucine) by isoleucyl-tRNA synthetase, the enzyme does not accept this analogue as a substrate.[125, 126] However, lactones are formed in two cases where the substrate is too voluminous (in the sense of the double sieve) by one methylene group, namely from γ-hydroxyvaline by valyl-tRNA synthetase (Fig. 8e)[125, 126] and from γ-hydroxyisoleucine by isoleucyl-tRNA synthetase.[127, 128] Both reactions are enzyme-catalyzed in yeast as well as in *E. coli*. In addition, homocysteine, a precursor of methionine, is released as a thiolactone by methionyl-tRNA synthetase *(E. coli)*[108] (Fig. 8g). These examples show that an intramolecular nucleophilic attack of the hydroxyl group of the amino acid on the carboxyl group is involved in the ester hydrolysis.

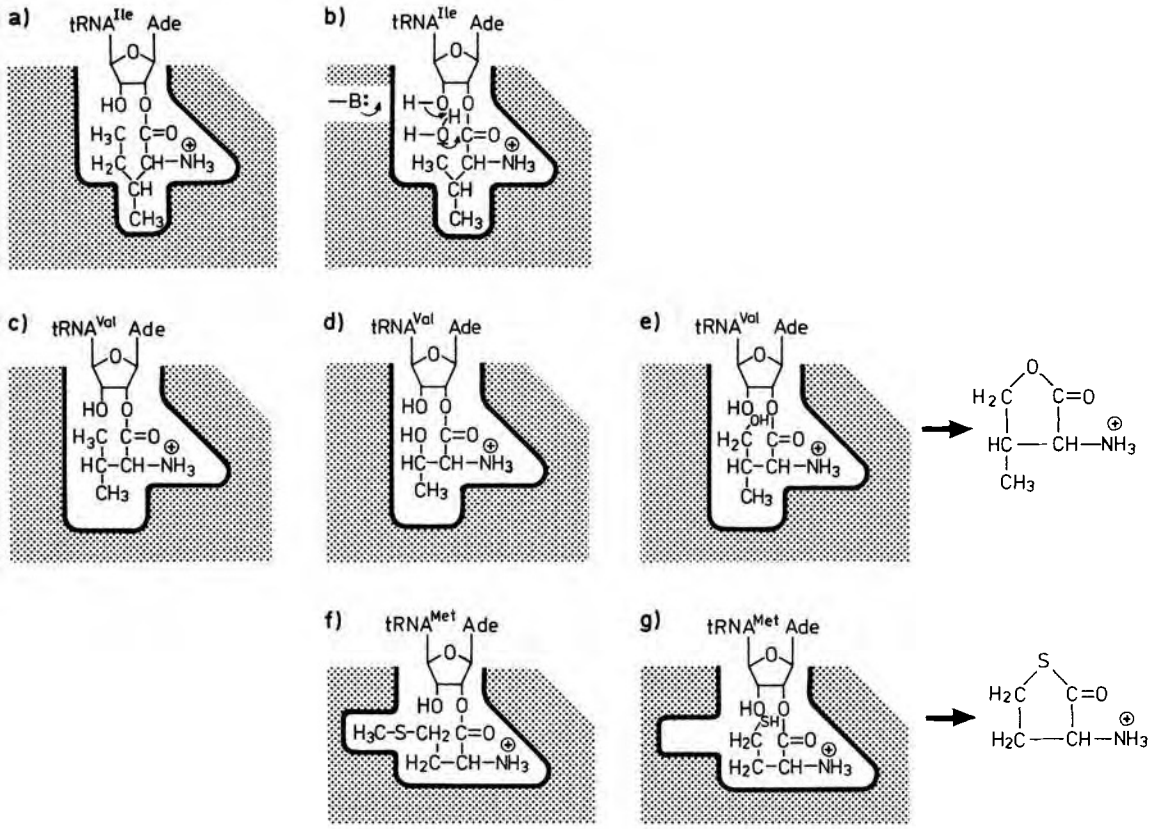


Fig. 8. Schematic representation of aminoacyl-tRNAs in the active sites of aminoacyl-tRNA synthetases: isoleucyl-tRNA synthetase and $tRNA^{Ile}$ with the amino acids isoleucine (a) and valine (b); valyl-tRNA synthetase with the amino acids valine (c), threonine (d), and γ-hydroxyvaline (e); methionyl-tRNA synthetase and $tRNA^{Met}$ with the amino acids methionine (f) and homocysteine (g).

Many other suggestions regarding the mechanism of proofreading are found in the literature, in which specific points of the reaction pathway,[129] the stability of intermediates and products,[130] the interaction of the subunits of aminoacyl-tRNA synthetases,[131] and the interaction of two tRNA molecules simultaneously bound to the enzyme are discussed[132] or high-energy conformational states of the enzyme are postulated[133] as possible ways to differentiate between correct and incorrect substrates. However, there is no conclusive experimental support for these ideas.

All measurements and calculations have in common a final error rate of about one mistake in 10^5 aminoacylations, a frequency which is ten times smaller than the overall error rate in protein biosynthesis. This is achieved by multiplication of error rates at three points: the initial discrimination of the amino acids by the synthetase, the proofreading of the aminoacyl adenylate (pre-transfer correction), and the proofreading of the aminoacyl-tRNA (post-transfer correction). Not every enzyme necessarily uses both pre- and post-transfer proofreading to select its cognate substrate. Recent investigations have shown, however, that isoleucyl-tRNA synthetase from yeast uses both steps in the discrimination between isoleucine and valine. The overall error rate, after the initial discrimination and both proofreading processes, is about 1:40000 ($10 \times 20 \times 200$).[102]

Probably, the error rates in protein biosynthesis are in the same range for all organisms, although detailed data are still lacking. What is known, on the other hand, is that the mode and extent of the proofreading step has undergone change during evolution: phenylalanyl-, isoleucyl-, valyl-, and leucyl-tRNA synthetases from different organisms show various combinations, ranging from very accurate initial discrimination and less-expressed proofreading up to sluggish initial discrimination and very accurate proofreading, which itself can be pre- or post-transfer only or a combination of both.[127, 128, 134–136] The different proofreading capacities of synthetases from *E. coli*, fungi, and mammals with respect to amino acid analogues is one possible starting point for the directed synthesis of therapeutic agents with protein biosynthesis as the specific target.[137]

5.2.2. *Aminoacylation without Proofreading*

Besides those aminoacyl-tRNA synthetases that have proofreading mechanisms (which include, according to *Fersht*,[112] those specific for alanine, valine, threonine, isoleucine, methionine, and, perhaps, phenylalanine and leucine), another class of synthetases exists for which no proofreading steps have been detected up till now. The reason for the lack of such proofreading systems is a very high initial discrimination of the amino acids, which already reduces the error rate below the overall error frequency of protein biosynthesis ($\approx 1:3000$). Examples of this type of synthetase are the histidyl-,[138] tryptophanyl-,[139] cysteinyl-,[113] lysyl-,[127] and tyrosyl-tRNA synthetases.[140] The observed error rates are in the range of $\approx 1:10^4$ to $1:10^5$ for the incorporation of tryptophan and

proline instead of histidine by the histidyl-tRNA synthetase, or of phenylalanine instead of tyrosine by the tyrosyl-tRNA synthetase. The error rate found for the activation of serine or alanine by the cysteinyl-tRNA synthetase was even lower, in the range of $\approx 1:10^8$.[113]

In the course of evolution, structures that differ sharply from those of other amino acids may have been selected for the amino acids that are directly involved in catalytic processes, e.g., histidine, tryptophan, or cysteine. The incorporation of the wrong amino acid, leading to an inactive enzyme, would thereby be avoided. Nevertheless, the above-mentioned amino acids are activated to a small extent by other synthetases.[141] In the course of evolution, therefore, the optimal balance of energy cost versus accuracy has been established for every amino acid in every protein.

6. Error Rates of Peptide Formation at the Ribosome

After release from the aminoacyl-tRNA synthetase, the aminoacyl-tRNA forms a ternary complex with the elongation factor Tu and GTP and diffuses to the ribosome. When the correct anticodon is present, the tRNA binds to the vacant aminoacyl-tRNA site with release of EF-Tu and hydrolysis of GTP to GDP. The peptidyl-tRNA, which carries the growing protein fragment, occupies the adjacent peptidyl-tRNA site. It transfers the polymer by peptide bond formation to the aminoacyl-tRNA (cf. Fig. 1). In the next step, called translocation, the deacylated tRNA leaves the peptidyl-tRNA site and the new peptidyl-tRNA binds to this site with movement of the mRNA by one triplet. After this reaction sequence, a new elongation cycle can start. Many proteins are involved in the ribosomal protein synthesis, which also requires energy provided by the hydrolysis of GTP. It is not fully known what fraction of the energy input is used for the peptide bond formation, the codon-anticodon binding, the regeneration of the helper proteins to active conformations, or for the other steps involved.[142-145]

In the course of protein synthesis errors can occur. First, the movement of the mRNA on the ribosome by two or four nucleotides instead of the usual three causes a shift in the reading frame, resulting in a completely different translation product. Second, the binding of a noncognate aminoacyl-tRNA to the mRNA leads to the incorporation of an incorrect amino acid in the translation product.

The frequency of a frameshift mutation is of the order of $\approx 1:10^4$ to $1:10^5$, a value that is in the range of the overall error rate and does not seem to require a proofreading step.[146, 147]

The binding of tRNAs that carry an anticodon with *one* mismatch with respect to the codon of the mRNA, e.g., binding of Leu-tRNA^{Leu} to a mRNA that codes for Phe-tRNA^{Phe}, however, occurs with a frequency of $\sim 1:10$ to $1:100$.[148] This unspecific binding is equivalent to the error rate in the formation of a complex of two tRNAs by base-pairing of their anticodons in ribosome-free in-vitro experiments.[149] Two proofreading models, the "time-delay" model of *Ninio*[130, 150] and the "kinetic proofreading" model of *Hopfield*[100, 101] propose dynamic processes for the rejection of incorrect aminoacyl-tRNAs after complexation to the ribosome and the mRNA. The key step in the first model is a conformational change of the tRNA, which occurs as a result of the codon-anticodon interaction; in the second model, the energy provided by GTP hydrolysis plays the major role. The experimentally proven increase in GTP consumption upon binding of noncomplementary tRNAs, which is regarded as an indication for the abortion and restart of the whole process with irreversible loss of the energy input, favors the kinetic proofreading model, but does not exclude the "time-delay mechanism" (Fig. 9).[151, 152]

In addition to these models, a third correction mechanism has been discussed, which takes place after the translocation step on the level of the peptidyl-tRNA. According to this model, incorrect peptidyl-tRNA dissociates quickly from the ribosome and is hydrolyzed by peptidyl hydrolase.[153-155] This type of correction, however, would result in a considerable energy loss, determined by the length of the fragment already synthesized: e.g., the hydrolysis of a protein containing 250 aminoacyl residues entails the loss of roughly 1000 GTPs (Fig. 9).

From the GTP hydrolysis data obtained by *Thompson* et al.[148, 151] and by *Kurland* et al.,[156] a reduction of error

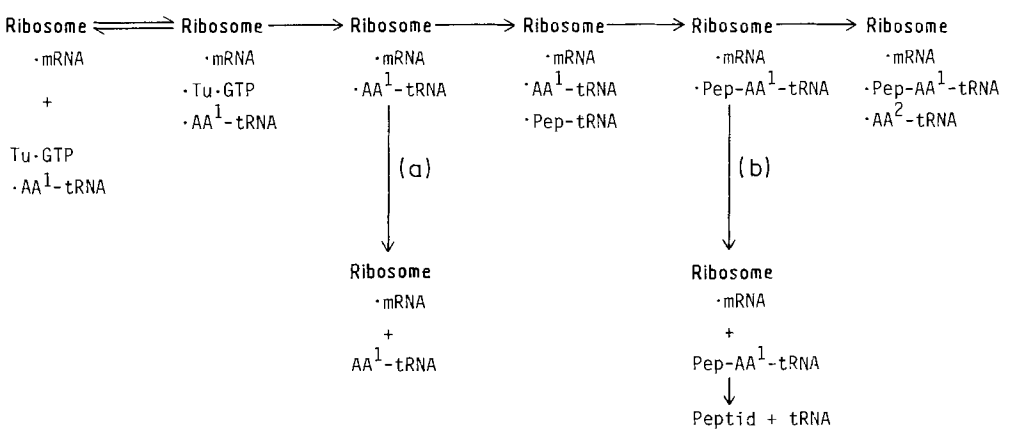


Fig. 9. The individual steps of prokaryotic ribosomal peptide synthesis including proofreading and correction steps before (a) and after (b) peptide bond formation (mRNA = messenger RNA, Tu·GTP = elongation factor·GTP complex, AA-tRNA = aminoacyl-tRNA, Pep-tRNA = peptidyl-tRNA).

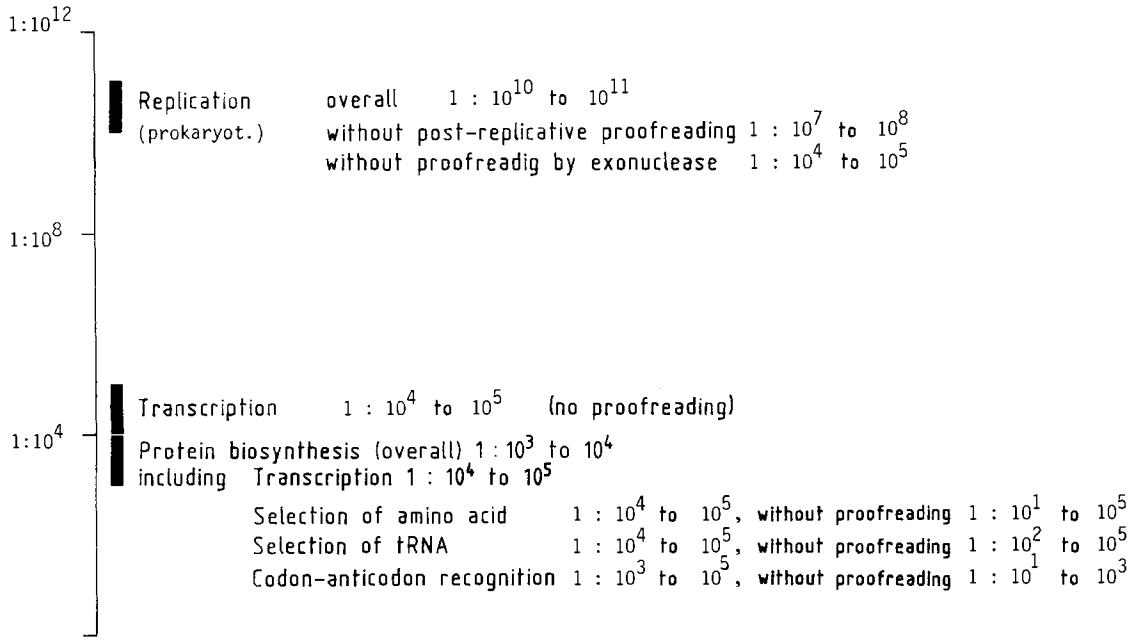


Fig. 10. Schematic display of average error rates of some reactions of replication and gene expression. The error rates given are averages of in-vitro measurements; error rates measured for a particular enzyme and a particular substrate may deviate considerably. The corresponding in-vivo error rates may also deviate considerably.

rates by a factor of ≈ 100 to 1000 may be ascribed to the proofreading, resulting in an overall error frequency for the peptide bond formation of $\approx 1:10^4$ to $1:10^5$.[157-159] The proofreading system of the ribosomes can be blocked by antibiotics, leading to increased error rates and a loss of GTP hydrolysis.[160] Furthermore, different ribosomal mutants exist which allow the binding of incorrect aminoacyl-tRNAs or inaccurate peptide bond formation to occur owing to mutations in ribosomal proteins.[161,162] However, nothing is known yet about the structural changes of the ribosomal proteins induced by the binding of antibiotics or by specific mutations.

7. Outlook on Solved and Unsolved Problems

In the absence of an efficient proofreading mechanism, DNA polymerases would work with error rates of $\approx 1:10^4$ to $1:10^5$; aminoacyl-tRNA synthetases, which have to discriminate between very similar amino acids, would work with error rates of $\approx 1:10^1$ to $1:10^2$, and the ribosomal protein synthesis apparatus would work with error rates of $\approx 1:10^1$ to $1:10^2$ (Fig. 10). The proofreading systems lower the error rates of prokaryotic DNA replication to $\approx 1:10^9$ to $1:10^{11}$, and in eukaryotic cells even to $\approx 1:10^{12}$. All reactions involved in the expression of the genetic information show error rates of $\approx 1:10^3$ to $1:10^5$. The overall error rate of protein biosynthesis, 1:3000, determined by *Loftfield*[11] in 1963, has been confirmed in different systems.[163-165] The latest data seem to indicate an additional dependence of the error rates on the speed of protein synthesis and on the codon used.[166-169]

In all cases examined so far, the energy-dependent correction systems lead to a reduction of error rates by a factor of ≈ 100 to 1000. If an even higher factor is necessary, an additional system, requiring further energy, has to be established, like the postreplicative proofreading of DNA replication.

The basic mechanisms accounting for the extremely high accuracy of DNA replication and protein biosynthesis were phenomenologically discovered, but there is still a lack of information about the chemistry of these mechanisms. Preliminary results of the X-ray analysis of a tryptic fragment of methionyl-tRNA synthetase *(E. coli)* and of tyrosyl-tRNA synthetase *(Bacillus stearothermophilus)* have been published.[170,171] In both structures, the shape of the amino acid binding site is clearly visible, but the carboxy terminus of nearly 100 amino acids is either missing or disordered in the electron density map. Although a high degree of homology in the amino acid binding sites of these aminoacyl-tRNA synthetases is present, the correlation of amino acids with the correction systems is still impossible. Deeper insight is expected from "site-directed mutagenesis" experiments,[172] such as those already carried out with tyrosyl-tRNA synthetase.[173] However, the tRNA binding site and the mechanism of transfer of the aminoacyl residue to the tRNA remain unclear due to the lack of the carboxy terminus in the X-ray structures.[174,175] For $tRNA^{Phe}$ and $tRNA^{Asp}$, however, the enzyme-binding regions have been characterized thoroughly.[176]

All experimental examinations and theoretical considerations of error rates of enzymes lead to the following principle: sufficient accuracy is not possible without energy input; infinite accuracy would require infinite amounts of energy. Data measured so far, showing an economic compromise between these extremes, correlate increasingly better with detailed mathematical models.[63,177-180] The flux of components, energy, and information has many characteristics of a system that works far from chemical equilibrium.[181]

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The Role of Hydrothermal Synthesis in Preparative Chemistry

By Albrecht Rabenau*

"Hydrothermal synthesis" usually refers to heterogeneous reactions in aqueous media above 100°C and 1 bar. The previously common distinction between hydrothermal conditions below and pneumatolytic conditions above the critical point is no longer made, since no discontinuities are observed upon exceeding the critical conditions. Under hydrothermal conditions, reactants otherwise difficult to dissolve go into solution as complexes, in whose formation water itself or very soluble "mineralizers" can participate. Thus, one can obtain the conditions of chemical transport reactions,[1] of which hydrothermal syntheses can be considered a special case. During recent decades in the geological sciences—in which the method is also historically rooted—it has received a strong impulse, whose effect on preparative solid state chemistry is discussed here.

1. Introduction

An excellent example of hydrothermal conditions, i.e. an aqueous medium over 100°C and 1 bar, is supplied by nature. Numerous minerals have formed under these circumstances. Through simulations in the laboratory, geologists and mineralogists have already been able to determine the conditions necessary for mineral formation and have thus contributed to the knowledge of geological processes. Even today hydrothermal investigations remain important in the field of geological sciences. In industry hydrothermal processes play a role in the concepts of hydrometallurgy, e.g. the classic Bayer process for the decomposition of bauxite. Hydrothermal conditions occur also in heating power stations and are the cause of many corrosion phenomena. The method was introduced into modern solid state research after World War II. Encouraged by the industrial preparation of quartz oscillator crystals, which was stimulated by *Nacken*, interest centered on the growth of extremely pure crystals with interesting physical properties and of sufficient size for the measurement and utilization of these properties. These requirements have left the unusual possibilities of this method for preparative solid state chemistry in the background, despite the great success of this concept in the past. Here the extreme requirements for purity, size, and perfection, e.g. those demanded in semiconductor physics, are avoided; i.e. the size necessary for a crystal structure determination, as a rule, lies orders of magnitude lower than that required for the measurement of other properties. Through the use of synchrotron radiation sources the volume necessary for crystal structure determinations has recently been lowered still further.[2] The present article deals with the use of hydrothermal synthesis in materials synthesis. It is shown that hydrothermal synthesis can be considered as a special case of chemical transport reactions. Thus, as a rule, a chemical reaction is combined with a transport process, as in SiO_2 transport:

$$SiO_{2(s)} + n\,H_2O_{(g)} \rightleftharpoons (SiO_2 \cdot n\,H_2O)_{(g)}$$

For sparingly soluble compounds with high melting points, a highly soluble transport substance ("mineralizer" in hydrothermal terminology) is added to increase the "solubility".

Hydrothermal synthesis, in contrast to conventional synthetic methods, offers a number of advantages, as can be shown by a few typical examples:

1. Compounds with elements in *oxidation states that are difficult to attain*, especially important for transition metal compounds, can be obtained in closed systems by hydrothermal synthesis. Ferromagnetic chromium(IV) oxide (Section 5) is produced by the oxidation of Cr_2O_3 with an excess of CrO_3 as follows:

$$Cr_2O_3 + CrO_3 \xrightarrow[H_2O]{350\,^\circ C,\ 440\ bar} 3\,CrO_2 \quad \text{and}$$

$$CrO_3 \xrightarrow[H_2O]{350\,^\circ C,\ 440\ bar} CrO_2 + 1/2\,O_2\uparrow$$

The decomposition of the excess CrO_3 leads to a build-up in the oxygen pressure, which stabilizes CrO_2 in relation to water at the high reaction temperature (Section 7). The product is produced in one step; it is very pure, since the only other reaction product is oxygen, and it forms uniform crystals.[3]

2. The hydrothermal method is also useful for the so-called *low-temperature phases*. Crystals of the zinc blende (γ)-phase of CuI (m.p. 605°C), important for its optical-electronic properties, can be obtained from solutions containing HI below the transformation temperature of 390°C. At these low temperatures chemical transport reactions through the gaseous phase are no longer a concern.[4]

3. *Metastable compounds*, such as the subiodides of tellurium Te_2I and β-TeI, are formed by the tempering of tellurium-rich probes in hydriodic acid *in a temperature gradient* of 265/280 or 192/198°C, respectively, and subsequent lowering of the temperature. Characteristic of the structure of the needle-forming crystals are infinite chains of tellurium atoms, which are obviously formed in the solution.[5] The syntheses of these low-temperature phases and metastable compounds can be conducted quite simply in glass or quartz glass ampoules. Numerous other examples are given in the text.

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In recent decades a series of review articles have appeared that treat hydrothermal synthesis chiefly from the point of view of the geological sciences or crystal growth,[6] through which the original works can be followed. In this article, original papers are cited only insofar as they relate directly to the theme at hand.

2. Historical Development

Dates important in the development of hydrothermal synthesis are listed in Table 1. Probably the first clue was found by *Schafhäutl*,[7] when he observed quartz microcrystals upon transformation of freshly precipitated silicic acid in a Papin's digestor. *Bunsen*[8a] described the use of thick-walled glass (or barometer) tubes; "*so that in liquids an easily measurable pressure of 100–150 atmospheres can be generated without any danger.*"[8b] In this way, through cooling an ammoniacal solution from 200°C and 15 bar, he obtained millimeter-long crystalline needles of $BaCO_3$ and $SrCO_3$.[8b] Thus, this experiment was the forerunner of visual hydrothermal synthesis, which has acquired still greater significance today. The introduction of hydrothermal synthesis in its modern form into geological science is ascribed to *de Sénarmont*.[9] As a method for laboratory investigations of the hydrothermal formation of minerals, it plays an important role to this day. For a reaction vessel he used sealed glass ampoules (Fig. 1), which were placed in

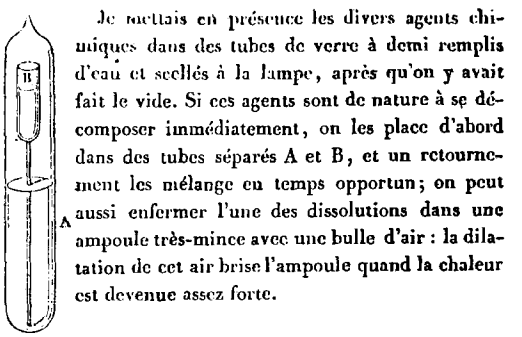


Fig. 1. Excerpt from the publication of *de Sénarmont* [9]. The ampoule B prevents the solutions from mixing with each other before A is sealed off.

an autoclave to avoid explosion. For autoclaves he used gun barrels (partially filled with water), which after being welded can be heated to a dull red glow. In spite of numerous breakdowns, he synthesized in this fashion a great number of oxide, carbonate, fluoride, sulfate, and sulfide minerals, including proustite, Ag_3AsS_3, which, because of its electronic properties, plays a role in modern solid state physics.

In the following years the method became widely used, especially in France.[10] By 1900 about 80 silicate minerals were synthesized in this way.[11] The use of sealed glass ampoules, which are heated in an autoclave to protect against explosions, was subsequently developed further by *Allen, Crenshaw*, and *Johnston*,[12] and by *Rau* and *Rabenau*,[13] and is especially suited for preparative work in neutral to acidic solutions. The introduction of corrosion-resisting and thermostable alloys was decisive in the development

Table 1. Hydrothermal Synthesis: Dates.

Year	Name	Arrangement	Comments	Ref.
1845	*Schafhäutl*	Papin's digestor	quartz microcrystals	[7]
1848	*Bunsen*	thick-walled glass tubes	carbonates; forerunner of the visual autoclaving	[8b]
1851	*de Sénarmont*	glass ampoules in autoclave	mineral carbonates, sulfates, sulfides, fluorides; founder of hydrothermal synthesis in geological sciences	[9]
1873	*von Chrustschoff*	noble metal lining	protection against corrosive solvents	[15]
1914	*Morey*	Morey-type autoclave	"closed" system; standard	[14]
1923	*Smith, Adams*	internally heated autoclave	very high pressures and temperatures: ≥ 10 kbar, ≥ 1400°C	[35a]
1943	*Nacken*	foundation for the industrial quartz growth	introduction of hydrothermal synthesis into solid state physics	[61]
1949	*Tuttle*	"cold seal" or test tube arrangement	external pressure regulation and measurement. More extensive working range than *Morey*. Standard	[16]
1973	*Capponi*	modified belt apparatus	extremely high pressures and temperatures: ≥ 100 kbar, ≥ 1500°C	[36a]

of apparatus for hydrothermal synthesis, and led to the version suggested by *Morey*,[14] which was to become the prototype of the so-called "closed" system. *von Chrustschoff*[15] had already introduced the autoclave lined with non-ferrous or noble metals (which in many cases cannot be dispensed with) by furnishing the autoclave with a galvanic gold lining. Besides the Morey principle, the "cold seal" technique[16] is a standard method today, while the techniques developed for the highest pressures and temperatures have remained confined to specialized laboratories. With the appearance of better materials, special techniques have been developed, such as those for the growth of large crystals (*Spezia*[17]). Around the turn of the century the focal point of activity shifted to Germany, Austria, and the USA, but remained the domain of geological scientists until the beginning of World War II.[18]

3. Water as a Reaction Medium

The physical and chemical properties of water and aqueous solutions in the pressure and temperature ranges required for hydrothermal syntheses are well known. These have been discussed in numerous review articles that have appeared in the last few decades, from which the original works are easily accessible.[19] This paper limits itself to a discussion of the properties which are important for the characterization of water and aqueous solutions. The pVT data for water up to 1000°C and 10 kbar are known accurately enough—to within 1% error.[19i, 19j] Figure 2 shows a temperature-density diagram of water, with pressure as a parameter. Within this range the ion product increases sharply with pressure and temperature. At 1000°C and 10 kbar, $-\log K_w = 7.85 \pm 0.3$, and there is evidence that water

at 150—200 kbar and 1000°C has a density of 1.7–1.9 g cm^{-3} and is completely dissociated into H_3O^+ and OH^-, behaving like a molten salt, isoelectronic with NH_4F or NaOH.[19i]

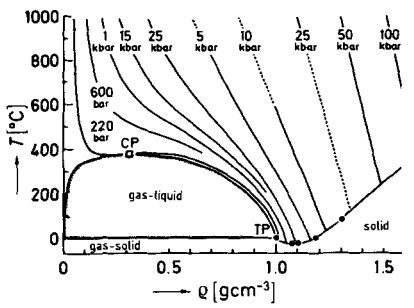


Fig. 2. Temperature-density diagram of water. The dotted isobars are interpolated. To maintain a density of 1 g·cm^{-3} at 500°C, a pressure of 9 kbar is required; at 1000°C, 20 kbar is required [19f]. CP and TP signify critial point and triple point, respectively.

The viscosity decreases with temperature, at 500°C and 100 bar amounting to 10% of its value under normal conditions.[19f] Hence, the mobility of molecules and ions in the supercritical range is much higher than under normal conditions.[19d] When using water as a solvent the dielectric constant is important. This decreases with rising temperature and increases with rising pressure, the temperature effect predominating[19e] (Fig. 3). The high dielectric constant typical of water is confined to a small region of rather low temperatures and high densities (pressures), although even in the supercritical region there is a large range where the dielectric constant is between 10 and 25–30.[19h,20] Electrolytes which are completely dissociated under normal conditions will therefore tend to associate with rising temperature,[21] and for a large number of substances this transition lies between 200 and 500°C.[22]

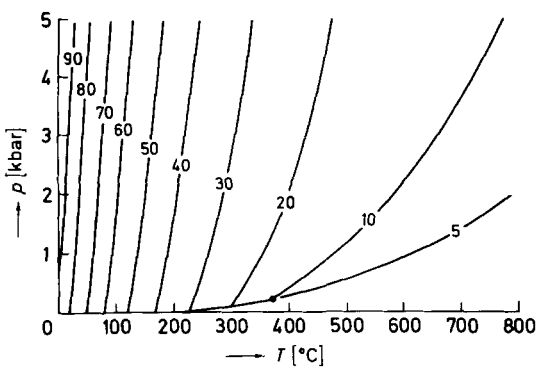


Fig. 3. Variation of the dielectric constant of water with temperature and pressure. The point • is the critical point of water [25].

Figure 4 shows a plot of the dissociation constants of NaBr. Under constant pressure they decrease with rising temperature, while with constant temperature they increase with rising density—and thus with pressure. Since in this region the ion product of water increases sharply,

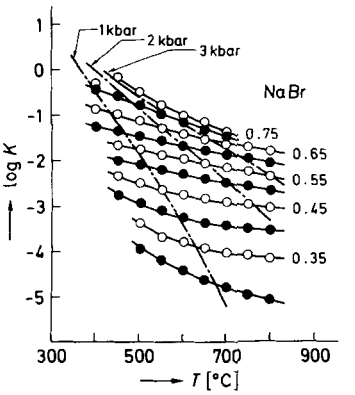


Fig. 4. Logarithm of the dissociation constant of NaBr as a function of temperature at constant density (g·cm^{-3}) or pressure [21]. The black circles denote the intensities 0.30–0.70.

hydrolytic reactions are favored. Thus, the equilibrium constant of the reaction

$$Cl^- + H_2O \rightleftharpoons HCl + OH^-$$

at 500°C and 2 kbar is about nine orders of magnitude greater than under normal conditions.[19j]

For experimental hydrothermal synthesis the PT diagram of water is important (Fig. 5). The pressure prevailing under working conditions is determined by the degree of fill, i.e. by the volume of the reaction vessel that was originally filled with solvent. With a degree of fill above 32%—0.32 g cm^{-3} is the critical density—the fluid-gas meniscus is curved upwards and the reaction vessel is completely filled with the fluid phase below the critical temperature of 374°C; e.g. with a degree of fill of 80% at 245°C. With a degree of fill below 32% the behavior is reversed, although such low degrees of fill are only seldom used, e.g. in dehydration processes (Section 4.3).

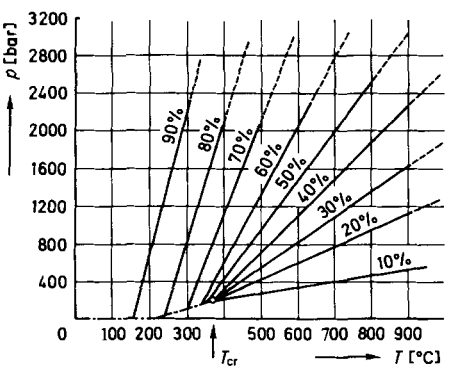


Fig. 5. The diagram relates to pure water, and shows pressure as a function of temperature, with the filling factor (degree of fill) of the autoclave as a parameter. The filling factor is usually between 50 and 80% and the pressure between 200 and 3000 bar. The chain-dotted line is the equilibrium line of vapor and liquid, T_{cr} is the critical temperature [6j].

Today, the concept of hydrothermal synthesis covers the entire region above room temperature and 1 bar. The distinction formerly made in geology between a hydrothermal regime below the critical temperature and a pneumatolytic one above it has been discarded, since scarcely any discontinuities in the behavior of the solution at the transition have been observed.[23a,23b] Moreover, the vapor pressure

over aqueous solutions is in general less than that over pure water, and the critical point is shifted to higher temperatures. With concentrated solutions the critical temperature can be several hundred degrees above that of pure water.[24] Because these critical temperatures are not known for the usually complex solutions at hand, one cannot distinguish between sub- and supercritical systems for reactions below 800 °C.

For hydrothermal reactions a minimum solubility of 2–5% for the least soluble component is necessary.[6d] Figure 6 shows an isobaric section of the pressure-temperature-concentration diagram of water and a very slightly soluble component A with a melting point much higher than that of ice. The region of conventional hydrothermal syntheses is shaded. The reason for the comparatively low temperature region arises from the limits imposed by the autoclaves. Under these conditions the required solubility in pure water is usually not obtained. Therefore, readily soluble components such as acids, bases, or other complex-forming substances are also added. These substances, known in geology as "mineralizers", form other, more soluble complexes than does pure water.[6d,i,o,s,25]

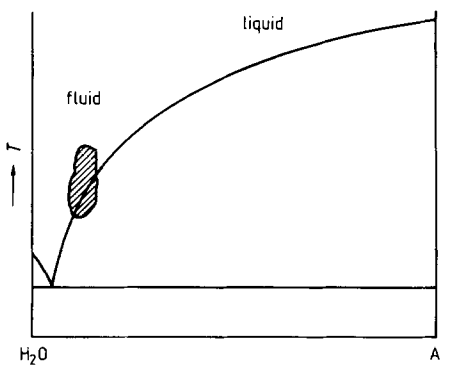


Fig. 6. Isobaric section from the pressure-temperature-concentration diagram of water and a very slightly soluble substance A above the critical pressure (schematic). The region of conventional hydrothermal synthesis is shown cross-hatched [6g].

Our current knowledge of the thermodynamic properties of aqueous solutions at high temperatures and pressures is summarized in review articles by *Helgeson*,[21] *Cobble*,[26a] and *Khodakovsky*;[26b] in the last-mentioned article numerous Russian contributions, often difficult to obtain, are treated.

4. Experimental

4.1. Autoclaves

To withstand the pressures involved in hydrothermal syntheses, the use of autoclaves is usually required. They serve to protect the reaction vessel; often the autoclave itself assumes the role of reaction vessel. A great number of papers exist concerning accessories for hydrothermal syntheses at high pressures and temperatures. The early summaries of *Eitel*[27a] and *Koenigsberger*[27b] contain many useful suggestions; the state of the art is summarized in a number of more recent reviews.[6c,l,p,r,28] Although there are numerous types of autoclaves for specialized uses, for preparative purposes they are limited to a few basic types.

The type first devised by *Morey*[14,29a] and subsequently further developed by him and his co-workers[29b] is the most suitable arrangement for work up to 400 °C and 400 bar because of its easy manipulation. The entire autoclave, including the joint, is placed within the oven; it can be operated with temperature gradients as well as isothermally. The autoclaves are best made of tool steel, with flat sealing surfaces (Fig. 7). This allows a complete lining with noble metals, so that the autoclave itself can serve as the reaction vessel. If the experiment is to be conducted with an ampoule inserted into the autoclave, then conical joints can also be used, which suffice up to 500 °C. Simple models for noble-metal linings have been described.[30] Appropriate arrangements for insertion of glass or quartz ampoules are dealt with in Section 9.

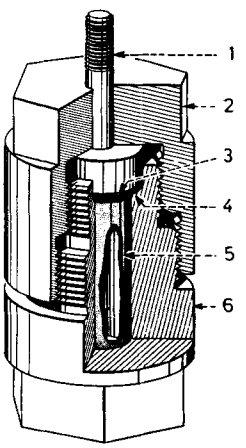


Fig. 7. Autoclave with flat sealing surface. 1) Upper part of the plunger-shaped lock (tools to withdraw the plunger have to be screwed on the thread); 2) hexagonal lock part, attached by wrench (for this the lower hexagonal head at the bottom of the autoclave is inserted into a stationary mount); 3) gasket ring; 4) bulging support on the reaction chamber for the gasket ring; 5) reaction chamber (diameter: 2.5 cm); 6) autoclave mantle [6p].

The simple arrangement of the Tuttle "cold seal" device[16] consists of a steel cylinder, into which an axial opening is drilled. The closed end is inserted in the oven, while the seal—in the simplest case with a conical joint—remains on the outside (hence the term "cold seal", although the temperature of the seal can still be several hundred °C). In order to ensure a tolerable temperature at the seal—and without making the autoclave too long—it can be provided with a water cooler.[6g,31] In contrast to the Morey arrangement, ampoules serve as reaction vessels and the pressure in the autoclave must be regulated externally, e.g. by a compressor system (Fig. 8). Autoclaves based on this principle,[6a,g,r,32,33] by utilizing Stellit 25, are operable up to 5000 bar at 750 °C, and also at somewhat higher temperatures with lower pressures. The use of René 41 enabled an extension of the working range (900 °C, 2 kbar). The names refer to cobalt- or nickel-based alloys.[6r,33] Commercial equipment[34a] for serial experiments up to 1100 °C and 3 kbar, with the name TZM-Apparatus, originate from an arrangement devised by *Williams*[34b] (Fig. 9).

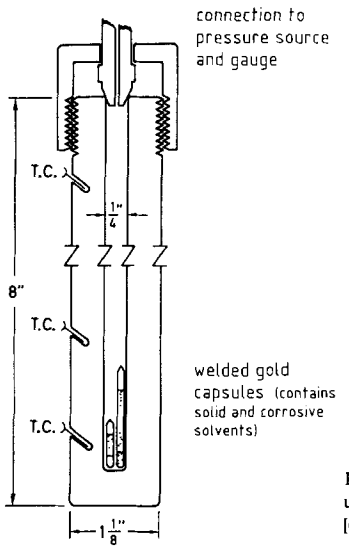


Fig. 8. "Cold seal" autoclave. The upper part lies outside the furnace [6g]. T.C.: thermoelement.

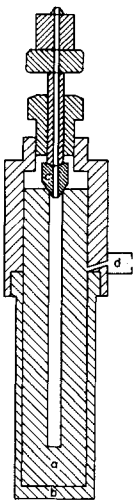


Fig. 9. TZM-autoclave with inert gas flushing. a) Autoclave body of TZM-(molybdenum) alloy; b) protective mantle of Inconel 750 (nickel alloy); c) conical seal; d) inlet vent for inert gas [6r].

For most practical purposes, the arrangements of *Morey* and *Tuttle* are satisfactory. More demanding requirements necessitate considerably greater experimental effort.

At higher temperatures it becomes necessary to cool the autoclave; therefore the heater, in the form of a small oven, is placed in the interior of a water-cooled steel jacket. One such arrangement was described by *Smyth* and *Adams* in 1923[35a] and was subsequently developed further by other workers.[35b] The pressure and temperature conditions which are thus achievable usually require a gas as the pressurizing medium. A detailed description of an internally heated autoclave, including pressurizer, was given by *Holloway*.[35c] Commercial devices with pressurizers, capable of being operated at 1400°C and 10 kbar, are available.[34a]

In recent years, the Belt technique has been used for conducting hydrothermal syntheses up to 1500°C and 100 kbar.[36a] Cylindrical platinum cells, 4 mm in diameter and 6 mm high, serve as the reaction vessels. Under these extreme conditions a series of new crystalline phases have been produced.[36b] A further variation using Teflon as a material was designed by *Herdtweck*[36c] for studies with hydrofluoric acid at 250°C and 30 kbar.

A great number of special autoclaves have been developed,[6m, u, 19e, 20, 37, 38] chiefly for investigations in physical chemistry. Generally, however, they play a minor role in preparative studies, and, as a rule, they necessitate considerable experimental effort.

4.2. Material Selection

The materials chosen for the vessel play an important role in hydrothermal reactions.[6c] Thus, the corrosive properties of the solution under the desired conditions, as well as the danger of undesirable contamination of the reaction product must be considered. Only in a few propitious cases, when using low-carbon steels, can the autoclave walls themselves serve as the reaction vessel. In NaOH-containing solutions this comes about through the formation of a protective surface layer of almost insoluble acmite, $NaFe(Si_2O_6)$. This is of importance for growing industrial quartz crystals, since in this environment the quality of the crystal is not affected. The liberation of hydrogen, associated with the formation of iron oxides, can lead to a build-up of hydrogen pressure (which must be remembered when opening the autoclave) as well as to hydrogen corrosion. As a rule, other materials must be considered. Unfortunately, the corrosion behavior of materials under hydrothermal conditions is not well known. Thus, it has been found that at 400°C copper and nickel in particular, and also titanium, vanadium, chromium, and iron are attacked by alkaline solutions. In the presence of solutions which contain sulfur, selenium, tellurium, arsenic, antimony, or bismuth, glass and quartz glass (in neutral or acidic medium), as well as graphite, titanium, and especially Teflon have been found suitable.[31] In the insertion of vessel materials a distinction is made between a lining and the so-called "floating insert".[6t] In the first case, the interior walls of the autoclave are completely lined with the vessel materials, generally a metal of sufficient ductility. Thus, the autoclave directly bears the pressure arising in the reactor chamber. The use of ampoules is required with nonductile materials such as glass, quartz glass, carbon, etc., and is also preferred with the insertion of metallic vessel materials. However, only a part of the autoclave volume is thereby used. Therefore, care must be taken that a large gradient between the pressure within the reaction container and that existing in the autoclave does not come about.

Borosilicate and quartz glasses are quite stable towards neutral and acidic solutions with the exception of hydrogen fluoride. This is also true for corrosive oxidizing media. The redox potential (Section 8) is hardly affected, and the danger of contamination by metallic impurities is slight. This last point plays an especially important role if the reaction product is to be subjected to physical measurements. Thus, in a neutral or acidic medium, glass or quartz glass are well-suited for hydrothermal syntheses, provided the pressure and temperature conditions permit it, and their possibilities have by no means been exhausted.

Glass and quartz glass have a great advantage in that, within a limited pressure and temperature range, the experiment can be directly observed. The maximum pressure

depends on the diameter of the ampoules, the strength of the walls, the temperature, and the mechanical properties of the glass being used.[39a] Thick-walled glass tubes can withstand a pressure of several hundred bars;[39b] this was exploited by *Bunsen*.[8a] The useful range for borosilicate glasses at higher temperatures is limited to 250–300°C. Quartz glass—despite its high softening point of around 1200°C—is only usable up to about 500°C, since at higher temperatures the walls are attacked. For visual autoclaving, safety precautions should be taken, such as working sufficiently below the bursting pressure—tabulated in [39b]—and the use of a safety shield of bulletproof glass or Plexiglass. For the observation of processes in the ampoules under specific temperature conditions, a suitable apparatus developed for the control of crystal growth can be used.[40a, 40b]

If the pressure-temperature range for visual hydrothermal synthesis is exceeded, the ampoule must be placed in an autoclave along with a pressure compensation, in order to prevent an explosion. Although the observability is thereby lost, the other advantages remain. An arrangement especially suited for preparative purposes, based on the method of *de Sénarmont*, was developed in the Philips Research Laboratory[13] and was used for the synthesis of a great number of previously unknown compounds[6j] (Section 9).

Experimental details of this method are described elsewhere.[41] Quartz glass ampoules for hydrothermal investigations are also described by *Speed* and *Filice*.[42] With the dimensions reported by the authors the experimental bursting points at 500°C lie above 300 bar. Although developed for batch experiments—ten or more ampoules heated simultaneously under the same conditions in the oven—the ampoules should also be suitable for visual hydrothermal synthesis. The pressure characteristics for sealed quartz glass ampoules up to 1000°C are reported by *Holland*.[43]

From the standpoint of behavior towards corrosion, Teflon is the ideal container material.[6r] Besides its resistance to hydrofluoric acid, Teflon is, in contrast to glass and quartz glass, also stable in alkaline media. Unfortunately, Teflon is only usable within a limited pressure-temperature range. Since it tends to be porous, only isostatically treated, potentially pore-free material (PTFE) can be used. Above 150°C the creep behavior becomes a problem.[44a] Autoclaves with Teflon inserts[44b] have found numerous uses as digestion bombs and are commercially available: they can be used at 200°C and 200 bar.[44c] There are units based on the same principle capable of operating at 275°C and 350 bar.[44a] Temperatures of 300–350°C can be reached if Teflon is used as a floating insert.[6m, 31, 45] Teflon seals are also used in combination with metallic inserts.[37, 46]

Inserts of pyrolytic graphite should prove useful for sulfur-containing solutions.[31] Glassy carbon[47a, 47b] has shown even better properties (permeability, etc.).[47c]

The choice of metal for the reaction vessel depends primarily upon its compatibility with the reactions being studied and, under some circumstances, upon its permeability towards hydrogen (platinum and silver-palladium alloys). Ductile metals are suitable for lining autoclaves, with no problems of mechanical stability arising. This use is limited to autoclaves of the Morey type (Section 4.1), in which the seal can also be lined. Thus, a tight seal is obtained through the cold weld effect. More common is the use of floating inserts, either as a closed crucible—in which the autoclave lid can be the cover—or as an ampoule. In both cases the possibility of a pressure gradient between the interior and the exterior must be considered; such a gradient can lead to explosion of the reaction vessel. In the case of ampoules, a simple bend is sufficient only in cases where the escape of just the solid components is to be prevented; usually the volatile constituents can equalize themselves. Complete sealing of the ampoule requires material-specific practice. Welding equipment and techniques have been described.[33] In many cases the internal pressure arising from the filling causes problems. This can be minimized by thorough freezing during the welding process[48a] or can be eliminated through the use of the cold weld technique.[48b] Ampoules of aluminum and copper can be sealed relatively simply by this last method. In addition to the works cited in the previous sections concerning the use of metals, mention should also be made of titanium,[37, 45, 46] platinum,[6c, 46] silver,[6c] and gold.[49]

4.3. Methods of Hydrothermal Synthesis

The methods developed in the last couple of decades for hydrothermal synthesis served chiefly for single crystal growth, but they are also of significance regarding preparative aspects. They are dealt with in several articles,[6m, t, u] wherein it is stated that hydrothermal crystal growth is a special type of chemical transport reaction,[1] the principles of which are immediately perceivable.

Isothermal methods include all arrangements in which no temperature gradient is deliberately introduced. This method is usually adequate for preparative purposes which do not require great transport efficiency and is of simple experimental application.

In the standard method for crystal growth, the *temperature gradient method*, the reaction products are transported from a region of higher solubility to one of lower solubility, usually from hot to cold. In the case of retrograde solubility the direction of transport is reversed, as for instance with elements.[50] A reverse in the direction of transport upon change of solvent has also been observed, as in the transport of ZrO_2 and TiO_2 in NaF (or KF) compared to that in NH_4F.[51] Since a temperature gradient leads to the separation of the reaction products, which facilitates their isolation, this method is also quite suitable for preparative work. It has been observed that certain—metastable—phases are formed only in temperature gradients.[5, 52] An arrangement for extreme temperature differentials[6t, 53] and for a spatial separation of the solution zones[54] has been described.

The *temperature-decrease method* is a variation of the temperature gradient method. The desired phase (saturated at a higher temperature) is separated from solution upon cooling. It is used primarily in crystal growth, but it is also useful, for example, if a modification stable only in a certain temperature range is desired, as in the formation of γ-CuI.[4a, 55]

Usually, the autoclaves are set up vertically or slightly inclined. In the case of retrograde solubility a *horizontal arrangement* is preferred. Also, in this arrangement the reaction products can be repeatedly transported from one zone into another, resulting in a purification effect.[51a] A further application exists in cases in which the starting materials are placed in separate zones. In hydrothermal synthesis reactions of solid starting materials take place by way of a fluid medium, which requires a degree of solubility on the part of the reactants. If the substances participating in the reaction exhibit strikingly different solubilities, it is preferable to separate these and thus to adjust the parameters *(separated charge method)*. Figure 10 shows the arrangement that was used for the preparation of ferrite from the binary oxides.[6c, 56] For the formation of $PbTiO_3$,

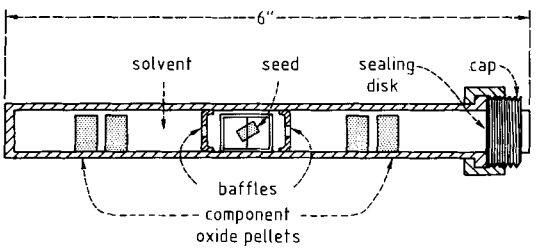


Fig. 10. Horizontal arrangement with separation of initial product. The reaction product—here on a crystallization nucleus—is formed through reaction of the diffusing species [6c].

TiO_2 was placed in the lower (hotter) part of the autoclave and PbO in the upper part.[51a, 57] $PbTiO_3$ is formed in the upper section. Compounds having the garnet structure were also synthesized as in Figure 10; Y_2O_3 was placed in the upper section, and Al_2O_3 (sapphire) was placed in the lower section. The resulting garnet (yttrium-aluminum garnet, YAG) forms between the two zones.[58] A relatively new variant is the so-called "two zone process", in which the starting materials are placed in different solvents in independent solution zones. This method was developed for the preparation of Sb_2O_4,[59] where Sb occurs in the +3 and +5 oxidation states (Fig. 11).[6s, t] Besides Sb_2O_4, the compounds ABO_4 ($A = Sb^{III}$, Bi^{III}; $B = Nb^{V}$, Ta^{V}, Sb^{V}) were obtained.[53, 60a, 60b] $Pb_7S_2Br_{10}$ was prepared analogously; the starting materials $PbBr_2$ and PbS were placed in different concentrations of HBr.[60c]

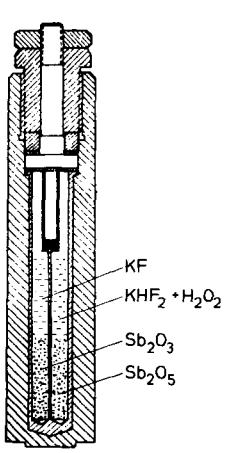


Fig. 11. Two-section liner for separation of starting materials in different solvents [6s, t].

A saturated solution of a *metastable phase* under given hydrothermal conditions is supersaturated relative to the stable phase. This can lead to the conversion of the metastable phase into the phase stable under the experimental conditions. For kinetic reasons, the presence of a seed crystal of the latter phase may be necessary. Examples are the transformation of quartz glass into quartz[61a] and the formation of α-Al_2O_3 (sapphire) from $Al(OH)_3$ (gibbsite) in temperature gradients,[62] whereby hydroxides are generally used for the synthesis of oxides. Besides crystal growth from a seed crystal of the same material, as is frequently used—the industrial preparation of quartz is an example—*deposition on another substrate* can be used to force the formation of certain compounds or crystal structures. *Roy* and *Theokritoff* have obtained cm-size GeO_2 crystals below 200°C on a quartz base,[63] while *Kolb* and *Laudise*[64] have prepared magnetic garnets on $Gd_3Ga_5O_{12}$ starting from $NaFeO_2$ and the corresponding rare earth hydroxides.

Doping the solution or starting material *with isotopes* has been used for elucidating reaction mechanisms, as with ^{18}O- and ^{17}O-enriched water in quartz preparation,[65a] or for the preparation of deuterated probes for structure determinations (ScOOD).[65b]

In *hydrothermal dehydration*, water is withdrawn from the hydrothermal solution through a spatially separated metal having a higher oxidation potential than that of hydrogen. Magnesium and zinc, which bring about the dehydration through formation of the corresponding hydroxide or oxide and hydrogen, have been used for this purpose. In such cases the degree of fill should be as low as possible (cf. Section 3). The method was used in the synthesis of chrysolite fibers, $Mg_6(OH)_8Si_4O_{10}$ (fibrous serpentine), from $Mg(OH)_2$, $MgBr_2$, and SiO_2,[66a] and of potassium hexatitanate, $K_2Ti_6O_{13}$, from TiO_2 in KOH.[66b]

A *sinter reaction* is the reaction of a metal powder with water under hydrothermal conditions. A sintering process is associated with the formation of the corresponding oxide,[67] and, just as in the dehydration process, hydrogen is liberated. Compact Cr_2O_3[68a] and ZrO_2[68b, c] have been formed this way, as well as brookite, TiO_2.[68d] Single crystals of magnetite, Fe_3O_4,[68e] and of iron titanium bronzes from TiO_2 and Fe,[68f] have been synthesized by this process.

5. Hydrothermal Synthesis in Industry

The most significant use of hydrothermal crystal growth is the industrial preparation of quartz crystals for oscillators (Fig. 12). Following the works of *Spezia*,[17] who first obtained crystals up to a cubic centimeter in size, *Nacken* et al. developed (during the second World War) processes serviceable on an industrial scale.[61] These works were stimulated by the shortage of natural crystals from Brazil. Accordingly, after the war commercial installations were developed, first in the USA and later in other countries. The crystals were grown in alkaline media in a temperature gradient of about 400° to 380°C and at a pressure of 1 kbar. In 1982, world production amounted to 600–700 tons, chiefly in the USA, USSR, Japan, France, and Czechoslovakia.

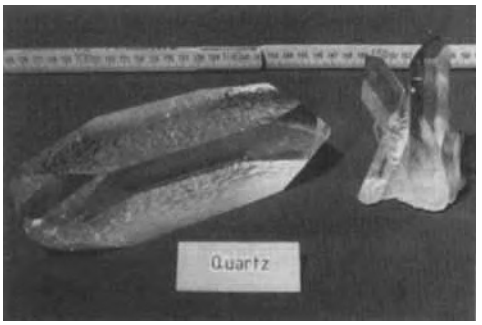


Fig. 12. Synthetic quartz crystal (left), ca. 1 kg, with natural quartz (right) (*R. Diehl*, Freiburg).

Hydrothermal crystal growth plays a certain role in the production of artificial gems,[69a-d] e.g. the quartz variants amethyst (+Fe and irradiation), citron ($+Fe^{3+}$), smoky quartz (+Al and irradiation), sapphire (or ruby), and emerald.[70] Because of the high cost of hydrothermal processes, only the production of emeralds has attained significance; synthetic emeralds, are produced almost without exception, by hydrothermal growth at 500–600°C and 1 kbar.[71] The cost of optical-quality synthetic emeralds is ca. \$300/g, compared to ca. \$7000–\$14000/g for the natural crystal.

Another area of application for hydrothermal crystal preparation lies in the field of magnetic oxides for information storage. Because of its favorable magnetic properties, chromium(IV) oxide has been employed for several years in magnetic tapes.[72] Starting compounds with tri- or hexavalent chromium are converted in a hydrothermal process at 300–400°C and 50–800 bar into microcrystalline needles of CrO_2.[3,73] Another large group of oxides useful for magnetic recordings such as γ-Fe_2O_3,[74] ferrites and garnets of the rare earths,[75] and barium ferrite, $BaFe_{12}O_{19}$,[76] can also be obtained by hydrothermal routes.

Hydrothermal processes have also found a place in chemical industrial processing.[19g,77a] Synthetic zeolites, used in great quantities as molecular sieves, require temperatures above 100°C in a closed hydrothermal system for their crystallization, especially the silicate-rich variants such as mordenite.[78] The processes employed for the pressure-decomposition of ores are listed under the designation "hydrometallurgy".[6b,77]

6. Nonaqueous Solvents

Besides water—the most important solvatothermal reaction medium for transformations above the boiling point and 1 bar—there are a great number of nonaqueous solvents which, in principle, also come into consideration for preparative purposes.[79a,79b] As long as a century ago *Hannay* and *Hogarth*[80] observed that an alcoholic solution of cobalt chloride does not change from its characteristic blue color above the critical point and thus they demonstrated the solubility of inorganic substances in a fluid medium of nonaqueous systems.[81] Although nonaqueous solvents (with the exception of ammonia) have until now attained little significance for solvatothermal transformations[6f] (Table 2), they can be considered in cases in which the required solubility cannot be reached in an aqueous medium, in which the solvent itself participates in the synthesis, and, most importantly, in cases where the reaction product reacts with water. Critical temperatures and pressures are often lower than those of water (Table 3). Formic acid is a limiting case, decomposing at elevated temperatures to CO and H_2O (or CO_2 and H_2). In this reducing and CO_2-rich reaction medium numerous oxides and carbonates are synthesized.[82a,82b] For nonaqueous solvents, arrangements with glass or quartz glass as reaction vessels are especially suitable (Section 4.2).

Table 2. Syntheses in Nonaqueous Solvents.

Solvent	Examples	Ref.
NH_3	nitrides, imides, amides, CsOH, Cs_2Se_2	[86]
HF	$MO_{3-x}F_x$ (M = Mo, W)	[119c]
HCl, HBr	$AuTe_2Cl$, AuSeCl, AuSeBr	[116]
	$Mo_3S_7Cl_4$	[141b]
Br_2	SbSBr, SbSeBr, BiSBr, BiSeBr	[124]
	$MoOBr_3$	[141b]
S_2Cl_2	MoS_2Cl_3, $Mo_3S_7Cl_4$	[141]
S_2Br_2	$Mo_3S_7Br_4$	[141b]
$SeBr_2$	SbSeBr, BiSeBr	[124]
$H_2S+(C_2H_5)_3-NHCl$	β-Ag_2S	[125]
C_2H_5OH	SbI_3, BiI_3	[60b]
CS_2	monoclinic Se (metastable mod.)	[110]
CCl_4	$SeCl_4$, $TeCl_4$	[60b]
C_6H_6	hexagonal Se	[60b]
CH_3NH_2	CH_3NHLi	[126]

Table 3. Critical data for selected solvents.

Solvent	Critical temperature [°C]	Critical pressure [bar]
Water	374.1	221.2
Ammonia	132.3	111
Chlorine	144	77.1
Hydrogen chloride	51.4	83.2
Carbon dioxide	31.3	73
Sulfur dioxide	157.8	78.7
Carbon disulfide	279	79
Hydrogen sulfide	100.4	90.1
Ethanol	243	63.8
Methylamine	156.9	40.7
Methanol	240	81
Formic acid	308	—

6.1. Ammonothermal Synthesis

While chemical reactions in liquid ammonia have long had their place in preparative chemistry,[83] investigations concerning such reactions at high pressures were first reported in the sixties,[84] as also was the first review article concerning special apparatus and the preparation of a series of amides, imides, and nitrides.[85] Although ammonia has a low dielectric constant with respect to water (Fig. 13), it can be considered, especially at high pressures, as a polar solvent. The rapid development of this method and nearly all the contributions in this field are due essentially to one research group, whose results are summarized in a review by *Jacobs* and *Schmid*, which appeared in 1982.[86]

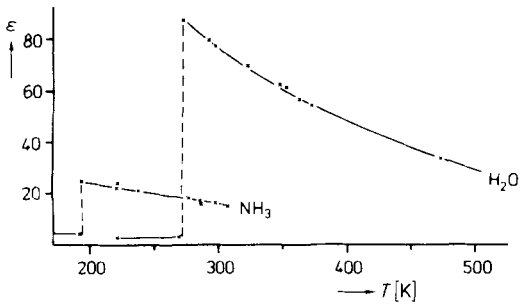


Fig. 13. ε-T Diagram for ammonia and water [86].

Two systems are in use; one is a closed system, in which the autoclave of high-alloyed steel (Vacumelt ATS 340) serves as the reaction-vessel. In this, pressures up to 6 kbar and temperatures up to 500 °C can be attained. The other system works with an adjustable nitrogen counter-pressure. Ampoules of Supremaxglas serve as reaction-vessels which are operable up to 200 °C and 2.8 kbar, or welded gold or silver ampoules, which are also operable at 2.8 kbar but with higher temperatures. With the adjustable counter-pressure the pressure in the ampoule can be compensated. Especially important and of general interest for preparative purposes are the detailed instructions concerning manipulation of the often extremely moisture- or oxygen-sensitive substances. Teflon-lined autoclaves have also been found useful for work up to 200 °C and 1 kbar in liquid ammonia.[87]

In the following section the broad preparative spectrum of the method will be demonstrated; original works will be cited only in cases which are not contained in Ref. [86].

Compounds which arise through reaction with the solvent include a great number of binary and ternary amides, including deuterated forms, such as $RbND_2$, $Mg(NH_2)_2$, $Li_3Na(NH_2)_4$,[88a] $RbBa(NH_2)_3$,[88b] $Rb_2[Mg(NH_2)_4]$,[88c] $Rb_3Y(NH_2)_6$,[88d] $Cs_2[Mg(NH_2)_4]$,[88e] and $Cs_2(NH_2)N_3$.[88f] There are also imides and nitrides such as BaNH, $Ce_3(NH)_3N$, and EuN. The size of the crystals is in many cases sufficient for a structure determination. A beautiful example of transport inversion is the preparation of Mn_3N_2 with iodine (hot→cold) or potassium (cold→hot).[88g]

Hydroxides and hydrogen sulfides are formed without participation of the solvent; in this way they were for the first time obtained free of water. The crystals are in a form suitable for structure determinations.

$$CsOH \cdot H_2O + CsNH_2 \rightleftharpoons 2\,CsOH + NH_3$$
$$CsOH \cdot H_2O + Cs \rightleftharpoons 2\,CsOH + 1/2\,H_2$$

Potassium hydrogen sulfide was obtained by reaction of KNH_2 with H_2S. The extremely water-sensitive chalcogenides such as Cs_2Se and polychalcogenides such Rb_2Te_5[89] can be synthesized in an analogous way.

7. *Eh*-pH Diagrams

Reactions in which elements that are capable of appearing in various oxidation states participate are dependent on the oxidation potential of the solution and also frequently simultaneously on the pH value. So-called *Eh*-pH diagrams,[6m,o,90] in which the reaction equilibria are plotted in relation to the redox potential and the pH,[91] can give considerable insight into these relationships. These diagrams were first devised in 1928 by *Clark* and subsequently have found a limited use in analytical chemistry.[92] They acquired significance in their application to corrosion problems; this was essentially due to the work of *Pourbaix*[93] and thus in the literature they are occasionally designated as Pourbaix diagrams. While *Eh*-pH diagrams are used increasingly in the geological sciences (for hydrothermal mineral syntheses), they have hardly been introduced into preparative chemistry. The construction of such diagrams is discussed in numerous papers.[23b,94]

The basic principles will be described with the Fe-H_2O system as an example. In Figure 14a the dash-and-dot lines enclose the region of thermodynamic stability for water. Outside this region, liberation of oxygen (or hydrogen) occurs. An increase in $p(O_2)$ or $p(H_2)$ by a power of ten displaces the lines by about 0.03 volts upwards or downwards, respectively. In practice the region for hydrothermal synthesis is not limited to this range, since the decomposition of water often proceeds very slowly and an overvoltage of up to 0.5 volts is observed. Three types of lines occur. Reactions without a change of oxidation number, such as the $Fe^{3+}(aq)/Fe(OH)_3$ equilibrium, lead to vertical lines; those which proceed independently of the pH, such as $Fe^{2+}(aq)/Fe^{3+}(aq)$, lead to horizontal lines. A depend-

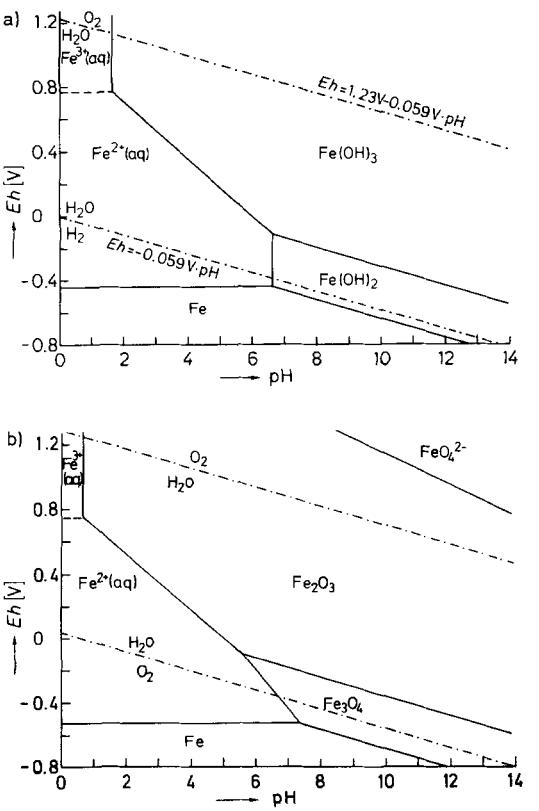


Fig. 14. Fe-H_2O system: a) *Eh*-pH diagram of the ions and hydroxides. The dash-and-dot lines correspond to the equilibrium between water and oxygen (or hydrogen). For the ions the activity is set at 1. $T=25$ °C, $p=1$ bar; b) *Eh*-pH diagram in thermodynamic equilibrium. Parameters as in a) [92a].

Table 4. *Eh*-pH-Diagrams above room temperature.

System	Range [°C]	Ref.	System	Range [°C]	Ref.
$B-H_2O$	25-300	[95]	$Fe-S-H_2O$	25-300	[95]
$C-H_2O$	25-300	[95]	$Fe-Cl-H_2O$	25-300	[95]
$Pb-S-H_2O$	25-300	[127]	$Ni-H_2O$	25-300	[95]
	0-300	[128]	$Ni-S-H_2O$	25-300	[95]
$N-H_2O$	25-300	[95]	$Ni-Cl-H_2O$	25-300	[95]
$S-H_2O$	25-300	[95]	$Cu-H_2O$	25-300	[95]
$Te-H_2O$	0-300	[103b]	$Cu-S-H_2O$	25-300	[95]
$Ti-H_2O$	25-300	[95]	$Ag-H_2O$	25-300	[131]
$Ti-F-H_2O$	25-300	[95]	$Ag-H_2O-NH_3-H_2SO_4$	25-250	[132]
$Zr-H_2O$	25-300	[95]	$Zn-S-H_2O$	25-300	[127]
$Cr-H_2O$	25-300	[95]	$Zn-Se-H_2O$	25-300	[127]
$Mn-H_2O$	25-300	[95, 129]	$Cd-S-H_2O$	25-300	[127]
$Mn-S-H_2O$	25-300	[127]		0-300	[128]
$Fe-H_2O$	25-300	[95]			
	25-200	[130]			

ence of the reaction potential on the pH value occurs when hydrogen ions participate in the reaction, e.g.

$$Fe^{2+} + 3\,H_2O \rightleftharpoons Fe(OH)_3 + 3\,H^+ + e^-$$

($Eh = 1.47\,V - 0.177\,V\ pH$).

The familiar situation, shown in Figure 14a, of the precipitation of hydroxides does not correspond to the thermodynamic equilibrium, according to which only hematite (Fe_2O_3) and magnetite (Fe_3O_4) occur (Fig. 14b). While the necessary thermodynamic data for the situation at room temperature are tabulated, necessary experimental data for hydrothermal synthesis at higher temperatures is scarce.[26a] The required data for the free energy of reaction (ΔG) is obtained by extrapolation of the room temperature data using entropy and heat capacity functions.[26a, 95] ΔG is related to *Eh* through the equation $\Delta G = nFEh$ (where F is the Faraday constant). Numerous element-H_2O systems have been calculated (and tabulated) in this way, mostly with the aid of computer programs (Table 4). As shown in Figures 15a and 15b for the $Mn-H_2O$ system, the shift in the equilibrium with temperature is considerable, and at the expense of the lower oxidation states of manganese. Despite the uncertainty in the extrapolated data they are useful for experimental formulations, since they show the "trend" and also allude to kinetic aspects.[96] Examples in use are the $Sb-H_2O$[59, 97] and $A^V-B^{VI}-C^{VII}-H_2O$[45] systems. *Eh*-pH diagrams of more complicated systems, e.g. the region of existence of SbSI in the $Sb-S-I-H_2O$ system (Fig. 16), are obtained by superposition of binary data. With the decrease in effort of computing the *Eh*-pH diagrams, their use should become well-established in preparative chemistry just as it has in the geological sciences. For many-component systems and at higher temperatures, the use of diagrams in which the logarithm of the oxygen activity is plotted against the pH has proven effective. These $\log a(O_2)$-pH diagrams are topologically identical to *Eh*-pH diagrams, but more comprehensible.[23b, 98]

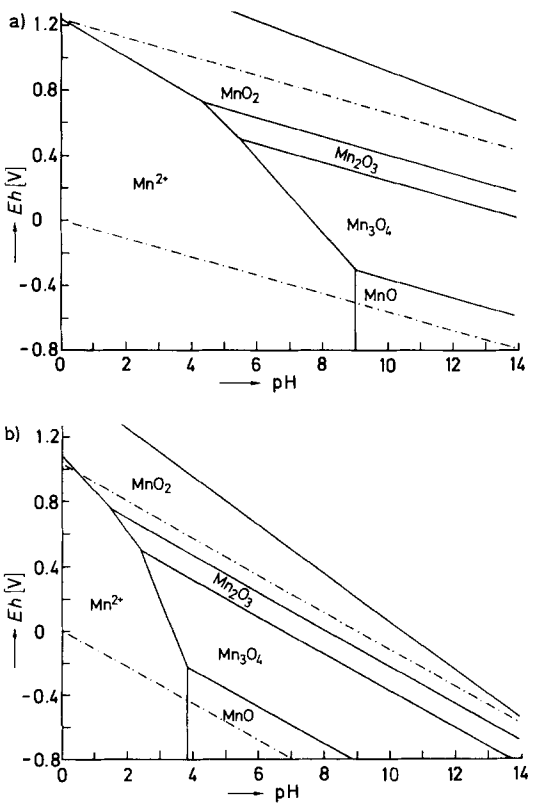


Fig. 15. *Eh*-pH diagram of the $Mn-H_2O$ system at a) 25°C; b) 300°C [129].

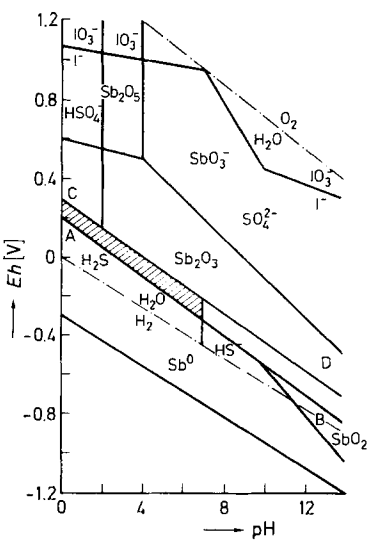


Fig. 16. *Eh*-pH diagram of the $Sb-S-I-H_2O$ system, with the region of existence for SbSI (shaded) [45].

8. Oxidation Potentials and Buffer Systems

From the preceding section it is clear that the oxidation potential plays an important role in hydrothermal syntheses and therefore warrants further discussion.[6d, h, m, o, u] The redox conditions are determined by the interactions between the reaction vessel—autoclave walls or ampoules—the solvent, and the solid reaction phases. Thus, reducing conditions prevail, largely by contact with metals, and even more so the higher the temperature.[99] Nor is the problem solved over longer periods by employing noble metals, since even silver and gold show some (albeit slight) permeability to hydrogen. For the stabilization of lower oxidation states, the reaction of the participating metal with water is called upon, e.g. vanadium for $VO(OH)_2$[100] and iron for magnetite, Fe_3O_4,[68e] iron titanium bronze,[68f] and fayalite, Fe_2SiO_4.[101] Besides the use of formic acid as

a reducing additive for Fe_3O_4,[102] a great number of oxidants have also been used as additives for achieving oxidizing conditions. While this presents no problem in vessels of inert materials such as glass, quartz glass, or Teflon, the capacity of the oxidants in metallic surroundings gradually becomes exhausted. Among those used are: $HClO_4$ for TbO_2,[103a] RhO_2 and PtO_2,[36b] TeO_2;[103b] $KClO_3$ for oxides $A^{VI}B_2^{III}O_6$;[103c] HNO_3 for PrO_2;[103d] $Ce(NO_3)_3$ for CeO_2;[103d] Cl_2 and Br_2 for complexes with trivalent gold as a transport agent;[50b] O_2 (or H_2O_2) for $BaMnO_3$,[103e] $SbTaO_4$, and $SbNbO_4$.[103f]

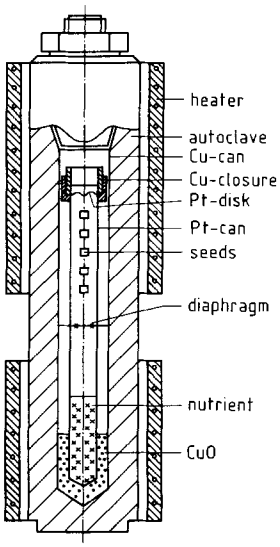


Fig. 17. Arrangement for growth of magnetic $REFe^{III}O_3$ crystals. The CuO buffer, separated from the reaction space by a hydrogen-permeable Pt partition prevents the formation of Fe^{2+} [75].

For the production of Fe^{2+}-free magnetic oxides of the type $REFeO_3$ (RE = rare earth), hydrogen evolved in a two-zone arrangement (Fig. 17) is trapped by CuO with formation of Cu_2O and H_2O.[75] This is an example for a solid state buffer system that was introduced by *Eugster* in 1957 for hydrothermal mineral synthesis[104a] and since then has been further developed in the geological sciences.[22, 104b-d] It was next a question of oxygen buffers, which could fix the oxygen potential at a given temperature through the equilibrium of two solid phases (Table 5). Thus, the buffer is separated from the reaction mixture by a semipermeable wall, which is permeable to hydrogen (Fig. 18). The reactants are placed in an ampoule of Pt or Ag—Pd alloy,[104e] while the buffer is arranged in a surrounding ampoule of gold or silver. Hydrogen diffuses through the wall of the inner ampoule, where the constant $f(H_2)$ is maintained, as long as the capacity of the buffer is not exhausted. Reactions in which O_2, H_2, or H_2O participate can be controlled with these buffer systems. The limitations of this method lie in the limited buffer capacity and also in the temperatures required to attain equilibrium within a reasonable length of time. The length of the experiment is limited, since as mentioned previously gold and silver are not completely impermeable to hydrogen. For these reasons the method is rarely employed for lengthy crystal-growth processes. It should, however, be suitable for problems of solid state chemistry, similarly as it is for mineral syntheses.

Table 5. Buffers.

Oxygen (H_2O)	Acid - Base
MnO - Mn_3O_4 [33, 133]	Ag - AgCl [105, 135]
Mn_3O_4 - Mn_2O_3 [33]	Ag - AgBr [136]
Mn_2O_3 - MnO_2 [33]	Ag - AgI [136]
Fe - $Fe_{1-x}O$ [33, 134]	Nitrogen (NH_3)
Fe - Fe_3O_4 [33, 134]	Cr - CrN [137]
Fe_3O_4 - Fe_2O_3 [133, 134]	Sulfur (H_2S)
Co - CoO [133]	Ag - Ag_2S [104c]
Ni - NiO [33, 133, 134]	$Fe_{1-x}S$ - FeS_2 [33, 104c]
Cu - Cu_2O [33]	
Fluorine (HF)	
$CaSiO_3 + 2HF \rightleftharpoons CaF_2 + SiO_2 + H_2O$ [138]	
$CaAl_2Si_2O_8 + 2HF \rightleftharpoons CaF_2 + Al_2SiO_5 + SiO_2 + H_2O$ [138]	

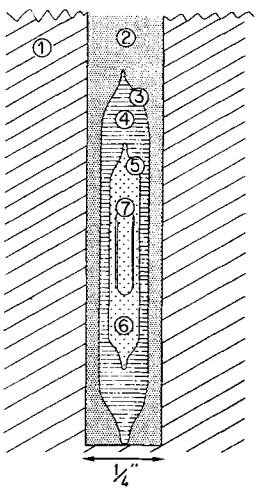


Fig. 18. Oxygen buffer assembly. 1) Pressure vessel; 2) pressure medium (H_2O); 3) sealed gold tube; 4) oxygen buffer; 5) sealed platinum tube; 6) charge. The open silver crucible 7 protects the charge before contact with the Pt wall [104b].

Adjustment of the redox potential alone, however, is not sufficient in many cases and additional buffer systems are required, such as acid/base buffers for pH-dependent reactions. The Ag-AgCl pair has proven useful as such a buffer,[105] and Figure 19 shows one such combined buffer system. Because of the low solubility of Ag under these reaction conditions, this buffer does not need to be separated from the reaction mixture. A series of additional buf-

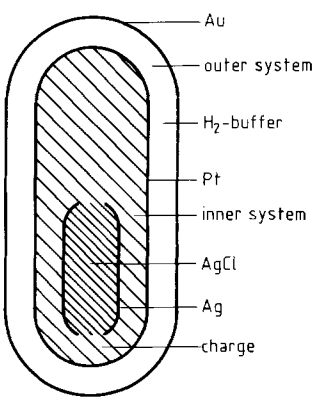


Fig. 19. Combined buffer system to maintain $f(O_2)$ and pH. The pH buffer consists of a mixture of Ag and AgCl in a silver foil [135].

fer systems is listed in Table 5. A detailed description of the buffer techniques is given by *Huebner*.[33] One disadvantage of the buffer systems is that the fugacity of, say, oxygen can only be altered gradually, and lower $f(O_2)$ values are especially difficult to maintain. *Shaw*[106] used an experimental arrangement described by *Tuttle* (Section 4.1), in which the autoclave interior is separated via a wall of $Pd_{30}Ag_{70}$, and on one side of which is hydrogen and on the other a hydrogen/argon mixture. In the H_2/Ar region the $f(H_2)$ can be adjusted exactly. Another suggestion by *Carapezza*[107] makes use of the fact that in solid solutions of oxides the $f(O_2)$ can change over a large range with composition. In the example cited, a series of (Ni,Mg)O-mixed crystals was employed. For the control of $f(S_2)$ in hydrothermal sulfide systems the work of *Barnes* should be noted,[108] along with the methods for its determination by *Kulonin*.[109]

9. Applications

Although crystal growth has hitherto stood in the foreground in preparative applications outside of the geological sciences, today several hundred compounds—excluding mineral syntheses—have been obtained by solvatothermal methods (Table 6). The following considerations should underscore the merits of the method for preparative purposes in the light of recent works.

Table 6. Reviews.

Author	Year	Comments	Ref.
Christensen	1969	oxides, hydroxides, no silicates	[6h]
Rooymans	1972	no silicates, no minerals	[6i]
Wilke	1973	Tab. 2.3.-6.: silicates Tab. 2.3.-7.: other compounds	[6p]
Demianets, Lobachev	1980	RE germanates	[139]
Demianets, Lobachev	1981	no silicates, crystals ≥ 1 mm	[6t]

Elements. Numerous elements are obtained as single crystals hydrothermally:[50a] as a rule the metals are transported to the higher temperature region. Metastable modifications, such as monoclinic selenium in carbon disulfide, are also obtained in this way.[110]

Oxides. Here the oxides of the transition elements are especially important: hydrothermal synthesis has proven effective in attaining prescribed oxidation states (see Sections 7 and 8). To attain lower oxidation states, reaction of the transition metal with water is exploited (Section 8), or also reaction of a metal with a compound in higher oxidation state. $K_2Mo_8O_{16}$, a molybdenum hollandite, is formed from a solution of K_2MoO_4 in KOH by reaction with molybdenum at 500–700°C in gold tubes.[111] Ferrimagnetic $YCu_3Mn_4O_{12}$ $[YCu_3(Mn_3^{IV}Mn^{III})O_{12}]$ is obtained from YCl_3, $CuSO_4 \cdot 5H_2O$, and $KMnO_4$ at 500–800°C above 1.5 kbar. The resulting reaction product occurs in a form that can be magnetically separated.[112] Preferred solvents for oxides are alkaline and alkali-metal halide solutions, especially fluorides for ternary and quaternary oxides. Salts of oxoacids are obtained from the corresponding acids, e.g. $AlPO_4$ from H_3PO_4 solution. Laser-active neodymium pentaphosphate crystals can be produced from phosphoric acid solutions at 300–700°C in vitreous carbon. The troublesome OH^- content decreases with increasing growth temperature and can be brought below 10^{19} per cm^3.[47c, 113]

Chalcogenides. The preparation of anhydrous alkali-metal chalcogenides via the ammonothermal route is cited in Section 6.1. In order to avoid hydrolysis in the hydrothermal method, neutral or acidic solutions are preferred, either in Teflon or glass (or quartz glass). An especially simple and reliable experimental arrangement is shown in

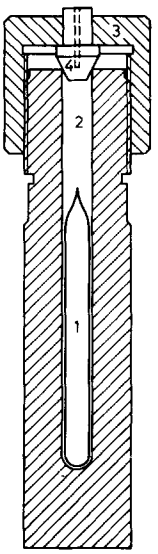


Fig. 20. Equipment for the hydrothermal method, using hydrohalic acids as solvent. The sealed quartz ampoule 1 is filled with the material to be converted and the solvent. A counter-pressure, produced by filling 2 with solid CO_2, prevents the ampoule from bursting. 3: Screw cap. 4: Sealing cone with hole for thermocouple [6j].

Figure 20. It is suitable for conditions up to 500°C and 1–2 kbar internal pressure. Upon filling the ampoule, the solvent is frozen in liquid nitrogen prior to the addition of the solid starting materials. This arrangement is not only suitable for the preparation of chalcogenides but also of chalcogenide-halides[114]—also with participation of the solvent—and for elucidation of the phase diagrams. The latter is demonstrated by the example of the chalcogenide-halides of copper and gold. At the beginning of these investigations only the silver ion conductors Ag_3SI and Ag_3SBr were known.[115] Instead of a methodical investigation of the copper or gold system, respectively, ternary phases (Fig. 21) were produced by the hydrothermal method from the elements and/or from binary boundary

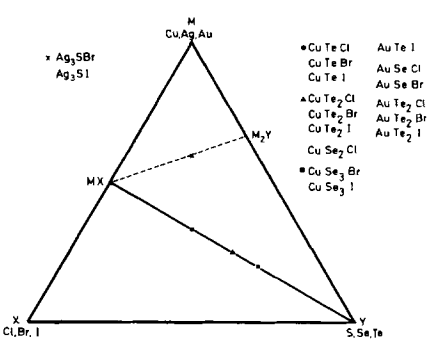


Fig. 21. Chalcogenide halides in the ternary system with the components: group 1B, Cu, Ag, Au; the chalcogens S, Se, Te and the halogens Cl, Br, I. The copper and gold compounds have been prepared for the first time using the arrangement in Figure 20 [6j].

phases. The reaction products appear as small crystals which can easily be sorted and identified (Fig. 22). The quasi-binary sections can easily be determined in the usual way from the information for the ternary phases. This is a real advantage over powder preparations, in which the presence of ternary phases but not their quantitative composition can be determined by X-ray diffraction. Products sensitive to hydrolysis can be obtained with anhydrous solvents such as HCl and HBr.[116] Under conditions similar to those for the metastable subiodides Te_2I and β-TeI (see Section 1), $(Te_2)_2I_2$ is formed, whose unusual intercalation structure was recently elucidated by *Kniep* and *Beister*.[117] Here the presence of "foreign elements" such as germanium or arsenic is required, although their presence in the reaction product cannot be detected.

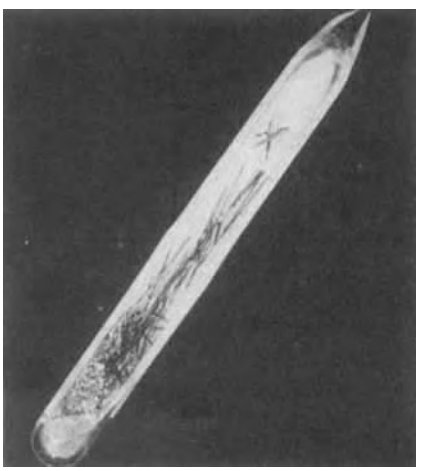


Fig. 22. Quartz-glass ampoule in which crystals of $AuITe_2$ together with gold have been grown. This result was obtained by bringing together gold and tellurium in equal numbers of gramme-atoms in 10-molar HI at a temperature of 450°C and then allowing it to cool for 10 days to 150°C (size of ampoule 15 cm) [6j, 140].

An example where the lower end of the temperature range is extended with respect to chemical transport reactions, is the transport of CuS and CuSe. While for CuS, with a decomposition temperature of 507°C, transport *via* the gas phase with HBr is still possible,[118a] for CuSe (decomposition temperature 379°C) this can only be achieved with the hydrothermal method, because of the low vapor pressure of CuBr.[118b]

Halides. Fluorides, fluoride hydroxides, and oxide fluorides are produced on a large scale from hydrofluoric acid solutions[119a] using gold ampoules as reaction vessels (Fig. 23). $In(OH)F_2$ is formed in this way from $InF_3 \cdot 3H_2O$ at 200°C. A variation of this is the transformation of a metal oxide with the corresponding metal into oxide fluorides.

$$n\,M + (m-n)\,M_nO_m \xrightarrow[\text{pressure}]{HF} m\,M_nO_{m-x}F_x$$

$V_2O_{5-x}F_x$ ($x \leq 0.025$), $VO_{2-x}F_x$ ($x \leq 0.2$) (500–600°C, 1 kbar)[119b] as well as $WO_{3-x}F_x$ ($0.17 \leq x \leq 0.66$) and $MoO_{3-x}F_x$ ($0.74 \leq x \leq 0.97$) with cubic ReO_3 structure[119c] were obtained in this way. Single crystals of blood-red $Fe^{II}Fe^{III}_2F_8 \cdot H_2O$ were produced at 250°C and 30 kbar in a modified Belt apparatus in Pt crucibles.[36] $Cs_2FeF_5 \cdot H_2O$, which has a paramagnetic-antiferromagnetic phase transition at 2.4 K, is formed at 200–450°C and 1 kbar in an autoclave lined with PTFE.[120]

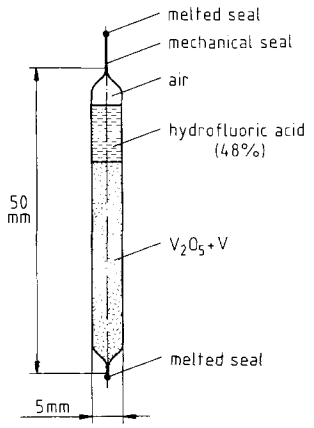


Fig. 23. Gold capsule for the preparation of oxide fluorides [119b].

Polyiodides of the type $Tl_6I_6M_2I_4$ (M = Ag, Au, Pb) were first obtained hydrothermally in hydriodic acid at 250–330°C.[121] Hexaiodoplatinate(IV), M_2PtI_6 (M = K, Rb, Cs, NH_4, Tl), is formed from PtI_4, MI, and I_2 in aqueous solutions in the presence of HI at 160°C in glass ampoules.[122] Finally, a new method for the synthesis of osmium(III), ruthenium(III), iridium (III), and rhodium(III) complexes with ethylenediaminetetraacetic acid (EDTA) and propylenediaminetetraacetic acid (PDTA) was developed through the transformation of the platinum-metal halides with EDTA or PDTA in water in a PTFE-clad vessel and heating to 150°C.[123]

10. Conclusion

The preparative possibilities of hydrothermal synthesis in solid state chemistry are by no means exhausted, as the relatively great success of ammonothermal synthesis in this field shows. From the beginning, this was oriented towards preparative work and played no role in the growth of large, perfect, single crystals. It should also be considered, that for modest requirements of pressure and temperature, the expense for the apparatus is kept within limits (see Visual Hydrothermal Synthesis, Section 4.2). Also, through judicious inclusion of *Eh*-pH diagrams and buffer systems, the state of pure empiricism can be abandoned, and hydrothermal synthesis should attain a significance in solid state chemistry similar to that already possessed by chemical transport reactions.

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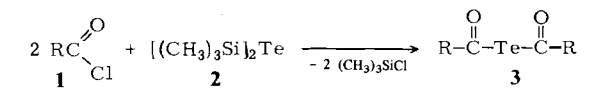
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Novel Reactions of Acyl Halides with Bis(trimethylsilyl) Telluride: C,Te and C,C Bond Formation**

By *Tevfik Severengiz, Wolf-Walther du Mont,* Dieter Lenoir,** and *Heike Voss*

Dedicated to Professor Max Schmidt on the occasion of his 60th birthday

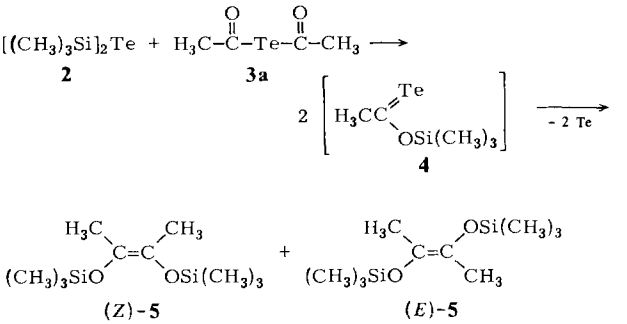
Telluro esters with C=Te groups should be of interest both as 1,2-dipoles and as soft ligands, but little is known about them. Only compounds with bulky substituents of the type *t*BuC(=Te)OR have been identified, the *tert*-butyl group being decisive for their stability.[1] In the course of seeking new tellurium reagents[2] and new olefin syntheses,[3] we found that bis(trimethylsilyl) telluride **2** does not react with simple ketones,[4] but does undergo spontaneous reaction with acyl halides.



a, R = CH_3; **b**, R = $C(CH_3)_3$

Diacetyl telluride **3a** is obtained in practically quantitative yield when acetyl chloride **1a** is allowed to react at -30 °C with a less than stoichiometric amount of **2**; in the same way, pivaloyl chloride reacts with **2** at -10 to -20 °C to give **3b**.[5,6] In the IR spectra of **3**, the characteristic pair of bands for each of the ν(C=O) appears; the mass spectra exhibit peaks for the molecular ions (correct isotopic distribution) as well as peaks for the fragments formed by loss of CO and acyl groups. In contrast to the dialkyl species, the diacyl tellurides **3** are extremely sensitive to air and moisture; the hydrolysis products include the corresponding diacyl ditellurides (identified by MS).[7]

Noteworthy is the reaction of **3a** with **2**: upon mixing of the two tellurium compounds (-20 °C, without solvent), the mixture rapidly turns intense blue and, simultaneously, tellurium starts to separate out. A mass spectrum (recorded immediately after mixing) shows the complete consumption of **3a** (no group of signals around *m/z* 216[6]); instead, new peaks appear which we ascribe to the trimethylsilyl telluroacetate **4** (*m/z* 246, $M^{\oplus}$ for ^{130}Te). The decomposition of **4** and the formation of the final products, (*E*)- and (*Z*)-**5**, can be followed by mass spectroscopy.[8]



The intermediacy of **4** is favored by the formation of the Si–O bond.[9] After 12–15 h at room temperature, the yield of **5** (mixture of isomers, (*E*)-**5** : (*Z*)-**5** ≈ 55 : 45), determined by NMR spectroscopy, is nearly quantitative (yield after distillation (b.p. = 68–78 °C/20 mbar): 60–70%).[10] The 2-butene derivatives **5** are also formed when **2** is allowed to react with molar equivalent amounts of acetyl chloride **1a** (yield after distillation: ca. 70%); tellurium separates out in an exothermic reaction and a blue color appears. Accordingly, acetyl chloride **1a** reacts with **2** in the sense of an acyloin condensation, leading (as in the system $(CH_3)_3SiCl/Na$) to the disilyl enediol ether.[11] The deep blue color is due to the labile intermediate **4**, which has a C=Te bond. In the reaction of **2** with equimolar amounts of pivaloyl chloride **1b** (or with **3b**), the corresponding telluro ester *t*BuC(=Te)OSi$(CH_3)_3$ was identified in the mixture;[12] in the UV/VIS spectrum, the absorptions characteristic for the C=Te group at $\lambda = 624$ and 350 nm (blue solution in *n*-pentane) are observed.[1] In this case, no acyloin-like C,C bond formation occurs, probably for steric reasons.[12]

The spontaneous breakdown of the ester **4** (which is free of bulky substituents) at room temperature with formation of a C=C bond and elimination of an elemental chalcogen has no precedent in carbonyl chemistry. Formally, this reaction is similar to the photochemical desulfurization of thioesters RC(=S)OR′.[13,14]

Experimental Procedure

3a: **2** (2.26 g, 8.3 mmol) was added dropwise to **1a** (3.58 g, 45.6 mmol) at -30 °C under argon. The brown suspension was then stirred for 30 min at -30 °C, and chlorotrimethylsilane and excess acetyl chloride were removed under reduced pressure. 1.3 g (74%) of **3a** remains as a yellow-orange liquid [6].—Correspondingly, **3b** (1.4 g, 85%) is obtained as a turquoise liquid from **1b** (3.2 g, 26.5 mmol) and **2** (1.5 g, 5.5 mmol) at -10 to -20 °C [6].

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[5] Synthesis of a telluro phthalic anhydride: J. Bergmann, L. Engman, *Org. Prep. Proced. Int. 10* (1978) 289.
[6] **3a**: yellow liquid; ^{1}H-NMR (C_6D_6, TMS ext.): $\delta = 2.1$; MS (70 eV/70 °C): *m/z* 216 (38%, $M^{\oplus}$), 188 (1, $M^{\oplus} - CO$), 174 (4, $CH_3COTeH^{\oplus}$), 173

(4, $CH_3COTe^{\oplus}$), 143 (7, $CH_3Te^{\oplus}$), 130 (26, $Te^{\oplus}$), 44 (38, $CH_3COH^{\oplus}$), 43 (100, $CH_3CO^{\oplus}$), 42 (56, $CH_2CO^{\oplus}$); correct elemental analysis; IR (CsI/film): ν = 260 (m), 460 (w), 555 (vs), 800 (w), 845 (w), 910 (m), 942 (m), 1073 (s), 1090 (sh), 1122 (w), 1226 (w), 1260 (w), 1342 (m), 1410 (m), 1712 (vs), 1756 (m), 1822 (w), 2915 (w), 2990 (w), 3410 (w) cm^{-1}. — **3b**: yellowish green liquid, ^{1}H-NMR (C_6H_6, TMS ext.): δ = 1.7; MS (70 eV, 70°C): *m/z* 300 (5%, $M^{\oplus}$), 272 (5, $M^{\oplus}-CO$), 216 (2, $C_4H_9COTeH^{\oplus}$), 130 (8, $Te^{\oplus}$), 86 (38, $C_4H_9COH^{\oplus}$), 85 (100, $C_4H_9CO^{\oplus}$); correct elemental analysis; IR (CsI/Nujol): ν = 1705 (vs), 1752 (m) cm^{-1}.

[7] The hydrolysis of dibenzoyl selenide to dibenzoyl diselenide proceeds similarly: H. Ishihara, S. Kato, *Tetrahedron Lett. 1972*, 3757. Diacyl tellurides are also formed in the reactions of Na_2Te with acyl halides: W.-W. du Mont, T. Severengiz, unpublished.

[8] MS data for **4** (70 eV, 70°C): *m/z* 246 (10%, $M^{\oplus}$), 117 (92, $M^{\oplus}-Te+1$), 75 (40, $(CH_3)_2SiOH^{\oplus}$), 73 (100, $(CH_3)_3Si^{\oplus}$), 45 (56%, CH_3CHOH), 43 (48%, $CH_3CO^{\oplus}$). The signals of **3a** decrease in favor of the signals of (*E*)- and (*Z*)-**5** (*m/z* 232 ($M^{\oplus}$)); after only 2–3 h at room temperature, most of **4** has been converted into **5**.

[9] For the role of Si–O bond formation in thio and seleno esters, see: a) S. Kato, W. Akada, M. Mizuta, Y. Ishii, *Bull. Chem. Soc. Jpn. 46* (1973) 244; b) M. Mikolajczyk, P. Kielbasinski, H. M. Schiebel, *J. Chem. Soc. Perkin Trans. 1 1976*, 564; c) [7].

[10] a) For the synthesis of (*Z*)-**5**, see R. Ugi, R. Schwarz, *Angew. Chem. 93* (1981) 836; *Angew. Chem. Int. Ed. Engl. 20* (1981) 789 (^{1}H-NMR ($CDCl_3$): δ = 0.09 (18 H), 1.63 (6 H); b.p. = 64°C/12 mbar); b) (*Z*)-**5**/(*E*)-**5**: ^{1}H-NMR (C_6H_6): δ = 0.29 and 0.38 (each 18 H), 1.83 and 2.0 (each 6 H); b.p. = 68–78°C/20 mbar; MS: *m/z* 232 (0.5%, $M^{\oplus}$).

[11] K. Rühlmann, *Synthesis 1971*, 236.

[12] tBuC(=Te)OSi$(CH_3)_3$: MS (70 eV, 70°C): *m/z* 288 (5%, $M^{\oplus}$ with ^{130}Te), 216 (1, C_4H_9COTeH), 159 (100, $C_4H_9COHSi(CH_3)_3^{\oplus} \triangleq M^{\oplus}-Te+1$), 130 (4, $Te^{\oplus}$), 86 (80, $C_4H_9COH^{\oplus}$), 85 (100, $C_4H_9CO^{\oplus}$), 73 (100, $(CH_3)_3Si^{\oplus}$). Attempts to purify **6** are in progress. Distillation affords the following decomposition products. B.p. = 25–27°C/1 mbar: **2** [^{1}H-NMR (C_6H_6): δ = 0.65; MS: *m/z* 276 ($M^{\oplus}$)] and tBu$_2$Te [^{1}H-NMR (C_6H_6): δ = 1.75; MS: *m/z* 244 ($M^{\oplus}$)]; b.p. = 50–52°C/1 mbar: tBu$_2$Te$_2$, [^{1}H-NMR (C_6H_6): δ = 1.7; MS: *m/z* 374 ($M^{\oplus}$ for 2 × ^{130}Te)] and $(CH_3)_3Si$-Te-t-C_4H_9 [^{1}H-NMR (C_6H_6): δ = 0.39, 1.25; MS: *m/z* 260 ($M^{\oplus}$)]. Together ca. 70% yield based on **2** and **3b**. The initial fraction contains $[(CH_3)_3Si]_2O$ (*m/z* 147 ($M^{\oplus}-15$)).

[13] U. Schmidt, K. H. Kabitzke, *Angew. Chem. 76* (1964) 687; *Angew. Chem. Int. Ed. Engl. 3* (1964) 641.

[14] A related type of reaction is the decomposition of $(EtO_2C)_2C{=}S{=}O$, which is unstable, to give, inter alia, the olefin $(EtO_2C)_2C{=}C(O_2CEt)_2$: R. W. Saalfrank, W. Rost, *Angew. Chem. 97* (1985) 870; *Angew. Chem. Int. Ed. Engl. 24* (1985) 855.

Non-Induced, Highly Diastereoselective Intramolecular Ene Reactions of 1,7-Dienes to *trans*-1,2-Disubstituted Cyclohexanes

By *Lutz F. Tietze** and *Uwe Beifuss*

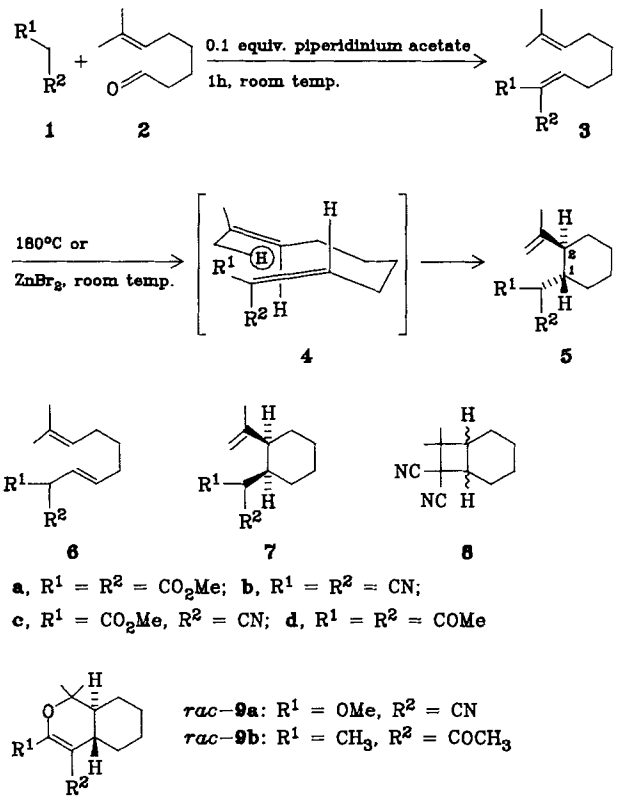
Dedicated to Professor Hans Jürgen Bestmann on the occasion of his 60th birthday

Compared with the mechanistically related Diels-Alder reaction, the ene reaction has so far been considered as less important with respect to the formation of C–C bonds, which may be attributed in many cases to lower stereoselectivity and poorer yields. The intramolecular mode, which has not yet been investigated in any depth, often leads to unsatisfactory results, too, especially in the case of 1,7-dienes.[1]

We have been able to show recently that in highly diastereoselective (*de* > 95%) hetero-Diels-Alder reactions alkylidene and arylidene derivatives of cyclic 1,3-dicarbonyl compounds afford either enantiomerically pure or racemic, *trans*- or *cis*-fused dihydropyrans.[2] This paper will show that alkylidene-1,3-dicarbonyl and analogous compounds also provide very reactive enophiles if the hetero-Diels-Alder reaction is prevented; this can be achieved by using C=C bonds bearing electron-accepting substituents that do not undergo cycloaddition reactions. In this way, the alkylidene derivatives **3** of acyclic 1,3-dicarbonyl and analogous compounds may be converted into the *trans*-substituted cyclohexane derivatives *rac*-**5** by a *non-induced diastereoselective* ene reaction.[3]

The term *non-induced diastereoselective* will henceforth be used to describe reactions that preferably form one of several possible diastereomeric chiral (racemic) products from achiral educts in an achiral environment. For transformations under the influence of one or more chiral elements, the term *induced diastereoselective* will be used. It is all the more reasonable to distinguish between these two types as both of them (*non-induced* as well as *induced*) often occur simultaneously in a single reaction with different diastereomeric excess.[4]

The educts **3** are easily obtainable in nearly quantitative yields by Knoevenagel condensation of **1** with the aldehyde **2**[5] in the presence of piperidinium acetate (20°C, 1 h). Heating of **3a–3c** in refluxing *o*-dichlorobenzene (180°C) leads to the *trans*-fused ene products *rac*-**5a–5c**;[6] the amount of the *cis*-fused cyclohexane derivatives *rac*-**7a–7c** lies between 1 and 8% (Table 1). **4** is assumed to be the conformation of the transition state[7] of the ene reaction leading to *rac*-**5**.



In the presence of Lewis acids[1c] the reaction temperature is lowered; with $ZnBr_2$ (1.1 equivalents) quantitative conversion is obtained within 15–45 min at 20°C. As by-products of the reaction of **3a** and **3b** the isomeric product **6a** (4%) and a mixture of the isomeric bicyclooctanes *rac*-**8**

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(14%), respectively, are found. For **3c**, the Diels-Alder adduct *rac*-**9a** (60%) is preferably formed under Lewis acid catalysis, while only 29% of the ene product *rac*-**5c** is obtained. The amount of *cis*-substituted cyclohexane derivatives is always less than 1%; for **3a**; no *cis*-fused ene product was detected. The alkylidene compound **3d**, though, behaves differently; in both the thermal and the Lewis-acid-catalyzed reaction, *rac*-**9b** and not the corresponding ene compound is formed[8] (Table 1).

Table 1. Thermal and Lewis-acid-catalyzed reactions of **3a**–**3d**.

Educt	Main product (yield [%]) [a] 180°C	Selectivity **5** : **7** [b]	Products (yield [%]) [a] $ZnBr_2$, room temp.	Selectivity **5** : **7** [b]
3a	*rac*-**5a** (73)	99 : 1	*rac*-**5a** (88) **6a** (4)	> 99 : 1
3b	*rac*-**5b** (71)	92 : 8	*rac*-**5b** (68) *rac*-**8** (14)	> 99 : 1
3c	*rac*-**5c** (89)	96 : 4	*rac*-**5c** (29) *rac*-**9a** (60)	> 99 : 1
3d	*rac*-**9b** (80)	—	*rac*-**9b** (89)	—

[a] Yield of isolated products. [b] The diastereomeric ratio **5** : **7** was determined by ^{13}C-NMR spectroscopy, HPLC, and GC-MS of the crude product mixture.

The *trans*-arrangement of the substituents in the ene products *rac*-**5a**–**5c** was shown by ^1H-NMR and ^{13}C-NMR spectroscopy. Thus, for *rac*-**5c** a value of 11 Hz is found for $^3J_{1\text{-H},2\text{-H}}$ as is usual with *trans*-diequatorially substituted cyclohexane derivatives.[6] The good yields and the high selectivity of the ene reaction of the 1,7-dienes are surprising since analogous triply activated compounds decompose upon heating.[9]

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[3] The selectivity of the reactions was determined by HPLC, GC-MS, and ^{13}C-NMR spectroscopy of the crude product mixture.

[4] With other terms suggested for the *non-induced* and *induced diastereoselective* reaction such as "*internal asymmetric induction*" and "*relative asymmetric induction*" (P. A. Bartlett, *Tetrahedron 36* (1980) 3) or "*simple diastereoselection*" (C. H. Heathcock in J. D. Morrison (Ed.): *Asymmetric Synthesis, Vol. 3*, Academic Press, New York 1984; M. T. Reetz, *Angew. Chem. 96* (1984) 542; *Angew. Chem. Int. Ed. Engl. 23* (1984) 556) the meanings of the terms may not so easily be inferred. Further advantages of the pair of terms induced/non-induced lie in the possibility of differentiating between externally and internally inducing elements of chirality as well as their number and—in the case of internally induced reactions—their position relative to the reaction center.

[5] The aldehyde **2** was synthesized by Wittig reaction of methyl 5-formylpentanoate, available through a technical process, and its subsequent reduction ($LiAlH_4$) and oxidation (dimethylsulfoxide, $(COCl)_2$), in an overall yield of 95%. L. F. Tietze, S. Brand, unpublished.

[6] *rac*-**5c**: ^1H-NMR (200 MHz, C_6D_6): δ = 0.84–1.8 (m; 8H, ring protons), 1.42 (m; 3H, $CH_2{=}C{-}CH_3$), 1.94 (tt, J = 3 and 11 Hz; 1H, 1-H), 2.11 (dt, J = 3 and 11 Hz; 1H, 2-H), 3.18 (s; 3H, CO_2CH_3), 3.39 (d, J = 3 Hz; 1H, $NC{-}CH{-}CO_2CH_3$), 4.72 and 4.93 (m; 2H, $H_3C{-}C{=}CH_2$).

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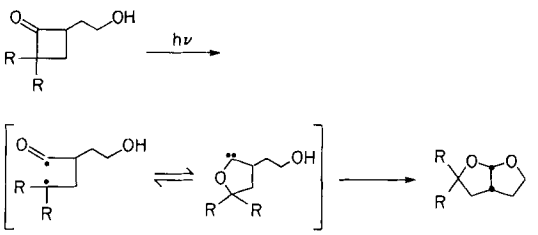
[8] In addition, small amounts of a decalin derivative were detected, which may have been formed via a tandem ene reaction.

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Bicyclic Acetals from Oxacarbenes**

By *Michael Pirrung**

The photochemical ring expansion of cyclobutanones to 2-tetrahydrofuranylidenes has been extensively studied mechanistically[1] but synthetic applications are few. A proposed mechanism involves α-cleavage followed by the establishment of an equilibrium between the singlet acyl-alkyl biradical and the oxacarbene, but a concerted mechanism may also operate.[2] Accordingly, the formation of products may be explained by the known reactions of the biradical or the carbene. We report here on the intramolecular trapping of photochemically generated oxacarbenes to provide bicyclic acetals.



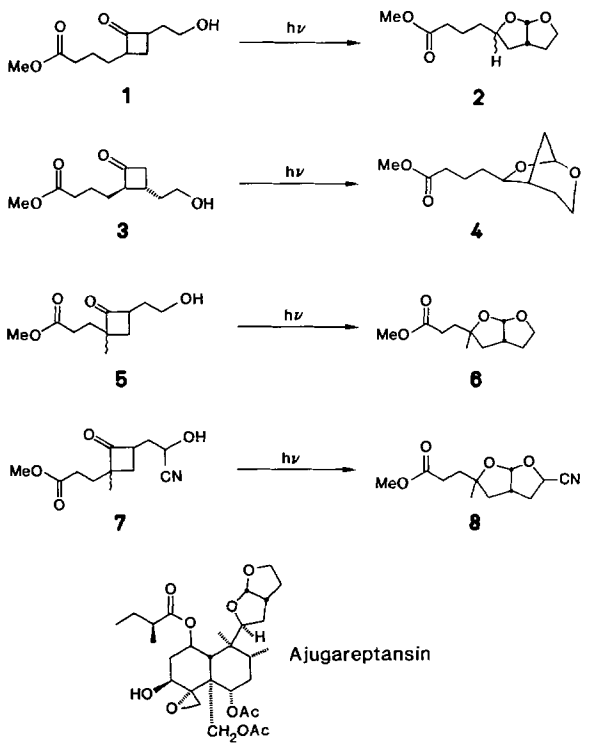
Compounds **1** (3 : 1 mixture of diastereomers) and **3** were prepared by *Ikeda*'s route.[3] Compounds **5** and **7** were prepared by modifying this method in order to begin with 2-hydroxy-3-methylcyclopentenone.[4]

4-Hydroxyethylcyclobutanone **1** provides a stringent test of this methodology, since (considering the stability of the resulting acyl-alkyl biradicals) either α-bond could be expected to cleave. In fact, irradiation (0.02 M CH_2Cl_2 solution, 450-W Hanovia lamp, Pyrex filter) results in complete conversion of **1** into **2** within two hours. Examination of the ^1H-NMR spectrum of the crude reaction mixture shows only two products (3 : 1), which may be isolated by chromatography (1 : 1 EtOAc/hexanes). Their structures were assigned from spectral data, particularly MS and ^1H-NMR, and comparison with literature data for ajugareptansin.[5] The major isomer shows data essentially identical to those of this diterpene natural product. In ether the reaction is extremely sluggish. The importance of the intramolecular trapping reaction is emphasized by the irradiation of the acetate of **1** in methanol. Complete consumption of starting material requires 24 h, and at least five products are observed by ^1H-NMR. Compound **1** is also consumed very slowly in methanol, producing **2** and a complex mixture of methyl acetals. These data suggest that an important control element may be the intramolecular hydrogen bonding evident in the IR spectrum of **1**.[6] The yield, while only 30% at room temperature, increases to 50% at −60°, consistent with the findings of *Miller* et al. that 1,4-acyl-alkyl diradicals undergo β-cleavage more readily at higher temperatures.[7]

With compounds **3** and **5**, no ambiguity exists regarding the preferred direction of bond cleavage, and irradiation at room temperature provides the bicyclic acetals **4** and **6** in 45 and 70% yield, respectively. The homothromboxane ring system[8] is embodied in the former structure. Finally, in order to provide an entry into the more highly oxidized skeletons of the aflatoxins[9] and caryoptins,[10] cyanohy-

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drin **7** was prepared from **5**. Irradiation in this case provides a mixture of cyanides such as **8** (51%).

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[4] Treatment of the enone with 3-butene-1-ol (*p*-TsOH, benzene, reflux, 67%, b.p. = 70°/0.5 torr) followed by intramolecular [2+2] photocycloaddition (acetone, 450-W Hanovia lamp, Pyrex, 16 h, 92%) gave exclusively the fused-ring tricyclic adduct. Baeyer-Villiger oxidation (*m*-chloroperbenzoic acid, CH_2Cl_2, room temperature, 12 h, 83% after chromatography) and methanolysis (or hydrolysis/methylation) yielded **5** (93%). Oxidation with pyridinium dichromate (2 equiv., CH_2Cl_2, followed by 2 equiv. Et_3N; 54%) and KCN/AcOH treatment gave **7** (quantitative). All new compounds reported herein gave satisfactory NMR, IR, and mass-spectral data.

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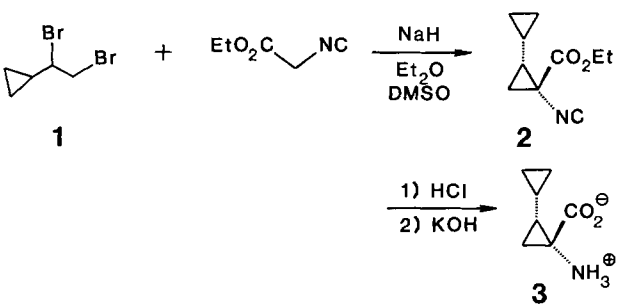
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Cyclopropyl-Substituted Aminocyclopropane Carboxylic Acid (Cyclopropyl-ACC) —an Investigation of the Mechanism of Ethylene Biosynthesis**

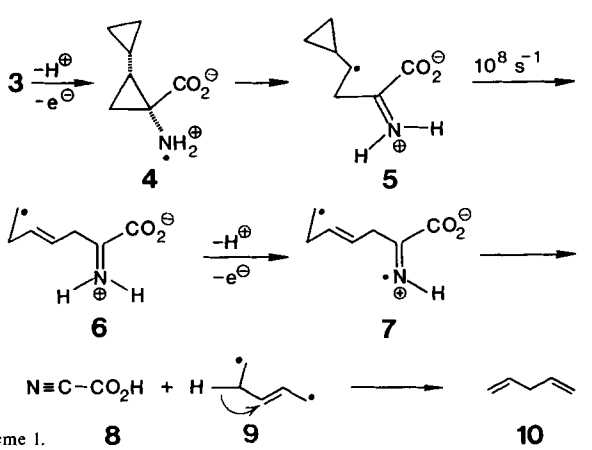
By *Michael Pirrung** and *Gerard M. McGeehan*

We report here the synthesis of 1-amino-2-cyclopropylcyclopropane carboxylic acid (cyclopropyl-ACC) **3** and its use in investigating the mechanism of ethylene biosynthesis in plants. The application of the *Schöllkopf*[1] procedure to 1,2-dibromides has proven the method of choice for synthesis of ACC analogues.[2] In this case, ethyl isocyanoacetate reacts with 1',2'-dibromoethylcyclopropane **1**[3] in the presence of NaH in ether/dimethylsulfoxide (DMSO) to give the protected bis-cyclopropane **2** in 20–27% yield. A two-step hydrolysis procedure and ion-exchange chromatography gives cyclopropyl-ACC **3**[4] as a mixture of stereoisomers (> 7 : 1) in 85–95% yield. The structure shown was assigned to the major isomer by comparison of its ^{13}C-NMR spectra with those of the known methyl-ACC[2] and by bioassay.



Yang et al. have established that in alkyl-ACC derivatives the alkyl and carboxyl groups must be in *trans* positions to be metabolized by plant tissue.[5] The *trans*-methyl-ACC serves as a good inhibitor of ethylene production ($K_I = 0.5$ mM) and is a substrate for propylene production in mungbean hypocotyl segments.[2] A Dixon analysis of the inhibition of ethylene biosynthesis in mungbean by cyclopropyl-ACC **3** shows a K_I of 1.5 mM.[6] The bulkier cyclopropyl group probably makes it more difficult for **3** to penetrate to the active center of ethylene biosynthesis.

Based on the previously proposed mechanism of ethylene biosynthesis,[7] it was anticipated that the radical **5**, in



Scheme 1.

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which the radical center is adjacent to a cyclopropane ring, would be generated via **4** during the metabolism of **3** by plants, and that this species might undergo a second ring opening. Incubation of apple tissue with **3** results in slow evolution of 1,4-pentadiene **10** (identified by GC/MS). In contrast, treatment of **3** with NaOCl, a reagent known to convert ACC into ethylene by a concerted mechanism,[8] provides only vinylcyclopropane.

Because **3** is a good inhibitor of ethylene biosynthesis but 1,4-pentadiene is generated only slowly, it seemed likely that an intermediate radical was being diverted by another reaction, perhaps with the ethylene-forming system. An assay for time-dependent inactivation was conducted by incubating mungbean hypocotyl segments with various concentrations of **3**. Samples were periodically removed and incubated with excess ACC. A decrease in the rate of ethylene production[6] with time was observed (Fig. 1). While not strictly first order, the rate constant for the inactivation was estimated to be $1.7 \times 10^{-5}\ s^{-1}$. Excess ACC protects against inactivation and oxygen is required but it was impossible to determine an inactivation/turnover ratio for **3** since the yield of 1,4-pentadiene was too low. Mechanism-based inactivation of ethylene biosynthesis in plants is thus shown for **3**.

Mechanistically, this study provides further evidence for the presence of a "half-opened" radical and the sequential

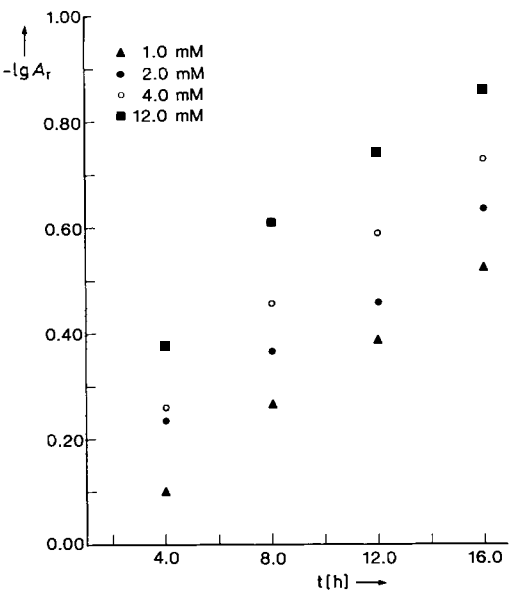


Fig. 1. Plot of the negative logarithm of the activity remaining ($-\lg A_t$) versus the incubation time. Top left: concentrations of **3**. See text.

single electron transfer pathway in ethylene biosynthesis. The formation of 1,4-pentadiene **10** is best accomodated by a mechanism involving a 1,2-hydrogen migration in a radical intermediate such as **9** (Scheme 1). It seems likely that the divergent reactivity of the "half-opened" radical formed from ACC and from **3** is responsible for the low conversion as well as the "suicide" inactivation.

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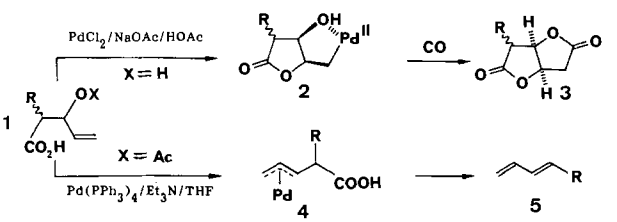
[1] U. Schöllkopf, R. Harms, D. Hoppe, *Justus Liebigs Ann. Chem. 1973*, 611.
[2] M. Pirrung, G. M. McGeehan, *J. Am. Chem. Soc.*, in press.
[3] Prepared in 59% overall yield from methyl cyclopropyl ketone by a procedure involving bromination (1. Br_2, MeOH, 0°C, 40 min; 2. H_2O, 20 min, room temperature), reduction ($NaBH_4$, MeOH, 0°C, 20 min) (89.6%, two steps), and OH→Br exchange (Ph_3P, Br_2, CH_3CN, 2 h). ^{1}H-NMR ($CDCl_3$): $\delta = 0.41$ (1 H, m), 0.68 (1 H, m), 0.77 (1 H, m), 0.96 (1 H, m), 1.30 (1 H, m), 3.64 (1 H, ddd, $J = 12.3$, 8.1, 5.4 Hz), 3.83 (1 H, dd, $J = 10.4$, 8.1 Hz), 3.89 (1 H, dd, $J = 10.4$, 5.4 Hz); IR (film): $\nu = 3090$, 3000, 1430, 1140, 1020, 935, 830 cm^{-1}; correct elemental analysis.
[4] M.p. = 211 (decomp.), ^{1}H-NMR (D_2O): $\delta = 0.14$ (2 H, m), 0.44 (2 H, m), 0.55 (1 H, m), 0.79 (1 H, t, $J = 6.5$ Hz), 1.22 (1 H, dd, $J = 9.8$, 6.5 Hz), 1.38 (1 H, ddd, $J = 9.8$, 6.5, 5.7 Hz); ^{13}C-NMR (D_2O): $\delta = 3.55$, 3.98, 7.35, 16.82, 27.17, 39.83, 175.68; correct elemental analysis.
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Pd^{II}-Catalyzed Stereoselective Bis-Lactonization

By *Y. Tamaru, H. Higashimura, K. Naka, M. Hojo,* and *Z. Yoshida**

Compared with the vast development of Pd^0-catalyzed organic reactions,[1] the Pd^{II}-catalyzed ones, despite their high potential for multifunctionalization accompanied by a change in the oxidation level of a substrate, have been less exploited.[2]

Here we describe a Pd^{II}-catalyzed, stereoselective, intramolecular double cyclization of 3-hydroxy-4-pentenoic acids **1** (X = H) to the bis-lactones **3**, carried out under CO (1 atm) (Scheme 1).[3] The *cis*-selective reaction is reminiscent of the *cis*-selective iodolactonization of **1** (X = H), which affords *cis*-3-hydroxy-4-iodomethyl-γ-butyrolactones.[4,5] The stereochemistry may be rationalized by assuming that attack of Pd^{II}[2e,2f] on the olefin is directed by the allylic OH group, forming the intermediate **2**. The results are summarized in Table 1.

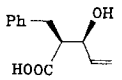
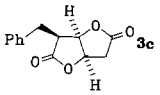
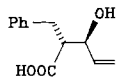
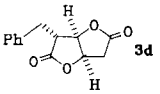
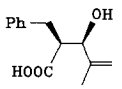
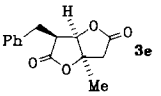
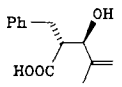
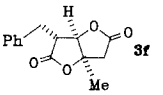
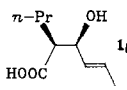
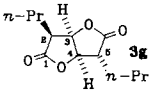
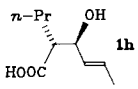
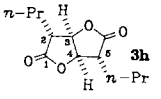
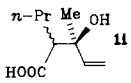
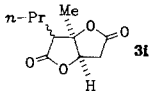


Scheme 1.

The reaction is characterized by several features. First, substitution at C-2 of **1** (X = H) increases the reactivity. Thus, the reaction of **1a** is slow, giving the bis-lactone **3a** in 18% yield (30°C, 2 days); the main products are the isomeric allyl acetates **6** (Scheme 2). *Trost* et al.[6] have shown that **1** (X = Ac) undergoes decarboxylative elimination to the *trans*-1,3-dienes **5** by the use of Pd^0 as catalyst (Scheme 1). In the case discussed here, the isolation of **6** (which is the reactant in *Trost*'s reaction) demonstrates the dramatic dependence of the reaction course on the catalytic species. The low yield formation of **3a** from **1a** is countered, however, by the reasonable yield of formation of **3b** (≡**3a**) from **1b** (room temperature, 3 d). Second, as shown by the reactions of **1c**–**1h**, substituents on the double bond do not significantly affect the yields—in contrast to other Pd^{II}-catalyzed reactions.[2f] Third, pairs of diastereomers show similar reactivities when the terminal double bond is unsubstituted (**1c**/**1d** and **1i**) and large differences

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Table 1. Reaction conditions and yields for the bis-lactonization of **1c**–**1i**.

Starting material	Reaction conditions [a]	Product	Yield [%] [b] (conversion [%])
 **1c**	room temperature, 1 d	 **3c**	60
 **1d**	room temperature, 1 d	 **3d**	60
 **1e**	room temperature, 1 d	 **3e**	84
 **1f**	room temperature, 1 d	 **3f**	39 (60)
 **1g**	room temperature, 1 d 30°C, 1 d	 **3g**	83 (81)
 **1h**	room temperature, 1 d 30°C, 1 d	 **3h**	88 (57)
 **1i**	room temperature, 2 d	 **3i**	78 [c]

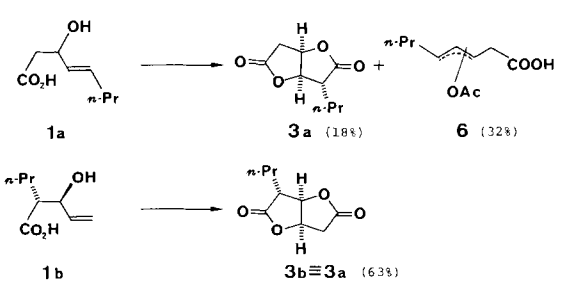
[a] **1** (1 mmol), $PdCl_2$ (0.1 mmol), $CuCl_2$ (3 mmol), NaOAc (3 mmol) in AcOH (5 mL) under CO (1 atm) [b] Yield of isolated product, based on the conversion of starting material Unless otherwise noted, the conversion is 100%. [c] From a 1 : 1 diastereomeric mixture of **1i**, a 1 : 1 diastereomeric mixture of **3i** was obtained.

of reactivity when it is substituted (**1e** and **1g** being more reactive than the corresponding diastereomers **1f** and **1h**, respectively). Fourth, and most important, the reaction is highly *cis*-selective, the *trans* products not being detected.

As shown by the reactions of **1g** and **1h**, carboxylate groups and Pd^{II} add to the double bond in a *trans* fashion. The C_2 symmetry and the *cis* configuration of the two propyl groups of **3h** are confirmed by the ^{13}C-NMR spectrum (six lines) and the ^1H-NMR spectrum ($2J_{H\text{-}2,H\text{-}3} = J_{H\text{-}4,H\text{-}5} = 0$ Hz). In the ^{13}C-NMR spectrum of **3g** the resonance of C-2 is shifted to high-field compared with that of C-5. The coupling constant $^3J_{H\text{-}2,H\text{-}3}$ is 5.4 Hz.

Experimental Procedure

3a≡**3b**: A solution of **1b** (167 mg, 1.1 mmol) in 5 mL of acetic acid was added under CO (balloon) to a flask containing $PdCl_2$ (17 mg, 0.1 mmol), $CuCl_2$ (405 mg, 3.0 mmol), and NaOAc (246 mg, 3.0 mmol) and the heterogeneous mixture was stirred at room temperature for 3 d. After dilution with benzene, the mixture was filtered through a cellulose column. The filtrate was neutralized with aqueous $NaHCO_3$, dried over $MgSO_4$, and the solvent was evaporated to give spectroscopically homogeneous **3a** as a colorless oil. ^1H-NMR ($CDCl_3$): $\delta = 1.00$ (br. t, $J = 7$ Hz, 3 H), 1.64 (m, 4 H), 2.88 (m, 3 H), 4.86 (d, $J = 4.9$ Hz, 1 H), 5.15 (m, 1 H); IR (neat): 1780 (vs), 1180 (s), 1040 (s).



Scheme 2.

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CAS-Registry-Numbers:
1a, 99098-21-2; **1b**, 99098-22-3; **1c**, 99098-10-9; **1d**, 99098-11-0; **1e**, 99098-12-1; **1f**, 99098-13-2; **1g**, 99098-14-3; **1h**, 99098-15-4; **1i**, (isomer 1), 99098-16-5; **1i**, (isomer 2), 99098-24-5; **3a**, 99098-23-4; **3c**, 99098-17-6; **3d**, 99147-26-9; **3e**, 99098-18-7; **3f**, 99147-27-0; **3g**, 99098-19-8; **3h**, 99147-28-1; **3i** (isomer 1), 99098-20-1; **3i** (isomer 2), 99147-29-2; **6**, 99098-26-7.

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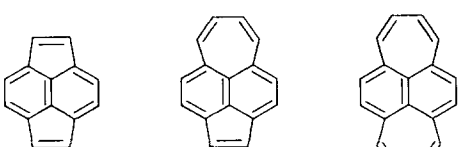
Synthesis of Dipleiadiene by "Serendipity"

By *Emanuel Vogel,* Brigitte Neumann, Wolfgang Klug, Hans Schmickler,* and *Johann Lex*

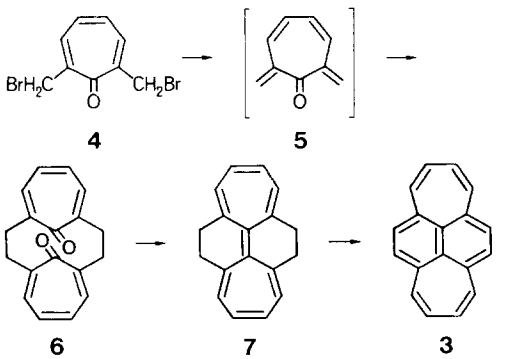
Dedicated to Professor Hans Musso on the occasion of his 60th birthday

Pyracylene **1**,[1] acepleiadylene **2**,[2] and the previously unknown dipleiadiene **3**[3] are theoretically interesting hydrocarbons, since—formally—they can be regarded, on the one hand, as *peri*-bridged naphthalenes, and, on the other, as "peripheral" [4n]- or [4n+2]annulenes with a central C=C bridge as a perturbation.[4] *Platt*'s model[5] suggests that **2** possesses [4n+2]annulene character, and this supposition is indeed borne out by the NMR spectra (diamagnetic ring current),[6a-c] the physical properties,[6d-g] and the chemical stability[2] of the compound.

On the basis of PMO- and PPP-SCF calculations and especially on the basis of the paratropism revealed in the ^1H- and ^{13}C-NMR spectra, the strained hydrocarbon **1**, which is stable only in solution, is looked upon as a perturbed [12]annulene.[1,7] Accordingly, the [4n]-perimeter in **1**, similarly to the [4n+2]-perimeter in **2**, would appear to be capable of governing the π-electronic structure of the molecule. A deeper insight into the bonding situation in "[4n]-perimeter molecules" should be provided by dipleia-



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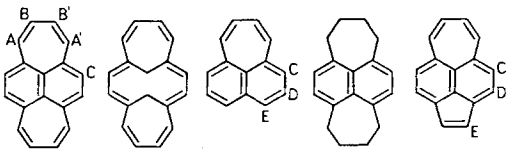
diene (dicyclohepta[*de,ij*]naphthalene) **3**, which has now been obtained as a relatively stable compound in connection with an entirely different study.

The primary target of the present investigation was the still unknown 2,7-dimethylene-3,5-cycloheptadien-1-one **5** and its utilization for the synthesis of 11-oxo-1,6-methano[10]annulenes via [8+2]-cycloaddition with acetylenes. 2,7-Bis(bromomethyl)tropone **4**[8] appeared to be the most suitable starting compound available for the generation of the presumably very reactive tetraene **5**. Treatment of **4** with zinc in dimethylformamide or with sodium iodide in acetone leads, in each case, to formation of the 17,18-dioxo[16]annulene derivative **6**[9] as the sole isolable product (from ether, pale yellow crystals; decomposition above 195°C; yield 15–30% and 25%, respectively), most likely formed from the hitherto undetected intermediate **5** by radical dimerization. The expectation of being able to trap **5** with acetylenes or maleic anhydride did not materialize.

It did not escape our notice that **6** is formally only two simple steps—an intramolecular reductive C=C coupling (e.g. McMurry reaction)[10] and dehydrogenation— removed from the much discussed dipleiadiene **3**, which defied all previous attempts at its synthesis. Indeed, **6** can be converted remarkably easily into **3**. Obviously favored by the intramolecular course of the reaction, **6** undergoes coupling almost quantitatively with titanium tetrachloride/zinc[11] in tetrahydrofuran to give the heptafulvalene **7**, which proves to be a very reactive compound [violet-black crystals (platelets) from ether; decomposition above 140°C; yield 90–95%]. While **7**, on reaction with 2,3-dichloro-5,6-dicyano-*p*-benzoquinone in benzene/hexane (3:1) at 0°C, failed to afford a defined product, it smoothly furnishes **3** when treated with the milder dehydrogenating reagent chloranil (under otherwise the same conditions). Hydrocarbon **3** is air-stable and crystallizes from ether in the form of reddish-black needles of m.p. 154–155°C (yield 80%).

Proof of the structure of **3** is based both on the spectra (see Tables 1 and 2) and on the X-ray structure analysis. A striking feature of the ^{1}H-NMR spectrum is the extremely high field location of all the signals. This is especially apparent when the ^{1}H-chemical shifts of **3** are compared with those of 1,6:9,14-bismethano[16]annulene **8**,[12] which, qualitatively, can be regarded as a model for the [16]annulene partial structure of **3**. The resonances of the "aromatic protons" of **3** are as close as 0.53 ppm to those of the corresponding protons of **8**, while the resonances of the seven-membered ring protons of **3** even appear by 0.44 and 0.63 ppm at higher field, respectively, than those of **8**. A comparison of the ^{1}H-NMR spectrum with those of the reference compounds **9**,[2,13] **10**,[3] and **2**[6a–c] also evidences the pronounced shielding in **3** (Table 1). In analogy to pyracylene **1**, **3** is thus distinguished by a paramagnetic ring current in the periphery of the molecule.

Table 1. Comparison of the ^{1}H-NMR data of **3** with those of **8**, **9**, **10**, and **2**. The frequency and solvent are quoted underneath each molecule.



	3	**8**	**9**	**10**	**2**
	300 MHz $CDCl_3$	300 MHz $CDCl_3$	100 MHz $CDCl_3$	60 MHz $CDCl_3$	100 MHz CD_2Cl_2
δ(A)	4.66	5.10	5.93	3.15	7.76
δ(B)	4.44	5.07	5.29	2.00	6.91
δ(C)	5.31	4.78	6.55	7.00	7.91
δ(D)			6.91		8.32
δ(E)			7.13		7.83
J(AB)	12.01 Hz	10.73 Hz	12.23 Hz		11.63 Hz
J(BB′)	6.94 Hz	8.74 Hz	6.73 Hz		8.36 Hz

Table 2. Some spectral data of **3**, **6**, and **7**. J in Hz.

3: ^{1}H NMR (300 MHz, $CDCl_3$): δ=4.44 and 4.66 (AA′BB′ system, 8H; J(AB)=12.01, J(AB′)=1.11, J(AA′)=0.81, J(BB′)=6.94), 5.31 (s, 4H, J(CC′)=7.58; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=129.26 (C_B), 129.89 (C_C), 140.61 (C_A), 140.70 ($C_{quart.}$), 147.39 ($C_{quart.central}$); MS (70 eV): m/z 228 (M^+, 53%), 202 ($M^+-C_2H_2$, 100); UV/VIS (EtOH): λ_{max}=201 nm (ε=28700), 241 (61200), 254 (33100) sh, 303 (5970), 314 (4900) sh, 393 (12200), 418 (12700), 487 (415) sh, 547 (234); IR (CsI): ν=3030, 1606, 834, 620 cm^{-1}

6: ^{1}H NMR (300 MHz, $CDCl_3$): δ=2.42 and 3.59 (AA′XX′ system, 8H), 6.63 and 6.94 (AA′BB′ system, 8H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=38.40, 131.02, 131.35, 150.62, 189.55; MS (70 eV): m/z 264 (M^+, 36%); UV/VIS (MeOH): λ_{max}=234 nm (ε=40000), 320 (10500); IR (KBr): ν=1622 cm^{-1} (C=C), 1591, 1580 (C=O)

7: ^{1}H NMR [300 MHz, $CS_2/(CD_3)_2CO$]: δ=2.25 (s, 8H), 5.48 and 5.60 (AA′BB′ system, 8H; J(AB)=7.43, J(AB′)=1.05, J(AA′)=0.12, J(BB′)=11.04); ^{13}C NMR [75.5 MHz, $CS_2/(CD_3)_2CO$]: δ=36.00, 123.92, 129.29, 131.52, 143.55; MS (70 eV): m/z 232 (M^+, 100%), 202 ($M^+-C_2H_2$, 62); UV/VIS (EtOH): λ_{max}=236 nm (ε=28900), 388 (19300), 403 (16100) sh; IR (CsI): ν=3021, 2955, 2904, 2848, 1551, 731 cm^{-1}

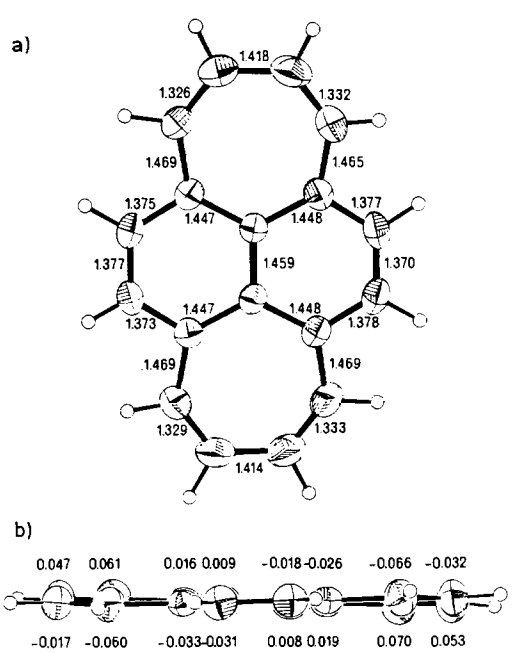


Fig. 1. Crystal structure of **3**: a) top view, bond lengths [Å]; b) longitudinal profile, distances [Å] of the carbon atoms from the mean ring plane. The values at the top refer to the rear series of atoms, those at the bottom to the front series of atoms. Atoms with negative values are located below the plane of the molecule.

The paratropism inferred from the ^{1}H-NMR spectrum of **3** would also seem to manifest itself in the ^{13}C-NMR spectrum, for, if naphthalene and pleiadiene **9** are taken as model compounds, a ring current contribution $\Delta\sigma$ of -3.2 ppm [**1**: $\Delta\sigma = -7.9$ ppm; **2**: $\Delta\sigma = +6.8$ ppm (mean value)] is obtained for the chemical shift of the central carbon atoms.

The electronic spectrum of **3** (see Table 2) is qualitatively consistent with the predictions made by *Yamaguchi* and *Nakajima*[4c] and by *DasGupta* and *Birss*[4g,14] on the basis of theoretical calculations.

Unlike **1** and **2**, dipleiadiene **3** was found to be amenable to an X-ray structure analysis.[15] The molecule shows a slight puckering of all rings (Fig. 1b; maximum distance of the carbon atoms from the mean plane: 0.07 Å), caused by non-bonding H,H-interactions. The naphthalene nucleus has, according to the C–C bond lengths, essentially maintained its integrity. In the case of the *peri*-bridges, the analysis (Fig. 1a) confirms the strong bond alternation already deduced from the ^{1}H-NMR spectrum on the basis of the magnitudes of the vicinal H,H-coupling constants J_{AB} and $J_{BB'}$ (Table 1).

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[8] 4 is the main product of the reaction of 2,7-dimethyltropone (obtainable according to the method of R. Noyori, S. Makino, H. Takaya, *Tetrahedron Lett. 1973*, 1745) with 1,3-dibromo-5,5-dimethylhydantoin (molar ratio 1 : 1) in boiling dichloromethane (irradiation with UV light); pale yellow crystals, m.p. 167–168 °C (decomp.), from chloroform; yield 50% (unpublished experiments in collaboration with D. L. Officer and W. Keck).

[9] According to an X-ray structure analysis of **6**, the carbonyl bridges are in the *anti* position. Several arguments lend support for **6** being present in the *anti*-conformation also in solution. **6** crystallizes orthorhombically, space group Pbca; $a = 15.144(2)$, $b = 11.959(1)$, $c = 7.459(1)$ Å, $Z = 4$; 644 reflections, $R = 0.035$.

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[15] **3** crystallizes monoclinically, space group $P2_1/c$; $a = 8.229(1)$, $b = 10.497(1)$, $c = 13.642(3)$ Å, $\beta = 90.84(1)°$, $Z = 4$; 1582 reflections, $R = 0.036$. Further details of the crystal structures of **3** and **6** are available on request from the Fachinformationszentrum Energie, Physik, Mathematik GmbH, D-7514 Eggenstein-Leopoldshafen 2, on quoting the depository number CSD-51480, the names of the authors, and the full citation of the journal.

1,4-Photocycloaddition of α-Morpholinoacrylonitrile to 1-Acylnaphthalenes**

By *Dietrich Döpp,* Carl Krüger, Hamid Reza Memarian,* and *Yi-Hung Tsay*

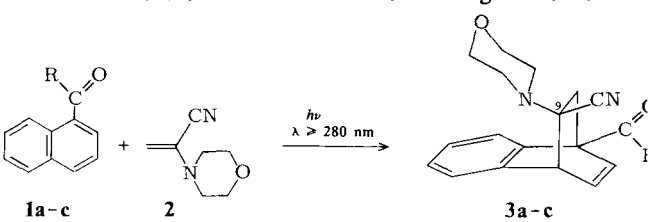
Dedicated to Professor Hans Musso on the occasion of his 60th birthday

In the course of investigations of the cycloaddition reactions of captodative[1] olefins, we found that α-morpholinoacrylonitrile **2**[2] can undergo smooth addition to electronically excited 1-acylnaphthalenes **1** with formation of 1-acyl-9-morpholino-1,4-dihydro-1,4-ethanonaphthalene-9-carbonitriles **3** (Table 1).

This is remarkable insofar as light-induced cycloadditions of alkenes to the naphthalene skeleton have—with one exception[3]—hitherto been unknown for acylnaphthalenes but are well known for naphthalene,[4] 1- and 2-naphthonitrile,[5] and naphthyl methyl ethers.[6] Both 1,2- and 1,4-additions are observed,[4] and the results for the additions to naphthonitriles support a mechanism involving the intermediacy of singlet exciplexes.[5]

Equimolar amounts of **1a–c** and **2** were irradiated for periods of time sufficient to obtain the conversions given (Table 1);[7] the yields of the thermally labile product **3** (which could not be recrystallized without loss of material) are based on the converted (i.e., non-recovered) starting material **1**. The photoaddition of **2** to 1-acetonaphthone **1b** is particularly convenient since the product **3b**[8] precipitates in fairly pure form during the irradiation, even at low conversions. Neither the mother liquors nor the crude precipitates of the product show evidence of other products in the ^{1}H-NMR spectrum.

The solvent effects observed are not large. The use of



1a–c **2** **3a–c**

Table 1. Photocycloaddition of **2** to **1** to give **3**. t = irradiation time. For conditions see [7]. Yields are based on unreacted **1**.

	R	Solvent	t [h]	Conversion of **1** [%]	**3** Yield [%]	M.p. [°C]
a	H	benzene	48	29	59	138
b	CH_3	cyclohexane	2	26	68	159
		benzene	2	25	72	
		acetonitrile	2	26	70	
		methanol	2	28	55	
c	C_6H_5	cyclohexane	5	4	66	154

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methanol results in a slight increase in the conversion of **1**. In this solvent, a maximum quantum yield of $\Phi = 0.02$, depending on the concentration of **2**, may be achieved for the consumption of **1b** at 313 mm. Tetramethyl-3,4-dihydrodiazete dioxide[9] inhibits the addition, which indicates the involvement of the triplet excited state of **1b**. A plot of Φ^{-1} against $[2]^{-1}$ results in a straight line and thus suggests a bimolecular interaction between electronically excited **1b** and **2**. The rate constant for the quenching of the triplet excited state of **1b** by compound **2** was estimated to be $k = 1.8 \times 10^8$ L mol^{-1} s^{-1}.[10]

The *endo* position of the morpholino group was confirmed for **3b** by an X-ray structure determination[11] (Fig. 1). Noteworthy are the significantly elongated bond distances between C1 and C10, C4 and C9, and C9 and C10. By analogy, the same configuration is also assumed to be valid for **3a** and **3c**.

In chloroform at 50°C, **3b** decomposes with a half-life of 6 d to give the educts **1b** and **2**.

Although 1-acylnaphthalenes can in principle undergo a Paterno-Büchi reaction,[12a] the formation of oxetanes with **2** was not observed. This and the finding that **1a–c** each form only a single photoadduct with **2**, along with the preferred *endo* orientation of the morpholino group, as established for **3b**, render the intermediacy of diradicals **4**, **5** (captodative stabilized at one terminus[1]) unlikely, but do not rigorously exclude this possibility.

Apparently, in the photocycloaddition described here, the radical-stabilizing properties ascribed to the captodative terminus in **2**[1] are less important than the ability of **2** to undergo complex formation. Nevertheless, **2**, with a first ionization potential of 8.68 eV,[13a] is more like an enamine such as cyclopentenylmorpholine (7.60 eV[13b]) than an α,β-unsaturated nitrile (acrylonitrile: 10.91 eV[13c]). A (triplet) exciplex, in which the lone electron pair of the morpholino group or the entire enamine portion of **2** lies above the π-system of **1a–c**, is therefore conceivable.

2-Acetonaphthone does not give a photoadduct with **2**, nor are oxetanes formed.[12b] Instead, a dimer of **2** is formed in low yield. The captodative-substituted olefin α-*tert*-butylthioacrylonitrile also can undergo photoaddition to **1a**, **b** and to 2-naphthaldehyde.[14]

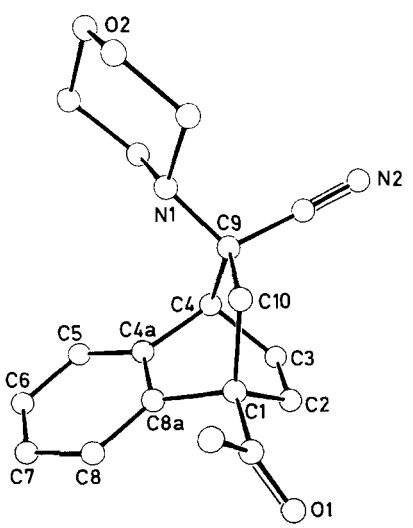
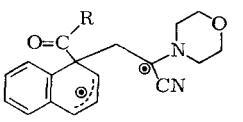
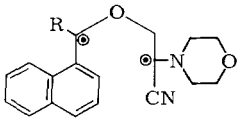


Fig. 1. Molecular structure of *rel*-(1*S*,4*S*,9*S*)-1-acetyl-9-morpholino-1,4-dihydro-1,4-ethanonaphthalene-9-carbonitrile **3b** in the crystal. Important bond lengths [Å] and angles [°]: C1-C10 1.572(3), C4-C9 1.575(3), C9-C10 1.567(3), C1-C2 1.520(3), C2-C3 1.320(3), C3-C4 1.515(3), C4-C4a 1.520(3), C4a-C8a 1.396(3), C1-C8a 1.531(3); C9-C4-C4a 107.0(1), C9-C4-C3 105.4(2), C3-C4-C4a 108.0(2), N1-C9-C4 113.3(1), N1-C9-C10 109.5(1), N1-C9-CN 110.9(1), C4-C9-C10 107.4(1), C4-C9-CN 106.5(1), C10-C9-CN 109.1(2), C1-C10-C9 110.6(1), C10-C1-C8a 105.1(2), C10-C1-C2 106.2(2), C10-C1-CO 112.5(2), C8a-C1-C2 106.7(2), C8a-C1-CO 112.6(2), C2-C1-CO 113.1(2), C1-C8a-C4a 112.8(2), C4-C4a-C8a 113.3(2), C4-C3-C2 114.7(2), C1-C2-C3 114.9(2).



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1a, 66-77-3; **1b**, 941-98-0; **1c**, 642-29-5; **2**, 5807-03-4; **3a**, 99033-58-6; **3b**, 99033-59-7; **3c**, 99033-60-0; 2-naphthaldehyde, 66-99-9; α-*tert*-butylthioacrylonitrile, 72314-64-8.

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[7] 100 mL, 0.1 M in both **1** and **2**, high-pressure Hg lamp TQ 150 Original Hanau, Duran immersion well ($\lambda \geq 280$ nm, only **1** undergoes excitation), purged with Ar or N_2.
[8] **3b**: IR (KBr): $\nu = 2230$ (CN), 1705 (C=O). – 80 MHz-^{1}H-NMR ($CDCl_3$, TMS): AB ($\delta_A = 1.92$, $\delta_B = 2.21$, $|^2J| = 12.6$ Hz, 10-CH_2), ABX [$\delta_A = 6.94$ (2-H), $\delta_B = 6.76$ (3-H), $\delta_X = 4.46$ (4-H), $^3J_{AB} = 7.8$ Hz, $^4J_{AX} = 1.3$ Hz, $^3J_{BX} = 6.0$ Hz], 2.54 (s, $COCH_3$), multiplets at 2.39–2.92 (4H), 3.4–3.7 (4H) and 6.9–7.4 (4H).—UV (CH_3CN): $\lambda(\varepsilon) = 284$ (29), 260 (227), 254 (200).
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[10] We thank Dr. *H. Görner*, Max-Planck-Institut für Strahlenchemie, Mülheim a. d. Ruhr, for these measurements.
[11] **3b**: $a = 8.5817(6)$, $b = 19.287(1)$, $c = 9.8179(5)$ Å, $\beta = 105.766(3)°$, $V = 1563.87$ Å^3, $\rho_{calcd} = 1.31$ g cm^{-3}, $Z = 4$, $\mu = 6.47$ cm^{-1}; space group $P2_1/c$, total number of reflections 3056, observed reflections 2161, refined parameters 288, $R = 0.040$, $R_w = 0.044$. Further details of the crystal structure investigation are available on request from the Fachinformationszentrum Energie, Physik, Mathematik GmbH, D-7514 Eggenstein-Leopoldshafen 2, by quoting the depository number CSD 51533, the names of the authors, and the journal citation.
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[14] All new compounds gave correct elemental analyses. The spectral results support the assigned structures.

Oxidation of 2-Propanol at Ti/Cr_2O_3 Anodes**

By *Harry Schulz* and *Fritz Beck**

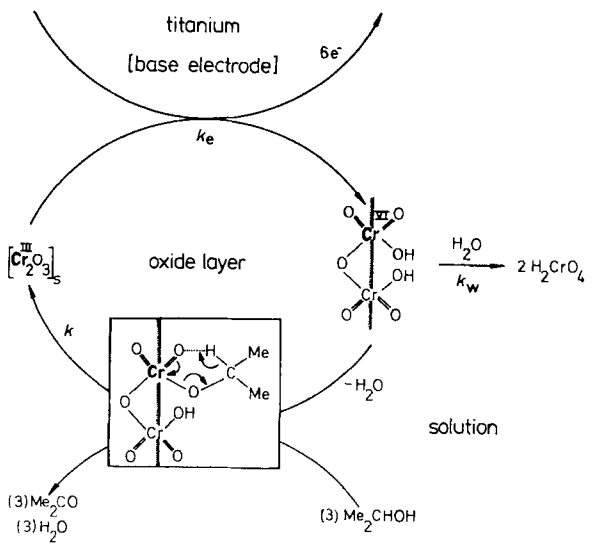
Chromic acid is a very important and frequently selective oxidizing agent in organic chemistry,[1,2] but separa-

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tion of the Cr^{III} salts formed in stoichiometric amounts when it is used, and their electrolytic reoxidation,[3] present problems. The mechanism of the homogeneous redox reaction has been elucidated by *Westheimer* et al.[4] (cf. [5]). Our interest was aroused in the possibility of developing an electrochemical method analogous to the chromic acid-oxidation method. Some 20 years ago, *Beer* first described the use of activated titanium electrodes in electrolysis[6] where they now play an important role in inorganic chemistry.

We have now developed a method for preparing Ti/Cr_2O_3 electrodes on the basis of a technique used for the production of ceramics.[7] The dark-green, excellently adhesive, microporous α-Cr_2O_3 layer, ca. 1 μm thick, can be stabilized by other oxides. Anodic polarization of the Ti/Cr_2O_3 electrode in 1 M H_2SO_4, leads to formation of a layer of CrO_3 on the surface, which after hydration (rate constant k_w) goes into solution (cf. Scheme 1). The rate



Scheme 1. Electrochemical oxidation of 2-propanol via heterogeneous redox catalysis at Ti/Cr_2O_3 anodes (schematic). The complex between surface-fixed chromic acid and 2-propanol is shown in the box.

constant of the $Cr^{III} \rightarrow Cr^{VI}$ electrochemical oxidation (k_e) increases exponentially with the anodic overvoltage. The possibility of using the resulting CrO_3 as an oxidizing agent for the oxidation of 2-propanal to acetone was tested (rate constant k); CrO_2 was formed, which either directly reoxidized electrochemically or, as in solution, rapidly underwent further follow-up reactions[4,5] to give Cr_2O_3. Turnover numbers of 100–10000 can be realized with catalytic amounts of Cr_2O_3 ("heterogeneous redox catalysis"[8,9]). The lifetime of the electrode is limited by the dissolution of CrO_3 and decreases with increasing k_w, but increases with k.[8]

The Cr_2O_3, which adheres as a very thin passive layer to the surface of chromium or chrome steels, has *no* catalytic properties. In the anodic polarization of such electrodes in sulfuric acid solutions of 2-propanol chromium dissolves transpassively with 6 F/mol.[10]

The initial reaction in the homogeneous oxidation of sterically unhindered alcohols with chromic acid is a rapid esterification; the rate-determining step is then a hydrogen shift, in which significant H/D isotope effects occur.[4b,5,11] Upon oxidation at Ti/Cr_2O_3 anodes, the esterification takes place on the electrode surface (cf. Scheme 1); this can be regarded as a special case of chemisorption. The following experimental findings prove that the rate-determining step is that of homogeneous oxidation:

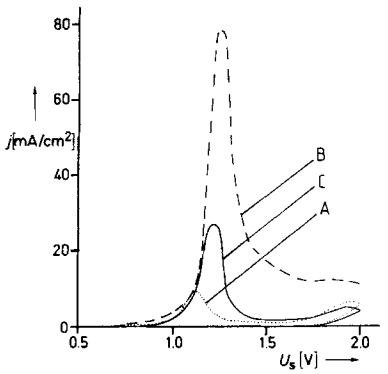


Fig. 1. Quasistationary current voltage curves for a Ti/Cr_2O_3 electrode [6, 8]. A in 1 M H_2SO_4, B in 1 M H_2SO_4 + 1 M 2-propanol, and C in 1 M H_2SO_4 + 1 M [D_8]2-propanol. Voltage scan rate: 5 mVs^{-1}. j = current density. U_s = potential referred to the Hg/Hg_2SO_4 electrode in 1 M sulfuric acid.

1) A comparison of curve B with curve A in Figure 1 shows the characteristic increase in current for the heterogeneous redox catalysis.[8,9] At higher overvoltages, a limiting current density j_{lim} of 78 mA cm^{-2} is established for the oxidation of 2-propanol. If the rate constant k_{hom} found for the homogeneous case[12] is used in Equation (a) then a

$$j_{lim} = z F k_{hom} [CrO_3]_s \qquad (a)$$

value of only ca. 0.1 mA cm^{-2} is obtained ($z = 2$, $Cr^{VI/IV}$, $[CrO_3]_s$ = surface concentration of CrO_3[8]). The discrepancy cannot be explained in terms of a roughness factor alone, and, furthermore, the medium effect—k_{hom} was determined in glacial acetic acid[12]—only lowers the limiting current to ca. 20 mA cm^{-2}. The activation entropy plays the decisive role:[13] Whereas ΔS in the homogeneous reaction is approximately -24 cal K^{-1} mol^{-1},[14] ΔS at the electrode must be larger. We obtain the observed limiting current density of the reaction j_{lim} using a value of -13.4 cal K^{-1} mol^{-1} for ΔS.

2) As shown by the curve C in Figure 1, a strong isotope effect is found with [D_8]2-propanol. j_{lim}, and thus also k,[8] decreases by a factor of 2.9. Primary isotope effects of 6.5–7 were found for the homogeneous oxidation.[4b,5,11,12] Isotope effects were also established in the reaction at the alkaline nickel oxide anode.[15]

3) We have converted 2-propanol into acetone on a preparative scale with 100% current efficiency at $j = 0.5$ mA cm^{-2}. This high selectivity is also obtained upon oxidation with chromic acid. In complete contrast, a current yield of only 70% is achieved on platinum.[16] The by-products of the oxidation include, inter alia, acetic acid.

4) When oxidation at the anode is carried out in the presence of 0.43 M $MnSO_4$, the limiting current density is reduced to 25% of the normal value. In the homogeneous reaction, a marked decrease in the conversion was established upon trapping the Cr^{IV} products formed in the first

$$Cr^{IV} + Mn^{II} \longrightarrow Cr^{III} + Mn^{III} \qquad (b)$$

oxidation step [Equation (b)], so that Cr^{IV} cannot be used for the oxidation.[17] The decrease in j_{lim} could also be attributed, in part, to a partial coating of the electrode with MnO_2.

5) Addition of acrylamide to the electrolyte (0.5 M) leads to a decrease of j_{lim} to 40% of the original value. The formation of polyacrylamide in the oxidation with chromic acid has been regarded as proof for the occurrence of radical intermediates.[18] In the oxidation at the Ti/Cr_2O_3 anode, however, the possibility that layers of polymers on the electrodes leads to a decrease in current cannot be ruled out.

Summarizing, it has been established that 2-propanol is oxidized to acetone at a Ti/Cr_2O_3 anode via a mechanism analogous to that postulated by *Westheimer* for homogeneous oxidation with chromic acid. The lifetimes of the electrodes are still too short for use on an industrial scale, but we have already been able to achieve substantial improvements by using Sb_2O_4 as additional oxide component.[8]

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Elucidation of the Structure of Epidermin, a Ribosomally Synthesized, Tetracyclic Heterodetic Polypeptide Antibiotic

By *Hermann Allgaier, Günther Jung,* Rolf G. Werner, Ursula Schneider,* and *Hans Zähner*

From the culture filtrate of *Staphylococcus epidermidis* Tü 3298, we have isolated a novel active compound which is highly effective, especially against the pathogen *Propionibacterium acnes* occurring in acne disease and against staphylococci and streptococci (Fig. 1). After adsorption on Amberlite XAD-8 and chromatography on Sephadex LH-20 the antibiotic could be isolated in pure form via two purification steps, by multiplicative countercurrent distribution.

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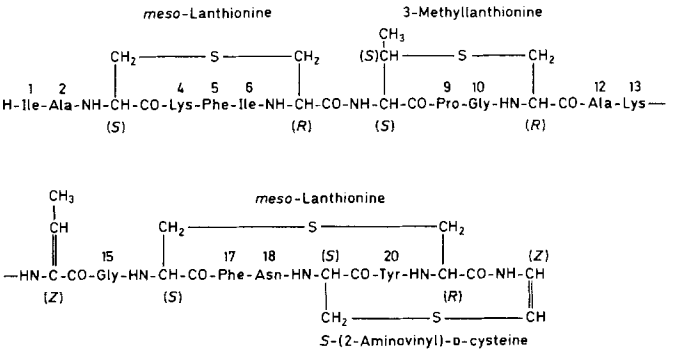


Fig. 1. Sequence of the tetracyclic heterodetic 22-peptide antibiotic epidermin. Trypsin cleaves behind Lys^{13} into the fragments P1 and P2 (cf. Fig. 2). All chiral amino acids without indicated configurations have the L-configuration, i.e. they belong to the (*S*)-series (exceptions are sulfur-containing amino acids such as cysteine: L-Cys is (*R*)-configurated).

The acidic total hydrolyzate of epidermin contained thirteen protein amino acids, two lanthionines, and one 3-methyllanthionine. The *meso*- and (2*S*,3*S*,6*R*)-configurations of lanthionine and 3-methyllanthionine, respectively, were determined by gas chromatography on chiral stationary phases.[1] In the nuclear resonance spectra of the antibiotic, two unsaturated amino acids could be detected; these were completely destroyed upon acidic total hydrolysis (Table 1).

Table 1. Characterization of epidermin. Dhb = dehydroaminobutyric acid (2-amino-2,3-didehydrobutyric acid).

Amino acid composition: L-Asn (1), L-Pro (1), Gly (2), L-Ala (2), L-Ile (2), L-Tyr (1), L-Phe (2), L-Lys (2), Dhb (1), *meso*-lanthionine (2), (2*S*,3*S*,6*R*)-3-methyllanthionine (1), *S*-(2-aminovinyl)-D-cysteine (1)

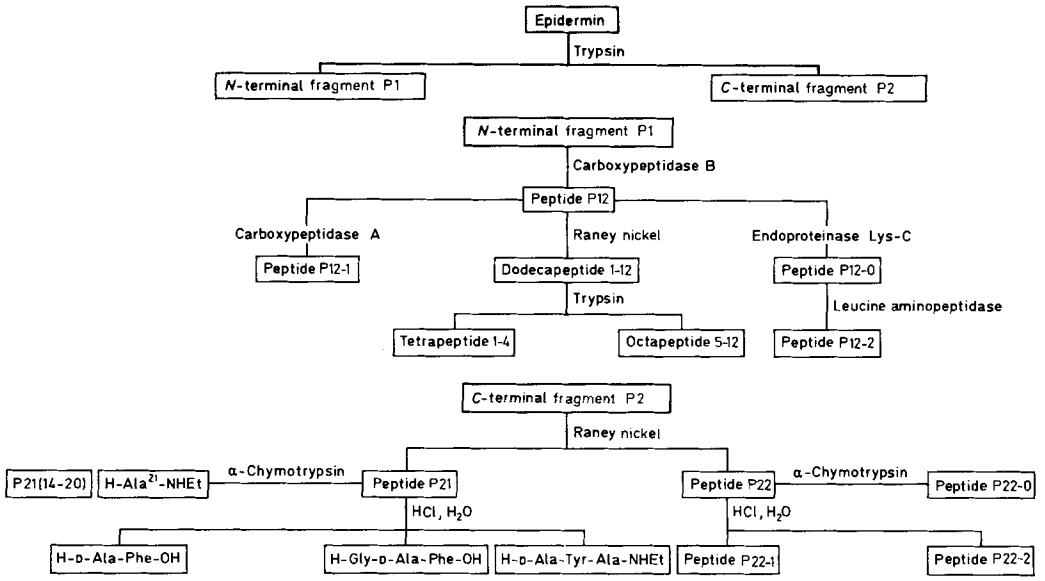
Thin-layer chromatography (silica gel $60F_{254}$ plates, Merck): chloroform/methanol/17% ammonia (2:2:1), $R_F = 0.73$; 1-butanol/glacial acetic acid/water (4:1:1), $R_F = 0.05$

Mass spectra: Fragment P1 $[M+H]^+$: *m/z* 1302 (FAB-MS), fragment P2 $[M+Na]^+$: *m/z* 904 (FD-MS)

UV spectrum ($c = 0.15$ mg/mL, water, pH = 7): $\lambda_{max} = 267$ nm, $\varepsilon_{max} = 11000$

Starting point of the sequencing of the complex basic polypeptide was the tryptic cleavage into an *N*-terminal fragment P1 and a *C*-terminal fragment P2. These fragments could be separated from each other, since P2 precipitated upon enzymatic cleavage of epidermin. *C*-terminal lysine could be cleaved from the tryptic fragment P1 by reaction with carboxypeptidase B (Fig. 2). A subsequent desulfurization with Raney nickel[2] afforded a bridge-free dodecapeptide 1–12, which was sequenced by FAB-MS and Edman degradation in a gas-phase sequencer. A further fragmentation of the dodecapeptide into the peptides 1–4 and 5–12 was achieved by further tryptic cleavage. The positions of the sulfur bridges in P1 could be determined by reactions with carboxypeptidase A and B, trypsin, and endoproteinase Lys-C, in combination with Edman degradation and FAB-MS (Fig. 2).

The tryptic fragment P2, which is insoluble in water, was *N*-terminally blocked with 2-oxobutyric acid and *C*-terminally blocked by the ε-amino group of the amino acid *S*-(2-aminovinyl)-D-cysteine. Tryptic cleavage furnished the 2-oxobutyryl residue, in which the dehydroaminobutyric acid (Dhb) after Lys^{13} was converted.[3] *S*-(2-Aminovinyl)-D-cysteine (Cys(Avi)), which is likewise labile under the conditions of acidic total hydrolysis, could be converted by



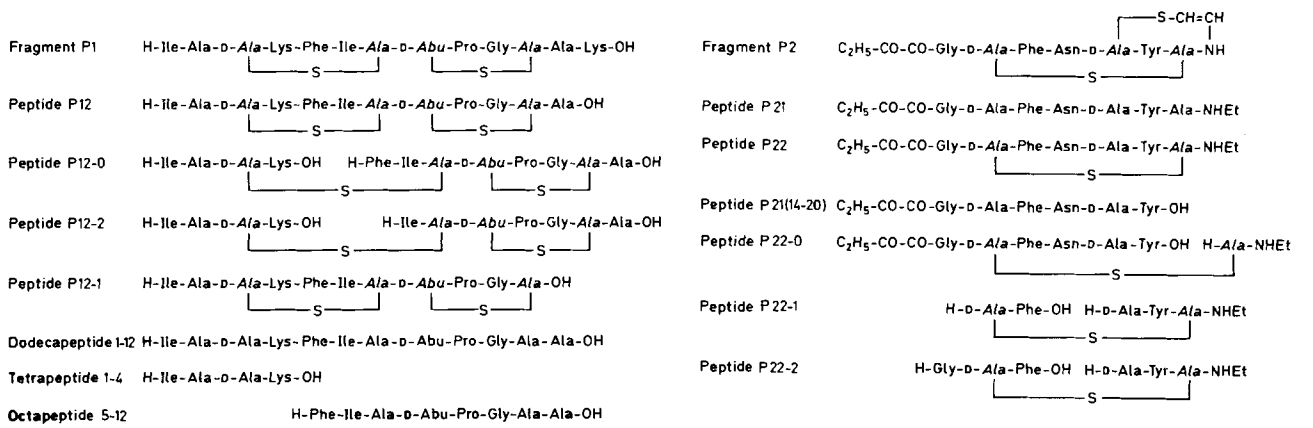


Fig. 2. Elucidation of the structure of epidermin. The halves of the thioether amino acids nearest to the *N*-termini are each D-configurated at C_α (cf. Fig. 1). Without this excessive fragmentation of the molecule, an assignment of the thioether bridges is impossible. D-Ala—S—Ala: *meso*-lanthionine; D-Abu—S—Ala: (2*S*,3*S*,6*R*)-3-methyllanthionine; D-Ala—S—CH=CH–NH_2: *S*-(2-aminovinyl)-D-cysteine).

hydrogenation of the native antibiotic into the stable amino acid *S*-(2-aminoethyl)-D-cysteine (Cys(Aet)), which was detectable by amino acid analysis and by mass spectrometry.

The key reaction for the elucidation of the structure of P2 was desulfurization with Raney nickel.[2] *S*-(2-Aminovinyl)-D-cysteine was thereby completely converted into D-alanine and *C*-terminal *N*-ethylamide. Under the chosen reaction conditions, *meso*-lanthionine could only be partly desulfurized, so that the bridge-free peptide P21 and the peptide P22 resulted, which still contained one *meso*-lanthionine bridge (Fig. 2). The sequencing of the *C*- and *N*-terminally blocked peptide P21 was accomplished by acidic partial hydrolysis. The assignment of the sulfur bridges in P2 was achieved by a combination of enzymatic and acidolytic cleavages with FAB-MS.

The 22-peptide (docosapeptide) epidermin, like nisin[4] and subtilin,[5] belongs to the polycyclic heterodetic class of peptide antibiotics. It differs from the latter mentioned peptides, however, not only in the primary structure but also by its extremely rigid conformation, as shown by comparative CD investigations. The recently described polycyclic heterodetic peptide ancovenin[6] is not antibiotically active, but it inhibits the angiotensin I-converting enzyme ACE.

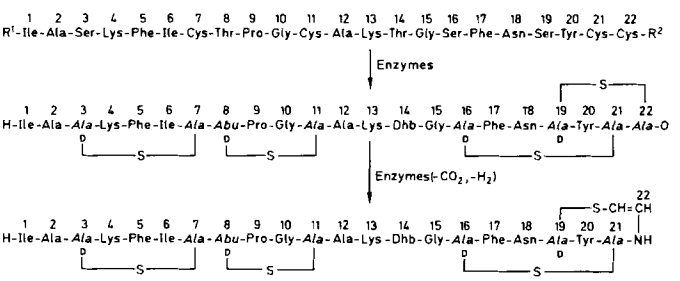


Fig. 3. Possible biosynthesis of epidermin from a postulated ribosomal precursor. The sequence of the steps—dehydration of serine and threonine, addition of the SH groups of cysteine with formation of the sulfur bridges, cleavage of CO_2 and H_2, thereby *C*-terminal formation of *S*-(2-aminovinyl)-D-cysteine—is presently being tested by isolation of the respective intermediates (see text). R^1 and R^2 have not been defined; *meso*-lanthionine and 3-methyllanthionine are abbreviated as in Figure 2; however, the configuration symbol D has been placed below "Ala".

The addition of inhibitors of the protein synthesis or RNA synthesis (erythromycin, rifampicin) to cultures of *Staphylococcus epidermidis* completely prevented the production of antibiotics. Epidermin thus belongs to the few antibiotics that are formed from a ribosomally synthesized precursor (Fig. 3) by posttranslational, enzymatic modification.[7] Dehydration of Ser^3, Thr^8, Thr^{14}, Ser^{16}, and Ser^{19} leads thereby to formation of dehydroalanine (Dha) and dehydroaminobutyric acid (Dhb). The subsequent or synchronous addition of thiol groups of the cysteine residues in the positions 7, 11, 21, and 22 to the CC double bonds of Dha and Dhb leads, with formation of sulfide bridges to *meso*-lanthionine and (2*S*,3*S*,6*R*)-3-methyllanthionine. The new *C*-terminal amino acid *S*-(2-aminovinyl)-D-cysteine is presumably formed by enzymatic oxidative decarboxylation, whereas the central dehydroaminobutyric acid remains unsaturated. We are at present attempting to detect and isolate precursor proteins with the aid of antibodies against synthetic segments of the postulated prosequence in order to prove this biosynthesis experimentally.

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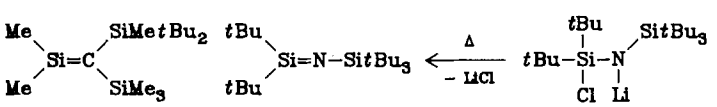
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Isolation of the Stable Silaketimine tBu$_2$Si=N–SitBu$_3$**

By *Nils Wiberg,* Klaus Schurz,* and *Gerd Fischer*

Dedicated to Professor Max Schmidt on the occasion of his 60th birthday

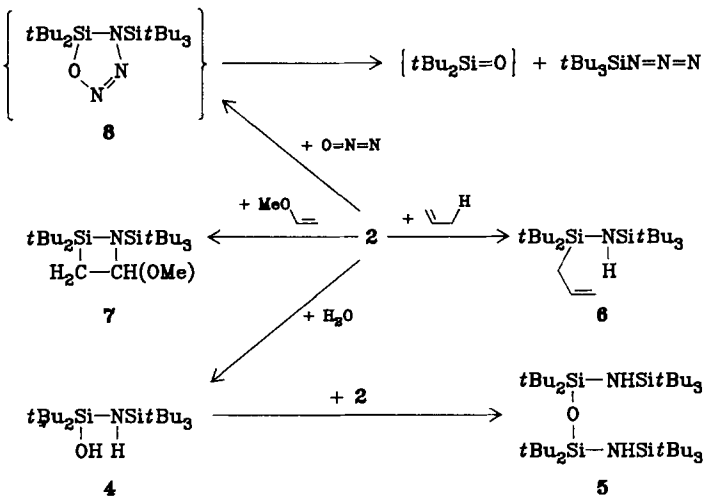
We were recently able to isolate the silaethene **1**, which is stable at room temperature.[1] We have now succeeded in preparing the first stable silaketimine **2**.



1 **2** **3**

2, like **1**, can be obtained by "thermal elimination of salt." The tetrahydrofuran (THF) adduct of compound **3**[2] serves as the precursor, which slowly eliminates LiCl upon heating.[3] In the presence of $CF_3SO_3SiMe_3$, **3** is transformed rapidly, even at room temperature, into the unsaturated system **2**, which can be crystallized from pentane at −78 °C.[5] The silaketimine **2** gives the expected ^{1}H-NMR, ^{29}Si-NMR, and mass spectra (see Experimental Procedure).

The unsaturated character of **2** is exhibited in a number of addition reactions (cf. Experimental Procedure). With water, **2** forms the addition product **4** (the product of insertion of **2** into an OH bond of H_2O), which, in turn, can react with **2** to form **5**. With propene, the ene reaction product **6** is formed, with methyl vinyl ether, the [2+2] cycloadduct **7**. Dinitrogen oxide also reacts with **2**; the primary product is probably the [2+3] cycloadduct **8**, which, however, is unstable and decomposes with formation of tri-*tert*-butylsilylazide and further products of tBu$_2$SiO, which have not yet been identified.



Experimental Procedure

Preparation of **2**: MeLi (15.99 mmol) in 17 mL of THF was added to tBu$_2$SiCl-NH(SitBu$_3$) **9** (6.27 g, 15.98 mmol) dissolved in 50 mL of THF at −78 °C. The mixture was allowed to react at −60 °C for 70 h (quantitative conversion according to ^{1}H-NMR spectroscopy). After removal of all volatiles in vacuum at room temperature, the residue was dissolved in 100 mL of pentane and the resulting solution treated with 2.9 mL (16 mmol) of $CF_3SO_3SiMe_3$. After 1 d, the solution was filtered to remove all precipitate formed (CF_3SO_3Li) and concentrated to 50 mL; THF-containing **2** crystallized out at −78 °C (80%). MS (15 eV): *m/z* 355 (M^+, 0.1%), 298 ($M^+ - t$Bu, 100%), 256, 214, 172, 130 (298$^+$ − n × propene, 3, 14, 7, 25). ^{1}H-NMR (THF, 28 °C): δ = 1.178 (tBu$_2$Si), 1.107 (SitBu$_3$). ^{29}Si-NMR (THF, 28 °C): δ = −2.555 (tBu$_2$Si), −16.571 (tBu$_3$Si).

Reactions of **2**: **2** (0.427 g, 1 mmol), dissolved in benzene, was allowed to react at room temperature with 0.5 or 1 mmol of H_2O and at 60 °C with 10 mmol of propene or 10 mmol of methyl vinyl ether. After removal of all volatiles in vacuum at room temperature, the analytically pure products **4**–**7** were obtained. The following melting points and ^{1}H-NMR signals (C_6D_6) were obtained for the samples characterized by elemental analysis and mass spectroscopy. **4**: m.p. = 130 °C; δ = 1.099 (s, SitBu$_2$), 1.216 (s, SitBu$_3$), 1.443 (s, OH).—**5**: m.p. = 344 °C (decomp.); δ = 1.279 (s, SitBu$_3$), 1.380 (s, SitBu$_2$).—**6**: m.p. = 121 °C; δ = 1.176 (s, SitBu$_2$), 1.192 (s, SitBu$_3$), 2.074 (m, SiCH$_2$), 5.129 (m, CH$_2$), 6.070 (m, CH).—**7**: m.p. = 114 °C (decomp.); δ = 1.148, 1.214 (s, SitBu$_2$), 1.290 (s, SitBu$_3$), 2.907 (s, CH$_3$), 4.934 (m, CH).

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2, 99112-70-6; **4**, 99112-71-7; **5**, 99112-72-8; **6**, 99112-73-9; 7, 99112-74-0; t-Bu$_2$SiCl-NH(Si-t-Bu$_3$), 99112-69-3.

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[**] Unsaturated Silicon Compounds, Part 10; Compounds of Silicon, Part 61. This work was supported by the Deutsche Forschungsgemeinschaft.—Parts 9 and 60: [1].

[1] N. Wiberg, G. Wagner, G. Müller, *Angew. Chem. 97* (1985) 220; *Angew. Chem. Int. Ed. Engl. 24* (1985) 229.
[2] **3** was synthesized in collaboration with Dr. *P. Karampatses*. An important intermediate is the compound **9**, which reacts with MeLi to give **3** (cf. Experimental Procedure). Synthesis of **9**:

$$t\text{Bu}_2\text{SiCl}-\text{N}=\text{N}=\text{N}-\text{SiNa}\xrightarrow[2.\,+\,\text{NMe}_3\text{HCl}]{1.\,+\,t\text{Bu}_3\text{SiNa}}\mathbf{9}+\text{N}_2+\text{NaCl}+\text{NMe}_3$$

(cf. N. Wiberg, G. Fischer, P. Karampatses, *Angew. Chem. 96* (1984) 58; *Angew. Chem. Int. Ed. Engl. 23* (1984) 59).

[3] LiX (X = electronegative partner) is usually eliminated intramolecularly from compounds of the type $R_2SiX-NLiR'$ according to our findings [4]. In the present case, the bulky *t*Bu groups force the elimination to occur intramolecularly.

[4] N. Wiberg, *J. Organomet. Chem. 273* (1984) 141.

[5] The crystals (m.p. = 139°C, decomp.) contain tetrahydrofuran, which is apparently weakly bound to the Si atom of the Si=N moiety of **2** [6].

[6] N. Wiberg, G. Wagner, G. Müller, J. Riede, *J. Organomet. Chem. 271* (1984) 381.

Synthesis of 6-Substituted Purines and Ribonucleosides with *N*-(6-Purinyl)pyridinium Salts**

By *Ryszard W. Adamiak,* Ewa Biała,* and *Bohdan Skalski*

The synthesis of 6-substituted purines and nucleosides—target compounds for biological and pharmaceutical studies—has usually been achieved by nucleophilic displacement reactions at C-6 of the purine ring. 6-Chloropurines, which can be prepared from hypoxanthines by reaction with $POCl_3$ in the presence of *N,N*-diethylaniline,[1] and the more reactive trialkyl(6-purinyl)ammonium salts,[2] or 6-alkylsulfonylpurines derived from them,[3] have proven to be the most suitable synthetic intermediates for such reactions.

We recently reported[4] on a virtually quantitative transformation of 2′,3′,5′-tri-*O*-acetylinosine **1a** and 9-methylhypoxanthine **1b** into fluorescent, water-soluble *N*-(6-purinyl)pyridinium salts **2a** and **2b** (87% and 75% yield), respectively, during pyridine assisted phosphorylations with 4-chlorophenyl phosphorodichloridate. Aqueous solutions of **2a** and **2b** are stable in the pH range 1.5–6.5 in the absence of light.[5]

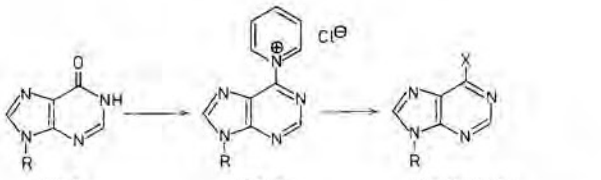
Easy access to these purines, equipped with a good leaving group at C-6, prompted us to study their reactivity towards nucleophiles. Herein, we report on a highly efficient, two-step synthesis of the 6-azido- **3a**, **b**, 6-alkylthio- **4a**, **5a**, and 6-methoxy-derivatives **6a**, **b** (Table 1).

Both **2a** and **2b** react with sodium azide in anhydrous dimethylformamide within a few minutes to give 6-azido-9-(2′,3′,5′-tri-*O*-acetyl-β-D-ribofuranosyl)purine **3a** and 6-azido-9-methylpurine **3b**, which could be isolated in 94 and 90% yields, respectively. Displacement with azide ion, although much slower, is also possible in aqueous solution.

When an aqueous solution of **2a**[4] was treated with 2-mercaptoethanol the purine derivative **4a** was formed within 1 h and could be isolated in 90% yield. The ethylthio derivative **5a** can be obtained directly from **1a** in an overall yield of 85% in a one-pot reaction.

The methoxy derivatives **6a** and **6b** are formed within a few hours upon reaction of **2a** and **2b**, respectively, with sodium methoxide in anhydrous methanol.

All the reactions described above proceed quantitatively under very mild conditions (checked by thin-layer chromatography on silica gel plates in chloroform containing 1–10% methanol). The products can be isolated in over 95% purity by simply concentrating the reaction mixture, if necessary, and water/chloroform extraction (with the exception of **6a**) - checked by thin-layer chromatography, elemental analysis, and ^{1}H-NMR spectra.



1a,b **2a,b** **3a,b**: X = N_3; **4a**: X = SCH_2CH_2OH; **5a**: X = SCH_2CH_3; **6a,b**: X = OCH_3

a: R = 2′,3′,5′-Tri-*O*-acetyl-β-D-ribofuranosyl

b: R = Methyl

Table 1. Some data of the products **3a**, **b**, **4a**, **5a**, and **6b**.

3a: λ_{max} (MeOH) = 252, 260, 287 nm (ε = 4200, 4600, 8100); λ_{min} = 240, 255, 264 (3400, 4100, 4300); ^{1}H NMR ($CDCl_3$): δ = 9.65 (1 H, s), 8.66 (1 H, s), 8.45 (1 H, s), 8.24 (1 H, s), 6.40 (1 H, d, J = 5.2 Hz), 6.25 (1 H, d, J = 5.1 Hz), 6.02–5.90 (2 H, m, 5.74–5.63 (2 H, *m*), 4.45 (6 H, *m*), 2.17–2.10 (9 H, 3 s) [a]

3b: m.p. 197°C; UV similar as for **3a**; ^{1}H NMR ([D_6]DMSO): δ = 10.10 (1 H, s), 8.60 (1 H, s), 4.01 (3 H, s); ^{1}H NMR ($CDCl_3$): δ = 9.50 (1 H, s), 8.69 (1 H, s), 8.17 (1 H, s), 7.97 (1 H, s), 4.08 (3 H, s), 3.90 (3 H, s) [a]

4a: λ_{max} (MeOH) = 286, 290 nm (ε = 18200, 18200); ^{1}H NMR ($CDCl_3$): δ = 8.68 (1 H, s), 8.18 (1 H, s), 6.22 (1 H, s, J = 5.0 Hz), 5.96 (1 H, t), 5.66 (1 H, t), 4.42 (3 H, s), 3.99 (2 H, t), 3.55 (2 H, t), 2.15, 2.11, 2.08 (9 H, 3 s)

5a: λ_{max} (MeOH) = 284, 290 (ε = 18300, 18300); ^{1}H NMR ($CDCl_3$): δ = 8.71 (1 H, s), 8.18 (1 H, s), 6.24 (1 H, d, J = 5.1 Hz), 5.97 (1 H, t), 5.74 (1 H, t), 4.43 (3 H, br. s), 3.38 (2 H, q, J = 7.3 Hz), 2.15, 2.11, 2.08 (9 H, 2 s), 1.45 (2 H, t, J = 7.3 Hz)

6b: m.p. 147°C; λ_{max} (H_2O) = 253 nm (ε = 11000); λ_{min} = 222 nm (ε = 2300); ^{1}H NMR ($CDCl_3$): δ = 8.56 (1 H, s), 7.89 (1 H, s), 4.19 (3 H, s), 3.89 (3 H, s)

[a] The ^{1}H-NMR spectrum in $CDCl_3$ is consistent with an equilibrium between the 6-azide and a tetrazole (see [3]).

The two-step synthesis of **3a**, **b**, **4a**, **5a**, and **6a**, **b** has a great advantage over the older methods[2,3], in that it requires fewer steps and affords higher overall yields.

As might be expected, the lack of substituents at the α-positions of the pyridinium ring of **2a**, **b** makes these sites likewise vulnerable to nucleophilic attack; this results in some limitations of the range of application of *N*-(6-purinyl)pyridinium salts. Strongly basic nucleophiles such as the hydroxide ion or some amines react with **2a**, **b** with quantitative formation of 6-aminopurine derivatives[4] (Zincke reaction).[6]

Experimental

3a, **b**: A solution of **2a** (983 mg, 2 mmol) or **2b** (495 mg, 2 mmol) in anhydrous dimethylformamide (10 mL) was treated with sodium azide (195 mg, 3 mmol). The resulting mixture was stirred at room temperature for 5–10 min, concentrated under vacuum at 35°C, and subsequently partitioned between water (10 mL) and chloroform (3 × 15 mL). The organic layer was dried over $MgSO_4$ and then evaporated down: yield 788 mg (94%) of **3a** and 315 mg (90%) of **3b**, respectively.

5a: A solution of **1a** (788 mg, 2 mmol) in anhydrous pyridine (10 mL) was treated with 4-$ClC_6H_4OP(O)Cl_2$ (0.56 mL, 3 mmol), initially at +5°C (10 min) and then at room temperature overnight in the dark. After removal of pyridine at 35°C the resulting residue was treated with ice-cold water (10 mL). After 10 min, dioxane (5 mL) and ethanethiol (0.70 mL, 10 mmol) were added and the emulsified mixture was stirred overnight. The reaction mixture was concentrated to half the volume, saturated with NaCl and extracted with chloroform (3 × 5 mL). The organic layer was dried over $MgSO_4$, concentrated, and passed through a layer of silica gel (Merck H60) in chloroform containing methanol (0–5%). Appropriate fractions were collected, concentrated to a small volume (2 mL), and added dropwise to hexane (150 mL); yield 745 mg (85%) of **5a** as precipitate.

6a, **b**: A solution of **2a** (983 mg, 2 mmol) or **2b** (495 mg, 2 mmol) in anhydrous methanol (50 mL) was treated portionwise with 0.1 M sodium methoxide in methanol (100 mL, 10 mmol) under stirring. After 6–8 h the reaction

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mixture was neutralized with acetic acid (ca. 0.6 mL) and evaporated to dryness under vacuum. – **6a**: The residue was dissolved in dry pyridine (50 mL) and, after concentration to ca. 20 mL, was treated with acetic anhydride (10 mL). After 1 h the mixture was treated with cold water and ethanol. Upon evaporation an oily residue was obtained; this was taken up in ethanol and treated with hexane, whereupon **6a** precipitated out: yield 702 mg (86%). – **6b**: The residue was partitioned between water (10 mL) and chloroform (3 × 15 mL). The organic layer was dried over $MgSO_4$, evaporated down, and **6b** was crystallized from chloroform; yield 280 mg (92%).

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CAS-Registry-numbers:
1a, 3181-38-2; **2a**, 99148-14-8; **2b**, 99148-15-9; **3a**, 99148-16-0; **3b**, 99148-17-1; **4a**, 99148-18-2; **5a**, 99148-19-3; **6a**, 99148-20-6; **6b**, 38917-25-8; 2-mercaptoethanol, 60-24-2; ethanethiol, 75-08-1.

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[6] a) T. Zincke, *Justus Liebigs Ann. Chem. 330* (1903) 361; b) F. Kröhnke, *Angew. Chem. 75* (1963) 317; *Angew. Chem. Int. Ed. Engl. 2* (1963) 380.

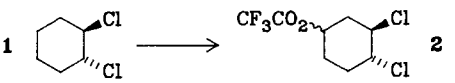
Selectivity of the Anodic Oxidation of CH- and CH_2-Groups; Selective Oxidation of Steroids at C-6**

By *Annegret Hembrock, Hans J. Schäfer,** and *Gesine Zimmermann*

Chemo- and regioselective functionalizations of CH- and CH_2-groups are especially useful in preparative chemistry, since they enable valuable products to be obtained in few steps from inexpensive starting materials. This is impressively exemplified by microbiological[1] and template-directed[2] oxidations of steroids. Hence, we became interested in studying the chemoselectivity of the anodic oxidation,[3,4] the possibility of inductively controlling the regioselectivity, and the oxidation of steroids.

Chemoselectivity: Anodic oxidation of methylcyclohexane in dichloromethane/trifluoroacetic acid affords 60% methylcyclohexyl trifluoroacetate. The statistically corrected reactivity of the hydrogen atoms on C-1, C-2, C-3, and C-4 of the educt is 10 : 2 : 2 : 1. Under the same conditions, *trans*-decalin affords 20–26% 1- and 2-decalyl trifluoroacetates and 54% oligomers (according to the mass spectrum, presumably tetramers and pentamers of decalin). In the less acidic electrolyte acetic acid/dichloromethane/Bu_4NBF_4 the oligomerization can be largely suppressed; decalyl acetates (43%) and fluorodecalins (32%) are obtained. With Bu_4NPF_6 as supporting electrolyte, 67% decalyl acetates and only 10% fluorodecalins are formed. The chemoselectivity of the acetoxylation at C-4a, C-1, and C-2 is 12 : 1 : 1. With Bu_4NOAc as supporting electrolyte, 77% decalyl acetate is obtained with equal selectivity without fluorination, but 35–40 F/mol are required for complete conversion; presumably because of a competing Kolbe electrolysis.

Regioselectivity by inductive effects: In the case of halogenations[5] or ozonolysis in superacids,[6] the site of reaction can be shifted by inductive effects; this also holds for the anodic oxidation. In dichloromethane/trifluoroacetic acid, chlorocyclohexane affords 23% 2-, 3-, and 4-chlorocyclohexyl trifluoroacetate in the ratio 1 : 1.7 : 3.2; cyclohexyl trifluoroacetate (16%), trifluoromethylcyclohexane (4%), and dichlorocyclohexane (30%, isomeric mixture) are additionally formed. In 2,2,2-trifluoroethanol the yields of byproducts are lower; 47% of the corresponding chlorocyclohexyl trifluoroethyl ethers are formed in the ratio 1 : 1.7 : 2.5. *trans*-1,2-Dichlorocyclohexane **1** affords 49% 3,4-dichlorocyclohexyl trifluoroacetate in dichloromethane/trifluoroacetic acid. A trifluoroacetoxylation in the α-position to the C–Cl groups is not observed.



Fatty acids **3** are preferentially trifluoroacetoxylated at the (ω – 2)- to (ω – 4)-CH bonds; no attack at C-2 to C-6 is observed, or, if at all, only very rarely (Table 1). The remarkable regioselectivity could be due to the inductive effect of the carboxyl group, which can also be protonated in the more strongly acidic region at the anode surface. In hydrogen abstractions from protonated substrates by radical cations, the methylene group furthest removed from the protonated position is preferentially attacked.[5] In the anodic oxidation of the CH-bond[3] the transition state is undoubtedly more positively charged than that in the radical abstraction and consequently is much more sensitive towards inductive effects. Skeletal rearrangements as in the oxidation in fluorosulfonic acid[7] do not appear to occur.

Table 1. Anodic oxidation [a] of fatty acids **3** to oxocarboxylic acids **4** [b].

3 $CH_3-(CH_2)_n-CO_2H \longrightarrow CH_3-(CH_2)_x-CO-(CH_2)_y-CO_2H$ **4**

n in **3**	**4** Yield [%]	**4** Rel. isomer distribution y:5	6	7	8	9	10	11	**3**, recovered [%]
12	40	3	7	19	28	20	16	7	27
10	15	12 [c]	23	26	29	10	—	—	42
8	3	39	46	15	—	—	—	—	71

[a] Electrolyte: CH_2Cl_2/CF_3CO_2H, 0.05 M Bu_4NPF_6, current consumption: 3–4 F/mol. [b] The trifluoroacetates were hydrolyzed, oxidized to the oxocarboxylic acids **4**, and identified by GC/MS with authentic compounds. [c] Less than 2% of 5- and 6-hydroxydodecanoic acid in the isomeric mixture.

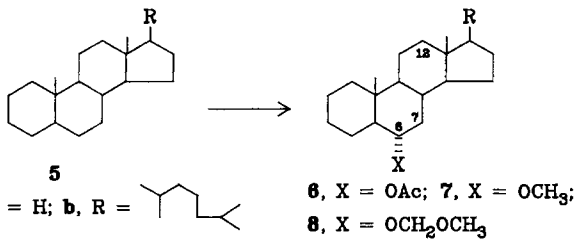
$$RH \xrightarrow[-e^{\ominus}]{} RH^{\ominus\oplus} \xrightarrow[-H^{\oplus}]{} R^{\odot} \xrightarrow[-e^{\ominus}]{} R^{\oplus} \xrightarrow[-H^{\oplus}]{R^1CO_2H} R^1CO_2R$$

*Oxidation of androstane **5a** and cholestane **5b**:* In dichloromethane/trifluoroacetic acid, the anodic oxidation of androstane proceeds unsatisfactorily. The main products are not fully characterized, high-molecular com-

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pounds, presumably oligomers. In glacial acetic acid ($CH_3CO_2H/CH_2Cl_2 = 3:2$, $i = 40$ mA/cm^2, $T = 20$°C, Pt electrode) 17% androstanyl acetate is obtained and 38% androstane is recovered. Remarkable is the selectivity of the oxidation: We found that the 6- (**6a**), 7-, and 12-acetates are formed in the ratio 35 : 1 : 2.5; other acetates could not be detected by us. Assignment of the structures was accomplished by hydrolysis, oxidation to the ketone, and comparison of the mass spectra with those given in the literature. The main product was characterized ^{13}C-NMR spectroscopically as 6α-acetoxy-5α-androstane (**6a**). The electrolysis in methanol (methanol/dichloromethane, 0.1 M $NaClO_4$, glassy carbon electrode) proceeds even more selectively. At a 53% conversion (47% androstane recovered) 14% 6-methoxyandrostane (**7a**) and 27% 6-(methoxymethoxy)androstane (**8a**) were formed.



5

a, R = H; **b**, R =

6, X = OAc; **7**, X = OCH_3; **8**, X = OCH_2OCH_3

In glacial acetic acid, cholestane affords 15% cholestanyl acetates; the 6-(**6b**), 7-, and 12-acetates are formed in the ratio 40 : 1 : 2. In methanol, 50% conversion was observed with formation of 15% 6-methoxycholestane (**7b**) and 25% 6-(methoxymethoxy)cholestane (**8b**). These findings reveal a surprising and remarkable selectivity. Of the 32 hydrogen atoms in androstane and the 48 in cholestane, predominantly only those on C-6 are oxidized. Acetates or methyl ethers originating from attack at the reactive tertiary hydrogen atoms on C-5, C-9, C-14, and, in the case of cholestane, also those on C-17, C-20, and C-25 are not found. An explanation for this would seem premature, but the selectivity could be effected by an association of the steroid molecules. In stacked androstane and cholestane, the tertiary hydrogen atoms would be shielded, while on the front and rear side of the stack the hydrogen atoms on C-6, C-7, and C-12 would be exposed to the electrode for the electron transfer.

The methoxymethyl ethers **8** could be formed by secondary oxidation of the methyl ethers **7**.[8] That the less reactive but obviously more easily accessible methyl group is hereby oxidized, and not the methine hydrogen, could be a further indication of the formation of stacked associates.

Thus, the anode is a cheap and easily employable reagent for the oxidation of CH-bonds. The chemoselectivity of the anode compares favorably with other reagents; R_s^t, the ratio of the rate of attack at tertiary and secondary CH bonds, is 12 for decalin.[9] The regioselectivity can be controlled by inductive effects. The steroid hydrocarbons androstane and cholestane are remarkably regioselectively oxidized at C-6.

Experimental

A solution of 5α-androstane (**5a**) (260 mg, 1 mmol) in CH_2Cl_2 (20 mL), methanol (30 mL), and $NaClO_4$ (0.612 g, 0.1 M) was electrolyzed at 20°C with a current density of 30 mA/cm^2 at a glassy-carbon anode (21 cm^2) in an undivided cell until consumption of 965 As. Gas chromatographic analysis (60 m capillary column, 0.3% SE 52) of the crude product revealed the presence of 14% **7a**, 27% **8a**, and 47% **5a** (calibrating standard: *n*-octadecane). The crude product was treated with sodium methoxide and, after removal of the solvent, the residue was taken up in cyclohexane and the supporting electrolyte removed by filtration. HPLC separation (CH_2Cl_2:*n*-hexane, 1 : 1) yielded 98 mg (38%) **5a**, 29 mg (10%) **7a** (^{13}C-NMR, INEPT), and 67 mg (21%) **8a**. **8a** was hydrolyzed with HCl in methanol to 5α-androstan-6α-ol (^{13}C-NMR comparison with 6α-androstanol [10]).

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Bis(2,4,6-tri-*tert*-butylphenyl)bicyclotetraphosphane

By *Ralf Riedel, Hans-Dieter Hausen,* and *Ekkehard Fluck**

So far, approximately twenty polycyclic organophosphanes have been isolated and characterized;[1,2] in addition, a few further representatives of this class of compounds have been detected spectroscopically.[1-3] We have now been able to synthesize bis(2,4,6-tri-*tert*-butylphenyl)bicyclotetraphosphane **1**, a derivative of the simplest bicyclic phosphane P_4H_2. **1** is formed along with bis(2,4,6-tri-*tert*-butylphenyl)diphosphene **2**[4] upon reaction of 2,4,6-tri-*tert*-butylphenyllithium and 1-bromo-2,4,6-tri-*tert*-butylbenzene with white phosphorus. Thus, it has been possible for the first time to isolate a product of the reaction of white phosphorus whereby only one bond of the P_4 tetrahedron is opened.

$$4\,RLi + 4\,RBr + 3\,P_4 \longrightarrow \underset{\mathbf{1}}{2\,R_2P_4} + \underset{\mathbf{2}}{2\,R_2P_2} + 4\,LiBr$$

R = 2,4,6-tBu$_2$C$_6$H$_2$

1 is ivory-colored, slightly sensitive to oxidation, stable at room temperature, and soluble in chloroform. The ^{31}P{^{1}H}-NMR spectrum ($CDCl_3$; standard: 85% H_3PO_4) of

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1 shows two multiplets, $\delta = -272$ (bridgehead P atoms) and $\delta = -130$, while the $^1H\{^{31}P\}$-NMR spectrum contains two singlets at $\delta = 1.27$ (4-*t*Bu) and 1.74 (2,6-*t*Bu) as well as a multiplet at $\delta = 7.0$. These findings are consistent with the results of an X-ray structure analysis (Fig. 1).[5]

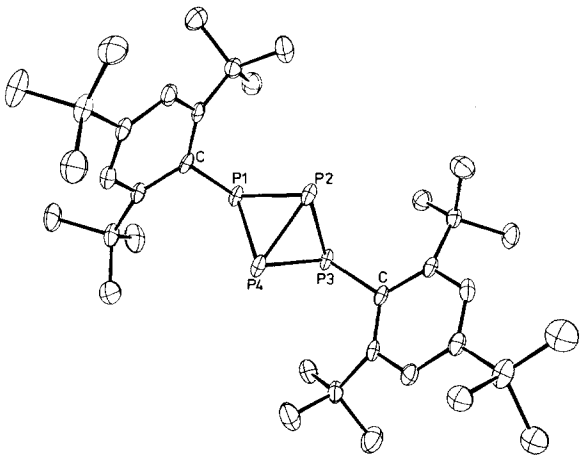


Fig. 1. ORTEP plot of the crystal structure of **1** (vibration ellipsoids at the 50% probability level). Bond lengths [pm] and bond angles [°]: P1-P2 222.3(4), P1-P4 223.5(7), P2-P3 222.2(3), P2-P4 216.6(2), P3-P4 223.6(9), P1-C 189.2(8), P3-C 188.5(1); P2P1P4 58.1(1), P1P2P4 61.2(1), P1P2P3 80.9(1), P3P2P4 61.3(1), P2P3P4 58.1(1), P3P4P2 60.6(1), P3P4P1 80.4(1), P2P4P1 60.7(1), CP1P2 98.2(1), CP1P4 97.3(1), CP3P4 99.2(1), CP3P2 97.8(1). The numbering of the P atoms is arbitrary.

The two 2,4,6-tri-*tert*-butylphenyl moieties in **1** are *cis* oriented. The folding angle of the P_4 bicycle, 95.5°, is just about the same as that in bis(trimethylsilylamino)bicyclotetraphosphane (95.2°), which has been synthesized from diphosphanes.[6] The P-P bonds in both compounds are (with exception of the central bond) about the same length as normal P-P single bonds (in **1** 222.2-223.6 pm); only the central P-P bond in **1** is slightly longer (216.6 pm) than in the bis(trimethylsilylamino) derivative (213 pm).

Experimental

All operations were carried out under argon. A solution of 1-bromo-2,4,6-tri-*tert*-butylbenzene [7] (61.55 g, 189.3 mmol in ether (500 mL) was treated at room temperature with 85 mL (212.6 mmol) of a 2.5 molar solution of *n*-butyllithium in *n*-hexane. The mixture was stirred for 3 h and then treated with 12.4 g (100 mmol) of white phosphorus. After 10 min, the resulting red solution began to boil and was then heated at the boiling point for a further 60 min. After 24 h, the mixture was hydrolyzed. A reddish-brown oil was obtained (72 g), from which an air-stable orange-red solid crystallized which was collected on a frit and washed with acetone. After recrystallization from benzene, 3 g of a coarsely crystalline mixture of **1** and **2** (ca. 3 : 1) was isolated. The crystals of **1** obtained by a second recrystallization were selected for the X-ray structure analysis.

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[5] **1** crystallizes monoclinically; space group $P2_1/n$, $a = 1677.2(4)$, $b = 1079.7(3)$, $c = 2071.5(3)$ pm, $\beta = 96.01(2)°$; $Z = 4$, $\rho_{calc} = 1.09$ g/cm^3). All atoms occupy the general positions of the space group. The structure was derived from 5516 independent reflections (4409 observed) via direct methods and Fourier syntheses and refined to $R = 0.051$. Further details of the crystal structure investigation are available on request from the Fachinformationszentrum Energie, Physik, Mathematik GmbH, D-7514 Eggenstein-Leopoldshafen 2, on quoting the depository number CSD-51578, the names of the authors, and the full citation of the journal.
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Computer-Controlled Precipitation of Metal Hydroxides and Hydrous Oxides—Preparation of Manganese Dioxide Having Uniform Particle Sizes**

By *Dieter H. Buss, Gottfried Schaumberg,* and *Oskar Glemser**

It is difficult to precipitate metal hydroxides and hydrous oxides[1] that always have the same properties from aqueous solution. Recently, we were able to obtain cobalt, nickel, and manganese hydroxides, as well as their double hydroxides with aluminum,[2-4] by computer-controlled precipitation at a constant pH value. Their compositions, structures, and discharge capacities could be well reproduced. We report here on the application of this technique to the Guyard reaction,[5] the formation of manganese dioxide from manganese(II) salts and potassium permanganate in acidic solution.

The precipitations were carried out at the potential that is established at an electrographite electrode (measured as U_{max} versus a Ag/AgCl//3 M KCl reference electrode), for a given pH value of the solution, after the manganese dioxide begins to precipitate and while a small excess of $MnO_4^{\ominus}$ is still visible. The excess or deficiency of $MnO_4^{\ominus}$ ions is controlled with this potential, which remains relatively stable (±5 mV) during the course of the precipitation (hours). The upper control limit is U_{max}, the lower, the approximately 20 mV more negative potential. Between these limits, nearly stoichiometric amounts of $KMnO_4$ and $Mn(NO_3)_2$ solutions are added simultaneously during the precipitation. When the lower limit of the potential is exceeded, $KMnO_4$ solution is added; when the upper limit is exceeded, $Mn(NO_3)_2$ solution is added.[6,7]

Using this procedure, it has been possible, for the first time, to prepare manganese dioxide having nearly uniform

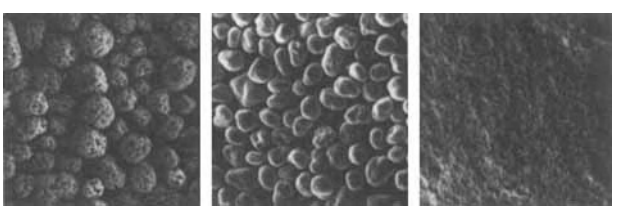


Fig. 1. Scanning electron micrograph of manganese dioxide that was precipitated with computer control at pH 0 and 1 (left and middle, respectively) or without computer control at about pH 1 (right). Left: Enlargement 110 times; potential limits 1407/1432 mV; 87.1 wt.-% active MnO_2; particle size 70 μm; bulk density 0.72 g/cm^3; BET surface: 169 m^2/g; discharge capacity $q_{max} = 73.9$ mA h/g.—Middle: Enlargement: 119 times; potential limits 1347/1357 mV; 80.1 wt.-% active MnO_2; particle size 45 μm; bulk density 1.53 g/cm^3; BET surface: 0.4 m^2/g; discharge capacity $q_{max} = 81.3$ mA h/g. —Right: Enlargement: 122 times; without control of potential; 85.7 wt.-% active MnO_2; bulk density 0.41 g/cm^3; BET surface: 108 m^2/g; discharge capacity $q_{max} = 11$ mA h/g.

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particle sizes at pH 0, 1, and 2; the precipitates settle quickly and are easy to wash. Particle size, surface characteristics,[9] bulk density, and electrochemical properties[10] of the product depend strongly on the pH value during the precipitation (Fig. 1, left and middle). The properties of the samples obtained at pH 2 and pH 1 are nearly identical. At the same pH values, uncontrolled precipitation affords precipitates that are difficult to filter and wash and that, after drying, are present as nonuniform agglomerates (Fig. 1, right). The preparations obtained by controlled precipitation belong structurally to the δ-MnO_2 group:[8] those prepared by uncontrolled precipitation are primarily amorphous.

Particularly noteworthy is the possibility of obtaining uniform particles with very large surface areas (169 m^2/g) and also with much smaller surface areas (0.4 m^2/g) by controlled precipitation of manganese dioxide at pH 0 and at pH 1 and 2, respectively. The latter are somewhat similar in appearance to the manganese nodules found in the ocean.

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[8] The Debye-Scherrer diagrams of the samples are identical with those of W. Buser, P. Graf, W. Feitknecht (*Helv. Chim. Acta 37* (1954) 2322) who obtained samples by precipitation from $KMnO_4$ solutions with acetic acid $MnCl_2$ solutions.
[9] We thank VARTA AG (Forschungs- und Entwicklungszentrum), Kelkheim, for the BET measurements.
[10] Determination of the electrochemical charge capacity: A paste prepared from 3 g of the sample being tested, 1.5 g of graphite, 3.5 g of Ni powder, and 1 mL of water was pressed into a 11-cm tube made of nickel wire mesh. This test electrode was galvanostatically cyclized in cylindrical plexiglass cells with a Cd sintered sheet as counter electrode using 30% KOH solutions as electrolyte. Discharge procedure: charging of the cell with 25 mA current, subsequent discharge with 25 mA countercurrent to a cell voltage of 0.8 V (vs. $Cd/Cd(OH)_2$ in 30% KOH solution).

4-[Tri(*n*-butyl)phosphonio]-2,5-diselenoxo-1,3-diselenacyclopentanide**

By *Heinz P. Fritz,* Gerhard Müller, Gabriele Reber,* and *Michael Weis*

The search for electronically or ionically conducting nonmetallic compounds has focused on charge-transfer salts, highly conjugated polymers, and graphite intercalation compounds.[1-4] A chainlike structure [-Se-C(Se)-]$_n$ has been postulated for poly-CSe_2,[5] which should be electronically conducting[5,6] and which is obtained from CSe_2 by polymerization under normal conditions or, better still, under high pressure. We have been able to characterize the two previously described[5,6] $(CSe_2)_n$ modifications as different polymers; the electrically conducting polymer is $(C_2Se_3)_n$.[7] The composition and structure of the amorphous polymerizate are unknown. Accordingly, it appeared to us worthwhile to seek possible routes for the uniform polymerization of CSe_2.

Trialkylphosphanes react with CSe_2 to form zwitterionic, partly oligomeric adducts of the type $R_3P(CSe_2)_n$,[8] which may be used as building blocks for a selective reaction to give a linear polymer. The reaction of nBu$_3$P with CSe_2 affords dark red, flat prisms,[9] which are readily soluble in the conventional organic solvents and which are not very sensitive to air and moisture. Elemental analysis and mass spectroscopy gave the unexpected formula nBu$_3$PC$_3$Se$_4$. IR absorptions at 1465, 968, 902, and 750 cm^{-1} indicate the presence of C=C, two different C=Se, and P–C bonds. The ^{31}P-NMR signal at $\delta = +20.78$ (relative to H_3PO_4) suggests a phosphorus ylide type structure; nBu$_3$P=Se and nBu$_3$P=O exhibit ^{31}P-NMR signals at $\delta = +37$ and 43.2, respectively.

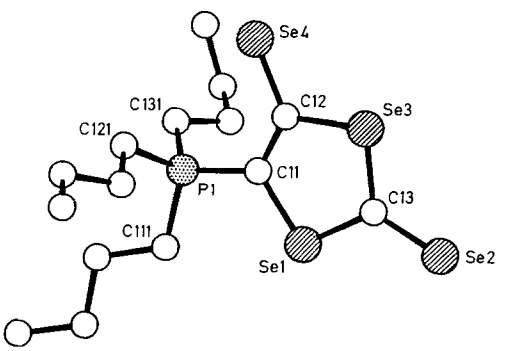
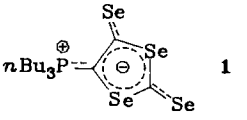


Fig. 1. Structure of one of the two crystallographically independent molecules of **1** (PLUTO). Important bond lengths [Å] for both molecules. P1-C11 1.77(1)/1.78(1), C11-C12 1.42(2)/1.38(2), C12-Se3 1.91(1)/1.88(1), C13-Se3 1.86(1)/1.87(2), C13-Se1 1.88(1)/1.88(1), C11-Se1 1.89(1)/1.91(1), C12-Se4 1.82(1)/1.87(1), C13-Se2 1.79(1)/1.77(1).

The X-ray structure analysis[10] shows the presence of planar C_3Se_2 five-membered rings in both crystallographically independent molecules in the crystal (Fig. 1). The ylide-like character is supported by the length of the P–C_{ring} bond (1.78(1) Å). The lengths of the exo- and endocyclic C–Se bonds (1.77(1)–1.91(1) Å) indicate a bond order between that of a formal double bond and that of a formal single bond.[11] The nearly identical C–Se distances and the slightly shorter (compared to single bonds) C–C bond in the ring suggest partial delocalization of the electron pairs at the ylidic carbon and the Se atoms. This is further supported by the ylidic P–C bond which is significantly longer than that in simple alkylidenephosphoranes. The compound is best described, therefore, by formula **1**.

Apart from the known, spontaneous oligomerization of CSe_2, the chalcogen abstraction and adduct formation of



1

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the phosphane apparently determines the course of reaction in this case. In agreement with this hypothesis, nBu$_3$P reacts with CS_2 to give only the zwitterion nBu$_3\overset{\oplus}{P}-\overset{\ominus}{C}S_2$.[7] An X-ray structure analysis of the corresponding triethyl derivative is available.[12]

1 represents a new type of phosphorus ylide which is readily accessible in high yields. The arrangement of the Se atoms in the five-membered ring is similar to that in tetraselenabisfulvalene derivatives, in which the intermolecular interactions between the heteroatoms are decisive for the (super)conductivity. In dibenzotetraselenafulvalenes, intermolecular Se···Se separations of 4.03 to 4.09 Å[13] are found; in $(TMTSF)_2AsF_6$ (TMTSF = tetramethyltetraselenafulvalene), 3.87 to 4.98 Å[14] (van der Waals radii for Se: 2.0[15] or 1.9 Å[16]). The shortest intermolecular Se···Se distances in **1** are 3.49(1) and 3.91(1) Å (Se1 and Se4, respectively). The specific conductivities measured with direct and alternating current on pellets, are small (10^{-9} and 10^{-8} S/cm, respectively, at room temperature), which may be due to the non-coplanar packing of the ring systems. However, derivatives of **1** might have the properties of "organic metals."

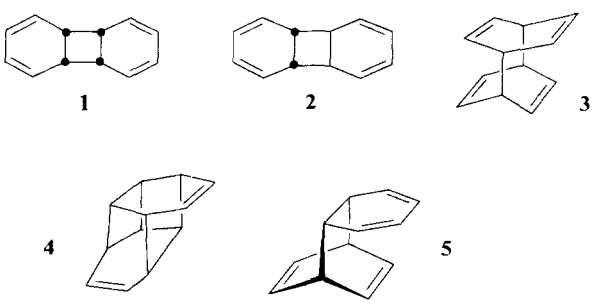
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[9] *Experimental procedure:* All operations were carried out under N_2. nBu$_3$P (3.9 mL, 15.77 mmol) in 30 mL of ether was added to a stirred solution of CSe_2 (1 mL, 15.77 mmol) in 30 mL of ether with isopropanol/CO_2 cooling. The reaction mixture was then heated to reflux with addition of ether. Polymeric material was filtered off, the ether was removed from the filtrate, and the residue was recrystallized from ether. Dark red, flat prisms (1.62 g, 80%) were obtained which decompose at 93.5°C. Correct elemental analysis (C, H, P). IR (KBr): ν = 2950 (m), 2920 (m), 2860 (m), 1465 (m), 1385 (s), 1092 (m), 968 (s), 902 (vs), 750 (m), 510 (w), 378 (w) cm^{-1}; ^{1}H-NMR (60 MHz, C_6D_6): $0.5 < \delta < 2.5$ (m, 27H); ^{31}P-NMR (36.43 MHz, C_6D_6): δ = 20.78 (s, 1P); MS: m/z 554 (0.20%, $M^{\oplus}$), 478 (0.20), 396 (0.12), 282 (11.98), 226 (21.73), 172 (100), 92 (24.14), 80 (56.52).
[10] Crystal structure data: $C_{15}H_{27}PSe_4$, M = 554.20; monoclinic, C2/c; a = 39.17(1), b = 13.414(3), c = 15.842(4) Å, β = 95.78(2)°, V = 8281.5 Å^3; ρ_{calcd} = 1.778 g/cm^3 for Z = 16; $\mu(Mo_{K\alpha})$ = 70.85 cm^{-1}, $F(000)$ = 4288, T = −35°C. 5713 measured, independent reflections, of which 2688 are observed with $I \geq 3.0\sigma(I)$, empirical absorption correction (ω-scan, $\Delta\omega$ = 1°, $((\sin\vartheta)/\lambda)_{max}$ = 0.55, +h, +k, ±l, $Mo_{K\alpha}$, λ = 0.71069 Å, graphite monochromator, Syntex $P2_1$). Solution by direct methods, R = 0.048, R_w = 0.043, $w = 1/[\sigma^2(F_0) + 0.00006F_0^2]$ (anisotropic, H constant, 361 parameters, full matrix, SHELX 76). $\Delta\rho$(final) = +0.86/−0.63 e/Å^3. Further details of the crystal structure investigation are available on request from the Fachinformationszentrum Energie, Physik, Mathematik GmbH, D-7514 Eggenstein-Leopoldshafen 2, by quoting the depository number CSD 51552, the names of the authors, and the journal citation.
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o,p'-Dibenzene**

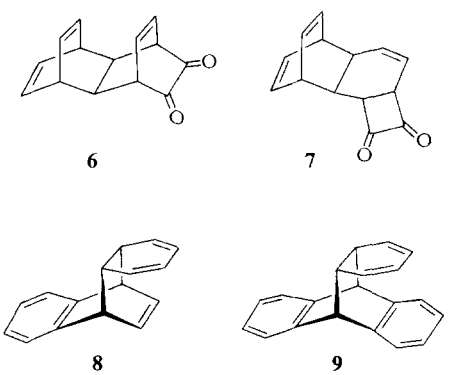
By *Ralf Braun, Matthias Kummer, Hans-Dieter Martin,** and *Mordecai B. Rubin**

The family of $(CH)_{12}$ hydrocarbons includes a number of formal dimers of benzene, among which are the [2+2] dimers **1** and **2**, the [4+4] compound **3**, ansaradiene (**4**), and the [4+2] dimer tricyclo[6.2.2.0^{2,7}]dodeca-3,5,9,11-tetraene ("*o,p'*-dibenzene") **5**. While these dimers have been of theoretical interest[1], the only compounds described in the literature to date are **2**[2a] and **4**.[2b] An organometallic complex of **5** has been reported;[3] however, attempted liberation of **5** from the complex resulted in isolation of benzene and not of its dimer. This result was attributed to the anticipated low thermal stability of **5**, which can revert to monomer by a thermally allowed, retro-Diels-Alder reaction. We report here on the successful preparation of **5** by low-temperature photolysis and the study of its thermal decomposition to benzene.



1 **2** **3** **4** **5**

The unsaturated diketone **6**, prepared in yields of 10% by [4+2]-cycloaddition of barrelene to *o*-benzoquinone in anhydrous tetrahydrofuran (THF) at room temperature[4] [UV (methylcyclohexane): λ_{max} = 456 nm (ε = 145); IR (methylcyclohexane: CH_2Cl_2 1:1) ν_{max} = 1740 cm^{-1}; m.p. 126–129°C (dec.); ^{1}H NMR (60 MHz, $CDCl_3$): δ = 2.45 (s, 2H), 3.43 (t, 2H), 3.61 (m, 2H), 5.93 (t, 2H), 6.14 (t, 2H),



6 **7** **8** **9**

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6.57 (t, 2H)], underwent the expected[5,6] photoisomerization to cyclobutanedione **7** [UV (methylcyclohexane): $\lambda_{max}=496$ nm (110); IR (methylcyclohexane : CH_2Cl_2 1:1) $\nu_{max}=1770$, 1795 cm^{-1}] upon irradiation at 404 or 436 nm, with isosbestic behavior in the early stages of the reaction (305, 374 and 482 nm).

Irradiation of **7** in methylcyclohexane at room temperature ($\lambda=496$ nm) resulted in its conversion into benzene, presumably via the intermediacy of **5**. The quantum efficiency for this reaction is greater than the maximum value observed for formation of **7** from **6**. When the irradiation was performed at $-80°C$, the spectrum of a new compound was obtained with maxima in the ultraviolet at 294, 282, 271 and 260 nm (sh). The extinction coefficients were of the order of 3000. The new compound is stable indefinitely at $-80°C$ (cf. Fig. 1).

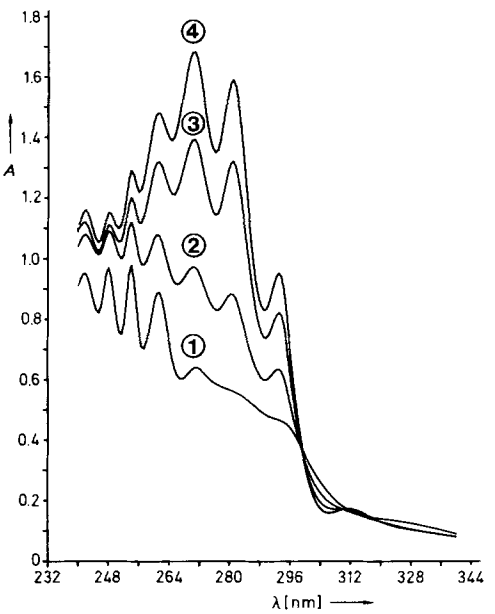


Fig. 1. UV spectroscopic monitoring of the generation of **5** from **7** at $-80°C$. Spectra after 10 ②, 30 ③, and 60 min ④ irradiation at $\lambda>380$ nm. ①: Spectrum after warming to $-50°C$ (complete decomposition of **5** to benzene).

The above absorptions are assigned to *o,p'*-dibenzene (**5**), on the following grounds: On the one hand, the spectrum is almost identical to that of the benzene-naphthalene adduct,[7,8] and, on the other, benzene is formed rapidly and quantitatively upon warming. The kinetics of this retro-Diels-Alder reaction were measured by following the disappearance of the maxima mentioned above at five temperatures in the range -68 to $-52°C$. Good first-order behavior was observed in all cases and identical rate constants were obtained from measurements at different wavelengths at a given temperature. The results obtained fit the Arrhenius expression:

$$\lg k\,[s^{-1}] = (11.78\pm0.5) - \frac{(14.7\pm0.4)}{2.303\,RT}\,[\text{kcal mol}^{-1}]$$

with $\Delta H^{\neq}=14.3$ kcal mol^{-1}, $\Delta S^{\neq}=-6$ cal mol^{-1} K^{-1}, $\Delta G^{\neq}=15.6$ kcal mol^{-1} (errors are double standard deviations). The minimal entropy change observed is consistent with a rigid transition state for this highly exothermic reaction. Comparison of the activation parameters for the thermolysis of **5** with those reported for the thermal decomposition of the formal [4+2] addition products of benzene and naphthalene **8**[7] or anthracene **9**[8] is instructive. The entropies of activation (25°C) for **8** and **9** are -5 and -3 cal mol^{-1} K^{-1}, respectively but the activation energies (19.5 kcal mol^{-1} for **8** and 24.9 kcal mol^{-1} for **9**) differ markedly, reflecting the difference between formation of two molecules of benzene from **5** vis-à-vis one of benzene and one of naphthalene from **8** or one of benzene and one of anthracene from **9**. We also note that the reported[2a] half-life of **2** at 40°C is 5.75 h, while $t_{1/2}$ for **5** is of the order of 5 ms at this temperature. Irradiation of **5** through quartz at $-80°C$ resulted in almost quantitative conversion (>95% by UV spectroscopy) into benzene. In addition, poorly defined bands of low intensity were observed at 355, 379, and 390 nm. Thus, the excited state of **5**, which has, a priori, many reaction paths available to it, proceeds to the same product as the thermal reaction (possibly in a stepwise fashion).

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CAS-Registry-numbers:
5, 7322-47-6; **6**, 99096-99-8; **7**, 99097-00-4; benzene, 71-43-2; barrelene, 500-24-3; *o*-benzoquinone, 583-63-1.

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$[(\eta^5\text{-}C_5Me_5)_2Fe_2S_4]$ and $[(\eta^5\text{-}C_5Me_5)_2Co_2S_4]$, Two Novel Bis(pentamethylcyclopentadienylmetal) Complexes Rich in Sulfur

By *Henri Brunner, Norbert Janietz, Walter Meier, Gertrud Sergeson, Joachim Wachter,* Thomas Zahn,* and *Manfred L. Ziegler*

The electronic and structural properties of $[Cp_2M_2S_4]$ complexes (Cp: C_5H_5, MeC_5H_4 or C_5Me_5) depend, like their reactivity, upon the transition metal M. Each of the elements V,[1] Cr, Mo, W,[2] and Fe[3] can be assigned to a particular structural type. So far, nothing has been reported about a corresponding Co compound.

The complex $[C_5Me_5(CO)Co)]_2$, containing a Co=Co bond, reacts with sulfur in toluene at room temperature with formation of the green complex **1** in 23–39% yield.[4]

$$[C_5Me_5(CO)Co]_2 + 1/2\,S_8 \xrightarrow[20°C]{\text{toluene}} [(C_5Me_5)_2Co_2S_4] \quad \mathbf{1}$$

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Elemental analyses and mass spectrum (dominating ions in the 70 eV spectrum: M^+, $[M-S]^+$, $[M-S_2]^+$) support this formulation. Compound **1**, which according to its ^{1}H-NMR spectrum ($\delta(CH_3)=1.62$, in $CDCl_3$) is symmetrical and is configurationally stable in solution, at least at room temperature. An IR absorption at 502 cm^{-1} is characteristic for disulfide ligands, whose multiple coordination possibilities have already been described in detail.[5] According to an X-ray structure analysis,[6] **1** has a center of inversion, the two Co atoms are bridged by two disulfide ligands (Fig. 1). These η^1,η^2-S_2 ligands are indeed primarily known as bridging elements,[5] but not in this step-like (*anti*-) arrangement of two such moieties. A relatively large Co–Co distance (3.38 Å) supports the assumption that the Co atoms achieve noble gas configuration without the necessity of Co–Co bonding. Hence, **1** represents a novel type of structure within the $[Cp_2M_2S_4]$-class of compounds.

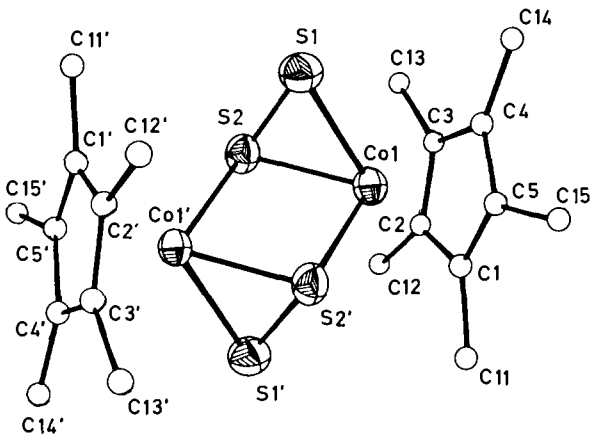


Fig. 1. Molecular structure of **1** (ORTEP plot). Selected bond lengths [Å] and angles [°] Co1-S1 2.247(4), Co1-S2 2.245(4), Co1-S2′ 2.244(4), S1-S2 2.062(6), Co1···Co1′ 3.38; S1-Co1-S2 54.7(2), S2-Co1-S2′ 83.1(2), Co1′-S2-Co1 96.9(1), Co1′-S2-S1 102.6(2).

Common to all compounds of this type is that their structures can only be elucidated with the aid of an X-ray structure analysis. Thus, the synthesis of two isomers of the composition $[(C_5H_5)_2Fe_2S_4]$, which are formed in moderate yields upon photolysis of $[C_5H_5(CO)_2Fe]_2$ with S_8 has recently been reported.[3] We have now found a high-yield synthesis of the permethylated derivative **2** by reaction of $[C_5Me_5(CO)_2Fe]_2$ with an excess of sulfur in boiling toluene.[7]

$$[C_5Me_5(CO)_2Fe]_2 + 1/2\,S_8 \xrightarrow[115\,°C]{\text{toluene}} [(C_5Me_5)_2Fe_2S_4] \quad \mathbf{2}$$

2 is formed as the sole isomer in 55–78% yield. Extension of this method to $[C_5H_5(CO)_2Fe]_2$, however, leads to formation of $[(C_5H_5)_4Fe_4S_4]$.[8] Owing to a lack of unequivocal IR spectroscopic data for comparison, an X-ray structure analysis also had to be carried out on **2**.[6] Complex **2** contains two disulfide ligands oriented perpendicularly to each other (Fig. 2). The bond lengths and bond angles are essentially in accord with those in $[(C_5H_5)_2Fe_2(\eta^1\text{-}S_2)(\eta^2\text{-}S_2)]$.[3] The influence of the pentamethylcyclopentadienyl moiety manifests itself in only a slight extension (0.01–0.03 Å) of the Fe–Fe, Fe–S, and S–S distances. Interestingly, in the two complexes **1** and **2**, both of which contain no direct metal-metal bond, the methyl residues of the two C_5Me_5 rings are staggered, whereas in $[(C_5Me_5)_2Mo_2S_4]$ they are eclipsed.[2c]

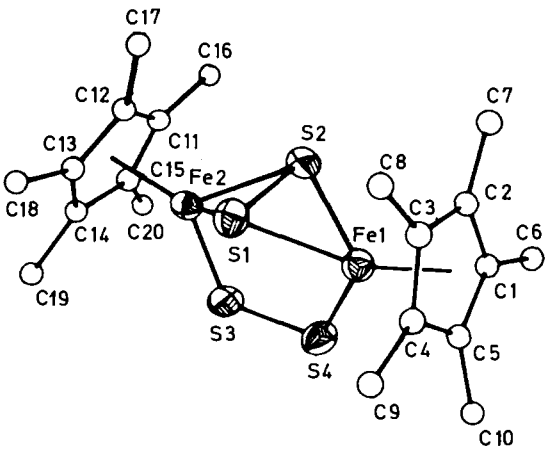


Fig. 2. Molecular structure of **2** (ORTEP plot). Selected bond lengths [Å] and angles [°]: Fe1-S1 2.282(1), Fe1-S2 2.273(1), Fe1-S4 2.129(1), Fe2-S1 2.269(1), Fe2-S2 2.268(2), Fe2-S3 2.122(2), S1-S2 2.055(2), S3-S4 2.021(2), Fe1···Fe2 3.53; S1-Fe1-S2 53.6(0), S1-Fe2-S2 53.9(0), Fe1-S1-Fe2 101.6(1), Fe1-S2-Fe2 101.9(1), Fe2-S3-S4 110.7(1), Fe1-S4-S3 110.8(1).

A comparison of **1** and **2** strikingly reveals the same overall contribution of eight valence electrons by the sulfur ligands in both cases. Nevertheless, the difference in the ligand combinations, as is also reflected in compounds of the 5th and 6th subgroups,[1,2] is impressive, and should also be observable in other systems.

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[4] A solution of $[C_5Me_5(CO)Co)]_2$ (333 mg, 0.75 mmol) in toluene (100 mL) was treated with S_8 (98 mg, 0.38 mmol) and stirred for 90 min at room temperature. The dark green mixture was filtered over Al_2O_3, and the filtrate concentrated to 15 mL and chromatographed on Al_2O_3 (Activity II–III). The green complex **1** was eluted with toluene. The complex could be recrystallized from toluene.

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[6] **1**: $P2_1/n$, $a=8.112(9)$, $b=14.236(11)$, $c=10.301(9)$ Å, $\beta=110.71(7)°$, $V=1112.70$ Å^3, $Z=2$. Stoe-Siemens diffractometer ($Mo_{K\alpha}$) $3° \leq 2\theta \leq 30°$, 739 measured reflections with $I>3.0\sigma(I)$, Patterson (Co, S) and Fourier methods, anisotropic refinement to $R_w=0.045$. **2**: $P2_1/a$, $a=14.980(6)$, $b=10.496(5)$, $c=15.315(5)$ Å, $\beta=109.36(3)°$, $V=2271.82$ Å^3, $Z=4$, Siemens diffractometer ($Mo_{K\alpha}$) $3°<2\theta<60°$, 3374 observed reflections with $I>2.5\sigma(I)$, Patterson (Fe, S) and Fourier methods, anisotropic refinement to $R_w=0.035$. Further details of the crystal structure investigations are available on request from the Fachinformationszentrum Energie, Physik, Mathematik GmbH, D-7514 Eggenstein-Leopoldshafen2, on quoting the depository number CSD-51547, the names of the authors, and the full citation of the journal.

[7] $[C_5Me_5(CO)_2Fe]_2$ (600 mg, 1.20 mmol) was allowed to react with S_8 (380 mg, 1.50 mmol) for 20 h in boiling toluene (100 mL). Chromatography on SiO_2 (eluent toluene) gave brown $[(C_5Me_5)_2Fe_2S_4]$. The complex could be recrystallized from CH_2Cl_2/Et_2O (1:1).—IR (KBr, [cm^{-1}]): $\nu(S-S)=520$. ^{1}H NMR ($CDCl_3$): $\delta(CH_3)=1.70$.

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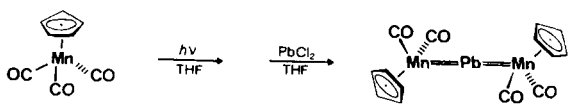
Multiple Bonds between "Naked" Lead and Transition Metals—The First Example**

By *Wolfgang A. Herrmann,* Heinz-Josef Kneuper,* and *Eberhardt Herdtweck*

Dedicated to Professor Max Schmidt on the occasion of his 60th birthday

Methods for the directed synthesis of complexes containing multiple bonds between transition metals appeared, until recently, to be better developed than those for the synthesis of analogous compounds between transition metals and substituent-free ("naked") main-group elements. This is true, above all, for compounds with the more electropositive elements of the fourth to sixth main groups.[1] From the pioneering investigations of *Huttner* et al., *Weiss* et al., *Herberhold* et al., and *Legzdins* et al.,[1,2] it was expected that a strong tendency of formation should exist for this class of compounds and that such compounds might undergo a wide variety of reactions.[1,3] At present, the elements germanium, tin, arsenic, antimony, sulfur, selenium, and tellurium (coordination numbers 2 and 3 with linear, bent, or trigonal-planar frameworks) are known to exist without substituents in the bridge position of organometallic complexes and to be bonded through multiple bonds to organometallic fragments. We have succeeded, for the first time, in binding divalent lead via two cumulative double bonds to a transition metal.

Whereas the hydride route is suitable for the coupling of substituent-free germanium atoms with organometallic fragments,[1,3b,3d] this strategy fails for the heavier homologue lead, probably on account of the instability of the binary hydride. Lead(II) dichloride appeared to be a more promising precursor, even though it was not expected to be completely transformed into the substituent-free main-group ligand in the presence of organometallic complexes. We therefore allowed the substitutionally labile solvent-complex $[(\eta^5\text{-}C_5H_5)Mn(CO)_2(thf)]$ (thf = tetrahydrofuran) to react with lead(II) chloride. After column chromatographic work-up of the crude product (silica gel, +15 °C), we obtained the Mn_2Pb complex **2** in ca. 20% yield.[4] **2** is



1 **2**

a relatively light- and oxygen-sensitive deep reddish brown compound which is nonetheless stable in air up to ca. 130 °C for a short period of time. Conclusive statements regarding the mechanism of formation of **2** are not yet possible, particularly since the reaction occurs with the precipitation of appreciable amounts of finely divided lead.

2 is not formed upon reaction of the organometallic presursor with elemental lead, even when the lead is transformed into a reactive form by high-performance ultrasound dispersion.[5] Possibly, dichloroplumbanediyl complexes are formed in the first step; in the case of germanium(II) chloride, the mono- and binuclear dichlorogermanediyl complexes $[(\eta^5\text{-}C_5H_5)Mn(CO)_2(GeCl_2)]$ (as solvent adduct) and $[(\mu\text{-}GeCl_2)\{(\eta^5\text{-}C_5H_5)Mn(CO)_2\}_2]$ (solvent free) are isolable species.[6] In the present case, **2** might result from consecutive halogen abstraction from labile intermediates of this type.

According to a single-crystal X-ray structure determination, **2** is the first complex containing a substituent-free lead atom that is bonded to a transition metal via multiple bonds. The three-atom MnPbMn structural unit is essentially linear (177.2(1)°), so that no contact exists between the manganese atoms, and the bridging element lead is dicoordinated (Fig. 1).

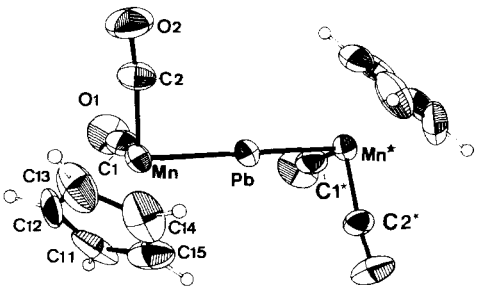


Fig. 1. ORTEP plot of the molecular structure of μ-lead-bis[dicarbonyl(η^5-cyclopentadienyl)manganese] **2** in the crystal. The ellipsoids of thermal vibration correspond to 50% probability; the positions of the hydrogen atoms are calculated. Crystals obtained from diethyl ether/dichloromethane, 294 K, I$\bar{4}$2d, $Z=8$, $a=1585.4(2)$, $c=1210.3(2)$ pm; $V=3042\times10^6$ pm^3; Enraf-Nonius CAD4, VAX 11/730; $R=0.022$, $R_w=0.028$.—Selected distances [pm] and angles [°]: Mn-Pb 246.3(1), Mn-C1 185.7(8), Mn-C2 181.3(7), C1-O1 111.1(8), C2-O2 113.6(7); Mn-Pb-Mn* 177.2(1), Mn-C1-O1 174.1(6), Mn-C2-O2 173.9(7), C1-Mn-C2 93.0(3), Pb-Mn-C1 89.9(2), Pb-Mn-C2 91.3(2), torsion angle C1-Mn-Mn*-C1* −22.2(5), C2-Mn-Mn*-C1* −115.2(5).—Further details of the crystal structure investigation are available on request from the Fachinformationszentrum Energie, Physik, Mathematik GmbH, D-7514 Eggenstein-Leopoldshafen 2, by quoting the depository number CSD 51613, the names of the authors, and the journal citation.

On the basis of the bonding proposed for the formally analogous germanium complexes $[(\mu\text{-}Ge)\{(\eta^5\text{-}C_5R_5)Mn(CO)_2\}_2]$ (R = H, CH_3; Mn-Ge 218-220 pm),[3a,c,d] cumulative multiple bonds having triple-bond character and involving the lead atom should be present.[7] The MnPb distances (245.9(1) pm) justify this view: MnPb single bond lengths (ca. 265-270 pm) may be fairly reliably estimated by extrapolation of known structural data.[8] For the MnPb double bonds, distances at least 20 pm shorter are expected, which should, at the same time, be about 20 pm longer than analogous MnGe double bonds. This

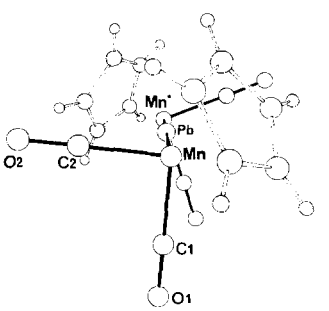


Fig. 2. Anticlinal conformation of the Mn_2Pb compound **2** in the crystal (projection along the MnPbMn axis).

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[**] Multiple Bonds between Main Group Elements and Transition Metals, Part 23. This work was supported by the Bundesministerium für Forschung und Technologie, the Deutsche Forschungsgemeinschaft, and the Fonds der Chemischen Industrie.—Part 22: W. A. Herrmann, E. Voss, U. Küsthardt, E. Herdtweck, *J. Organomet. Chem. 295* (1985) C37.

continues the trend for lead chemistry observed by *Huttner* et al. for the germanium and tin complexes $[(\mu_3\text{-}E)\{W(CO)_5\}_3]$ (W=Ge 250.2, W=Sn 270.2 pm[2a]).

Of the possible conformers discussed earlier,[3d] only the anticlinal form is found for the lead complex **2** in the crystal; the antiperiplanar conformation (*trans* orientation of the C_5H_5 ligands) is not observed (Fig. 2).

Lead is the heaviest main-group element to be combined with transition metals so far.

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[1] Reviews and literature: a) W. A. Herrmann in B. L. Shapiro (Ed.): *Organometallic Compounds: Synthesis, Structure, and Theory, Vol. I*, Texas A & M University Press, College Station, TX, USA 1983, p. 383 ff; b) W. A. Herrmann, *Angew. Chem.* (1986), in press.

[2] Recent work: a) G. Huttner, U. Weber, B. Sigwarth, O. Scheidsteger, H. Lang, L. Zsolnai, *J. Organomet. Chem. 282* (1985) 331; b) W. A. Herrmann, J. Rohrmann, H. Nöth, C. K. Narula, I. Bernal, M. Draux, *ibid. 284* (1985) 189.

[3] a) W. Gäde, E. Weiss, *J. Organomet. Chem. 213* (1981) 451; b) W. A. Herrmann, J. Weichmann, U. Küsthardt, A. Schäfer, R. Hörlein, C. Hecht, E. Voss, R. Serrano, *Angew. Chem. 95* (1983) 1019; *Angew. Chem. Int. Ed. Engl. 22* (1983) 979; *Angew. Chem. Suppl. 1983*, 1543; D. Melzer, E. Weiss, *J. Organomet. Chem. 263* (1984) 67; d) J. D. Korp, I. Bernal, R. Hörlein, R. Serrano, W. A. Herrmann, *Chem. Ber. 118* (1985) 340.

[4] Spectroscopic characterization: IR (KBr, ν(CO), [cm^{-1}]): 1959 (w), 1921 (s), 1892 (s), 1839 (s); (THF): 1966 (br. s), 1938 (m, sh), 1905 (m), 1860 (w).—^{1}H-NMR (90 MHz, +28°C, [D$_8$]THF): δ=4.58 (s, C_5H_5).—^{13}C NMR (+28°C, [D$_8$]THF): δ=78.7 (C_5H_5).—EI-MS: *m/z* 560 (M^+, ^{202}Pb).—A correct elemental analysis (C, H, Mn, O, Pb) was obtained for the pure substance.

[5] Heat Systems Ultrasonics, Inc., Model W-375.

[6] a) P. Jutzi, W. Steiner, *Chem. Ber. 109* (1976) 3473; b) W. A. Herrmann, H.-J. Kneuper, E. Herdtweck, unpublished (synthesis and X-ray structure analysis of $[(\mu\text{-}GeCl_2)\{(\eta^5\text{-}C_5H_5)Mn(CO)_2\}_2]$: $P\bar{1}$; Mn–Ge 235.7(1), 238.7(1) pm.

[7] N. M. Kostić, R. F. Fenske, *J. Organomet. Chem. 233* (1982) 337.

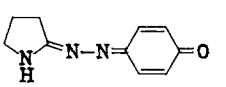
[8] MnGe single-bond lengths lie in the range 243–250 pm (e.g., $[(CO)_5MnGeH_3]$, 249 pm) and are therefore 20–30 pm longer than the cumulative MnGeMn multiple bonds in complexes of type **2** (Ge instead of Pb). The 1°(2°) covalent radii are taken to be 122 (112) pm for Ge, 140 (130) pm for Sn, and 144–150 (134–140, estimated) pm for Pb; the covalent radius (144 pm) obtained from the structure of Pb_2Me_6 (Pb–Pb 288 pm) appears to be a lower limit. Cf. A. F. Wells, *Structural Inorganic Chemistry*, 5th ed., Clarendon Press, Oxford, England 1984.—Estimated covalent radii in organomanganese(I) complexes of the $[(\eta^5\text{-}C_5R_5)Mn(CO)_x]$ series: 130–133 (1°), ca. 120 (2°), ca. 109 pm (3°), cf. [3d], footnote 19).

The Chemistry and Antibiotic Activity of the Toadstool *Agaricus xanthoderma* (Agaricales)**

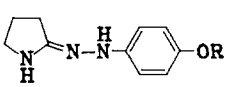
By *Sabine Hilbig, Thomas Andries, Wolfgang Steglich,** and *Timm Anke*

Dedicated to Professor Hans Grisebach on the occasion of his 60th birthday

Fruit-bodies of the toadstool *Agaricus xanthoderma* Gen. stain intense chrome-yellow when bruised and develop a phenol like odor. Treatment with alkalis turns the flesh orange-yellow. Extracts of the toadstool exhibit a strong antibiotic activity, which *Atkinson*[1] ascribed to a photolabile compound "psalliotin". Later, work-up of the methanolic extract in the presence of sodium sulfite afforded "agaricin", which exhibits strong antibiotic and cancerostatic properties.[2] In neither case was the active substance chemically characterized in detail. First insights into the chemistry of *A. xanthoderma* were gained by *Gill* and *Strauch*,[3] who were able to isolate phenol, hydroquinone, 4,4′-dihydroxyazobenzene, and 4,4′-dihydroxybiphenyl from the ethanol extract. In this communication we describe the elucidation of the structures of compounds which are responsible for the antibiotic activity and the yellow discoloration of the fungus. When fruiting bodies of *A. xanthoderma* are extracted with cold ethyl acetate and the extracts are carefully concentrated by evaporation and chromatographed at 0–3°C, an intense yellow zone can be separated. Further chromatographic separation furnishes agaricone **1**[4] (yield 5×10^{-4}%), which according to its mass spectrum has the empirical formula $C_{10}H_{11}N_3O$ and which in its ^{1}H-NMR spectrum shows signals typical of a $-(CH_2)_3-$ unit, as well as signals in the aromatic region.[5] The characteristic MS fragments *m/z* 107 (C_6H_5NO), 106 (C_6H_4NO), 94 (C_6H_6O), 93 (C_6H_5O), 84 ($C_4H_8N_2$), and 83 ($C_4H_7N_2$) indicate structure **1**, which has been confirmed by synthesis. The butyrolactim methyl ester was allowed to react with *N*-(4-benzyloxyphenyl)hydrazine hydrochloride in methanol to give the hydrochloride of the pyrrolidonehydrazone **2** (yield 75%), which upon hydrogenolysis with Pd/carbon in methanol afforded the crystalline hydrochloride of **3**.[4]



1



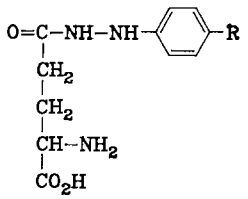
2, R = $CH_2C_6H_5$
3, R = H

When **3** is dissolved in water and treated with sodium hydrogencarbonate the solution immediately turns yellow in color on being exposed to air. Oxidation proceeds especially smoothly upon addition of sodium periodate; **1** can be recovered by extraction with ethyl acetate; it is identical in all respects with the yellow pigment from *A. xanthoderma*. It can therefore be assumed that the toadstool contains leucoagaricone **3** which is oxidized to **1** by atmospheric oxygen (oxidases) when the fruiting body is damaged.[6]

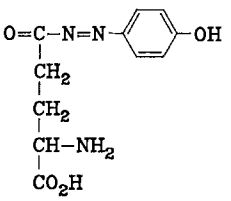
When fresh fruit-bodies are extracted with SO_2-saturated methanol and all chromatographic steps are carried out under argon at 0–3°C, a colorless chromogen (yield 1×10^{-3}%) can be separated from large amounts of mannitol after chromatography on Sephadex LH 20 (eluent methanol/water 9:1) and repeated further chromatography on LichroPrep RP8 (eluent: water). The separation can be monitored by spot testing with $K_3[Fe(CN)_6]/NaHCO_3$ solution (orange-yellow color reaction!). The chromogen, called xanthodermin by us,[4] gives a positive ninhydrin reaction and shows signals typical for a glutamic acid residue as well as a signal in the aromatic region of the ^{1}H-NMR spectrum. This finding and the fact that ions containing three nitrogen atoms occur in the mass spectrum of the peracetyl derivative would suggest the structure of a γ-glutamyl-*N*′-(4-hydroxyphenyl)hydrazide **4** for the chromogen. This has been confirmed by synthesis. In the case of the α-benzyl ester of *N*-(benzyloxycarbonyl)-L-glutamic acid the γ-carboxy group was converted in 70% yield into

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[**] Antibiotics from Basidiomycetes, Part 22. This work was supported by the Deutsche Forschungsgemeinschaft.—Part 21: T. Anke, J. Heim, F. Knoch, U. Mocek, B. Steffan, W. Steglich, *Angew. Chem. 97* (1985) 714; *Angew. Chem. Int. Ed. Engl. 24* (1985) 709.



4, R = OH
5, R = CH_2OH

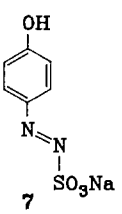


6

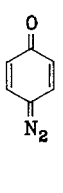
the *N'*-(4-benzyloxyphenyl)hydrazide with *N*-(4-benzyloxyphenyl)hydrazine according to the 4,6-diphenylthieno[3,4-*d*][1,3]dioxol-2-one 5,5-dioxide method.[7] Removal of the protecting groups with H_2/Pd-C afforded **4** in quantitative yield, which proved to be identical with the natural product. Treatment of an aqueous solution of **4** with $K_3[Fe(CN)_6]$/sodium hydrogencarbonate or sodium hydroxide leads to an intense yellow coloration of the solution. The same phenomenon is observed with the aqueous extract of the fungus.

The anion of the acylazo compound **6** is responsible for this color reaction. Hence, the fungus contains two chromogens, **3** and **4**, which participate in the yellow discoloration of the fruiting body and its color reaction with sodium hydroxide.

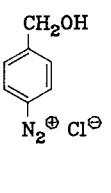
In the initial separation on Sephadex the last fractions contain the yellow solid sodium 4-hydroxybenzenediazosulfonate **7**[8] (yield 5×10^{-3}%). **7** is an artefact which is formed from the 4-diazo-2,5-cyclohexadien-1-one **8** present in the fruiting bodies. **8** can be detected in the methanolic extract of the fungus by azo coupling with resorcinol or β-naphthol[9] and, after work-up of the fungus with cooling and exclusion of light, but without addition of SO_2, can be identified by TLC comparison with the authentic compound.[10]



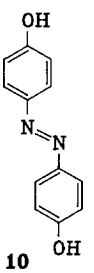
7



8



9



10

Interestingly, neither phenol nor 4,4'-dihydroxyazobenzene **10** are detectable during the work-up of the fungi with methanol containing SO_2, so these compounds isolated by *Gill* et al. are probably formed from the precursors described by us during the work-up.[11]

Merocyanines of the agaricone type, **1**, had already been obtained by *Hünig* et al.[12] by oxidative azo coupling, but have so far never been found in Nature. In contrast, **4** and **8** find a parallel in the compounds agaritine **5**[13] and 4-(hydroxymethyl)benzenediazonium chloride **9**,[14] which have been isolated from other *Agaricus* species.

1, **4**, **7**, and **8** are antibiotically active against *Bacillus subtilis* (Table 1). Especially active against bacteria and fungi are the diazo compounds **7** and **8**, whose minimal inhibitory concentrations are comparable with those of established antibiotics. Using the same assay as described in Table 1, 1 μg of penicillin G or streptomycin sulfate gave inhibition zones of 25 and 11 mm diameter, respectively, with *Bacillus subtilis* as test organism. Using *Mucor miehei* as test organism, 10 μg of the antifungal nystatin yielded an inhibition zone of 16 mm diameter. As gleaned from a comparison of the IR and UV spectra with those in Ref. [2], **7** is identical to "agaricin".[15] The antibiotic activity of "psalliotin"[1] observed by *Atkinson*, as well as its sensitivity to light, lend support to its identity with **8**.

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[1] N. Atkinson, *Nature (London) 174* (1954) 598; *Aust. J. Exp. Biol. 33* (1955) 237, 381.
[2] K. Dornberger, W. Gutsche, R. Horschak, A. Zureck, *Z. Allg. Mikrobiol. 18* (1978) 647; K. Dornberger, H. Lich, C. Schönfeld, H. Knöll, DDR-Pat. 132878 (15. Nov. 1978); *Chem. Abstr. 91* (1979) P 87622e.
[3] M. Gill, R. J. Strauch, *Z. Naturforsch. C39* (1984) 1027.
[4] **1**: red crystals, m.p. 115°C (decomp.); R_f: 0.26 (silica gel; eluent: ethyl acetate); UV (MeOH): λ_{max} (lgε) = 242 (3.74), 427 nm (4.19); ^{1}H NMR (CD_2Cl_2) [5]: δ = 2.11 (tt, *J* = 7 Hz, 2H), 2.81 (t, *J* = 7 Hz, 2H), 3.56 (t, *J* = 7 Hz, 2H), 5.59 (br. "s", NH), 6.37 ("d", *J* = 10 Hz, 2H), 7.37 ("d", *J* = 10 Hz, 2H); MS (DE 180°C): *m/z* 189.0906 (M^+, 100%, calc. for $C_{10}H_{11}N_3O$ 189.0902), 188 (7.0), 161 (11.4), 160 (25.7), 121 (4.9), 109 (5.0), 107 (4.9), 106 (5.8), 94 (5.8), 93 (22.4), 84 (19.6), 83 (23.9), 69 (7.6), 55 (4.3), 41 (37.8).—**3**·HCl: m.p. 224°C.—**4**: m.p. 164–166°C (decomp.); R_f = 0.20 (cellulose, 1-butanol/glacial acetic acid/water 4:1:1); $[\alpha]_D$ 5.5 (*c* = 1, 1N HCl); UV (water): λ_{max} (lgε) = 228 (3.34), 292 nm (3.90); after addition of one drop of NaOH λ_{max} = 242, 348, 445 nm; ^{1}H NMR (D_2O): δ = 1.98 (dt, *J* = 8.2, 6.3 Hz, 2H), 2.31 (m, 2H), 3.59 (t, *J* = 6.3 Hz, 1H), 6.65 ("s", 4H); ^{13}C NMR (D_2O): δ = 28.0, 31.4, 56.0, 117.4, 118.0, 142.4, 151.9, 175.7, 176.4; MS (180°C) *m/z* 253.1091 (0.01%, calc. for $C_{11}H_{15}N_3O_4$ 253.1062), 152 (0.04), 130 (1.9), 129 (7.0),

Table 1. Antibiotic activity of the constituents of *A. xanthoderma* in the plate diffusion test on a complex medium at the given concentrations of active substance [μg/disk] [a, b].

Test organism	**1**			**4**	**7**			**8**			**10** [3] [b]	
	[100]	[50]	[10]	[10]	[100]	[10]	[1]	[100]	[10]	[1]	[10]	[1]
Bacteria:	Diameter of inhibition zone [mm]											
Bacillus brevis	32	28	19	15	30	25	15	35	24	11i	10i	–
Bacillus subtilis	25	21	10i	22	35	30	20	40	25	10i	–	–
Acinetobacter calcoaceticus	19	12	–	–	35	25	20	40i	22i	+	–	–
Micrococcus luteus	20i	11i	–	–	30	17	10	45	30	–	+	–
Fungi:												
Mucor miehei	18	14i	–	–	30	14	–	38	20	–	+	–
Paecilomyces varioti	40i	30i	10i	+	20	11	–	26	15	–	10	–
Nematospora coryli	16	13	+					46	25	–	10	–
Penicillium notatum	20i	11i	–					16	–	–	10	–
Fusarium oxysporum	16i	10i	–					25	11	–	7	–

[a] The antibiotics were applied to paper disks (6 mm diameter). The disks were put on petri dishes containing the test organisms seeded in nutrient agar, and the plates were incubated at 27°C or 37°C for 12–16 h. The inhibition zones are delineated by the clear area around the paper disks in which no growth of the test organism occured (–: no inhibition; i: incomplete inhibition). [b] 4,4'-Dihydroxybiphenyl[3] shows no inhibition towards the given microorganisms at 100 μg/disk.

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123 (0.2), 122 (1.25), 110 (18.3), 109 (100, C_6H_7NO), 108 (15.5), 94 (78.1), 84 (62), 80 (41.9), 66 (19.9), 56 (6.6).—7: ^{1}H NMR (MeOD): δ = 6.86 and 7.76 (AA'BB' system, J = 9 Hz).

[5] The ^{1}H-NMR spectrum of **1** shows a temperature-dependent broadening.

[6] **1** also occurs in the fungus, e.g. in the yellow zones of the stem base. In contrast, we have so far been unable to isolate the leuco compounds **3** from the fungus.

[7] O. Hollitzer, A. Seewald, W. Steglich, *Angew. Chem. 88* (1976) 480; *Angew. Chem. Int. Ed. Engl. 15* (1976) 444; W. Steglich, G. Höfle, *Angew. Chem. 81* (1969) 1001; *Angew. Chem. Int. Ed. Engl. 8* (1969) 981.

[8] R. Schmitt, L. Glutz, *Ber. Dtsch. Chem. Ges. 2* (1869) 51.

[9] Identification of the azo dyes by comparison with the authentic compounds. According to spot tests on fresh fruiting bodies, **8** is concentrated primarily in the lamellae.

[10] **8**: R_f = 0.25 (silica gel; eluent CH_2Cl_2/MeOH = 9:1; red color upon spraying with resorcinol in 1 N NaOH).

[11] The occurrence of a 4-hydroxybenzenediazonium salt as a precursor of phenol etc. had already been presumed by *Gill* et al. [3].

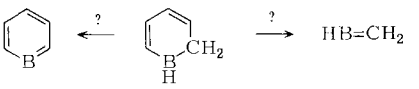
[12] Cf. e.g. S. Hünig, H. Balli, E. Breither, F. Brühne, H. Geiger, E. Grigat, F. Müller, H. Quast, *Angew. Chem. 74* (1962) 818; *Angew. Chem. Int. Ed. Engl. 1* (1962) 640.

[13] R. B. Kelly, E. G. Daniels, J. W. Hinman, *J. Org. Chem. 27* (1962) 3229; B. Levenburg, *J. Biol. Chem. 239* (1964) 2267.

[14] B. Levenberg, *Biochim. Biophys. Acta 63* (1962) 212.

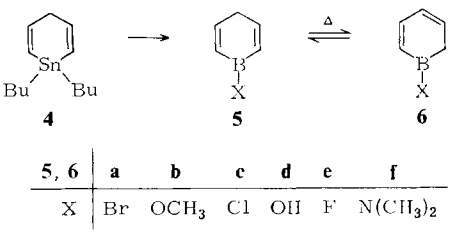
[15] In the meantime, the identity of agaricin (now renamed agaridin) with **7** has also been proven by K. Dornberger, W. Ihn, W. Schade, D. Tresselt, A. Zureck, L. Radics, *Tetrahedron Lett.*, in press. For the antifungal action of **7** cf. also S. Petersen, W. Gauss, E. Urbschat, *Angew. Chem. 67* (1955) 217.

lation of **1** as pyridinium-betaine,[3] we now describe the synthesis and properties of two simply-substituted boraethenes.



1 **2** **3**

Using the method described by *Ashe* et al.,[4] 1,1-di-*n*-butyl-1-stanna-2,5-cyclohexadiene **4**[5] was converted into the bromide **5a**, which, in turn, was transformed by reaction with dimethyl ether into the methoxy compound **5b**.[6] According to our findings, reaction of **4** with boron trichloride smoothly furnishes the chloride **5c**, and hydrolysis of **5b** affords the hydroxy derivative **5d**. Upon halo-



4 **5** **6**

5, 6	a	b	c	d	e	f
X	Br	OCH_3	Cl	OH	F	$N(CH_3)_2$

Table 1. Reaction conditions, yields, and spectroscopic properties of the compounds **5c–5f** and **7b** and **7f**; NMR ($CDCl_3$): δ values (rel. TMS). RT = room temperature. The molecular weights were determined by high-resolution mass spectroscopy (exception: **7b**).

Cpd.	Properties	Reaction conditions	Yield [%]	^{1}H-NMR	^{13}C-NMR
5c	colorless liquid	hexane, −78 °C, 3 h RT	85	3.20 (m, 2H), 6.58 (m, 2H), 7.38 (m, 2H)	36.7 (CH_2), 156.3 (C-3) [a]
5d	colorless needles, m.p. 98 °C	CH_2Cl_2, 15 min RT	86	3.03 (m, 2H), 5.03 (m, 1H), 6.05 (m, 2H), 7.10 (m, 2H)	35.4 (CH_2), 153.2 (C-3) [a, b]
5e	colorless liquid	paraffin oil, −78 °C, 2 h RT	60	2.32 (m, 2H), 5.36 (m, 2H), 6.58 (m, 2H) [c]	35.0 (CH_2), 158.0 (C-3, d, $^3J(^{\text{natural}}C,^{19}F)$ = 18.5 Hz) [a, c]
5f	colorless liquid	pentane, −78 °C, 1.5 h RT	96 [d]	2.90 (s, 6H), 2.97 (m, 2H), 6.32 (m, 2H), 6.85 (m, 2H)	34.6 (CH_2), 39.1 (CH_3), 147.0 (C-3) [a]
7b	colorless oil	$CHCl_3$/pentane, 48 h −30 °C	58	0.74 (m, 2H), 3.60 (m, 1H), 3.70 (s, 3H), 4.14 (m, 1H), 6.76 (m, 2H)	38.5 (CH), 57.2 (OCH_3), 130.1 (olefin.), 135.1 (olefin.) [e]
7f	colorless crystals, m.p. 51 °C	$CHCl_3$/pentane, 48 h −30 °C	49	0.71 (m, 2H), 2.56 (s, 3H), 2.80 (s, 3H), 3.71 (m, 1H), 3.96 (m, 1H), 6.12 (m, 2H)	38.9 (CH), 39.7 (NCH_3), 42.0 (NCH_3), 131.1 (olefin.), 133.3 (olefin.) [e]

[a] C-2 not recorded because of broading by CB coupling. [b] [D_6]acetone. [c] Capillary. [d] Mixed with **6f**. [e] The remaining signals were not recorded because of broadening by CB and CF coupling.

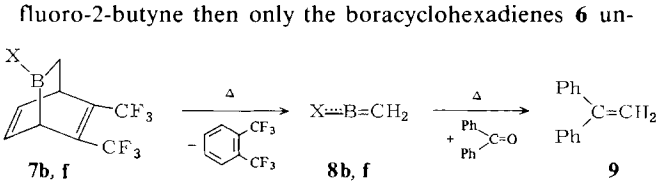
Simply Substituted Boraethenes**

By *Günther Maier,* Jochem Henkelmann,* and *Hans Peter Reisenauer*

Dedicated to Professor Hans Musso on the occasion of his 60th birthday

Starting from silacyclohexadienes we were able to synthesize both silabenzene[1] as well as silaethene.[2] This sugested that the method might possibly be extended to the synthesis of borabenzene **1** and boraethene **3** from 1-bora-2,4-cyclohexadiene **2**. Following our recent successful isogen-exchange with antimony trifluoride, **5c** yields the fluoride **5e**, while reaction of **5c** with *N,N*-dimethyl(trimethylsilyl)amine affords a mixture of the two isomeric boracyclohexadienes **5f** and **6f** (see Table 1). In all cases an isomerization of **5** to **6** can be achieved by passing the 2,5-isomer through a quartz tube at 800 °C (8 × 65 mm; 10^{-3} torr) and condensing the product on a "cold finger" cooled with liquid nitrogen. The product ratio **5** : **6** (determined NMR spectroscopically; a clean separation of the conjugated isomer **6** is not possible) is then ca. 1:2 (**a, b, c, d**) or 1:1 (**e, f**).

If the product mixture **5/6** is allowed to react with hexafluoro-2-butyne then only the boracyclohexadienes **6** un-



7b, f **8b, f** **9**

b, X = OCH_3; **f**, X = $N(CH_3)_2$

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[**] Hetero π-Systems, Part 14. This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie. Part 13: G. Maier, K. Schöttler, H. P. Reisenauer, *Tetrahedron Lett. 26* (1985) 4079.

dergo a Diels-Alder reaction. The adducts **7**, however, are only stable when they bear methoxy- or dimethylamino-substituents (Table 1).

Do the adducts **7** yield the corresponding boraethenes upon thermal cycloreversion? The answer is yes! On the one hand, co-pyrolysis of **7b** and **7f** with benzophenone (the solutions of the components in [D_6]benzene were added dropwise into a quartz tube (13 × 240 mm, Raschig rings) heated at 400 °C) not only lead to formation of hexafluoro-*o*-xylene (17 and 41% yield, respectively) but also of 1,1-diphenylethene **9**, which could be the product of a Wittig-type reaction between benzophenone and the intermediary boraethenes **8b** and **8f**. On the other hand, the pyrolysis products (quartz tube (hot zone 8 × 50 mm), 600–800 °C, ca. 10^{-4}–10^{-5} torr) can be isolated in an argon matrix at 10 K and identified IR spectroscopically; besides the bands for hexafluoro-*o*-xylene, other bands occur which can be assigned to the boraethenes **8b** and **8f**. This is further supported by the appearance of pairs of absorptions in the intensity ratio 1 : 4 (**8b**: 1765/1721, 1542/1508, 1441/1411 cm^{-1}; **8f**: 1829/1780 cm^{-1}), as are to be expected on the basis of the $^{10}B/^{11}B$ ratio. We assign the latter, very intense pair to the antisymmetric stretching vibration of the $N^{10}BC$ and $N^{11}BC$ units—consistent with the IR spectrum of the stable 9-fluorenylidene-2,2,6,6-tetramethylpiperidinoborane (ν_{as} = 1740 and 1717 cm^{-1}) recently isolated by *Nöth* et al.[7] Accordingly, **8f** also has an allene structure. Both boraethenes **8b** and **8f** are extremely reactive; upon thawing the matrix, the characteristic IR bands already disappear at 40 K (**8b**) or 80 K (**8f**).

Summary: The existence of electroneutral compounds with a B=C bond[8] at the doubly coordinated boron atom[7] is not limited to derivatives with bulky substituents. Also simply substituted derivatives of the type **8b/8f** are detectable. The question remains, whether the presence of a donor group at the boron is indispensable for the existence of such derivatives.

Experimental

5f/6f: A solution of *N,N*-dimethyl(trimethylsilyl)amine (580 mg, 5 mmol) in pentane (5 mL) was treated at −78 °C with 450 mg (4 mmol) of **5c**; the mixture was stirred for 1.5 h at room temperature (RT), and, after removal of the volatile components in a vacuum (RT/0.5 torr), the isomeric mixture **5f/6f** was condensed in a cold trap.

7f: A solution of the isomeric mixture **5f/6f** (500 mg) in $CHCl_3$/pentane (1 : 1) (4 mL) was treated with 5.0 g of hexafluoro-2-butyne and the mixture stirred for 48 h at −30 °C; the excess hexafluoro-2-butyne was condensed in a cold trap and the solvent was removed in a vacuum. The unreacted compound **5f** was separated from the adduct by fractional recondensation. Pure **7f** was obtained by sublimation at 10^{-2} torr.

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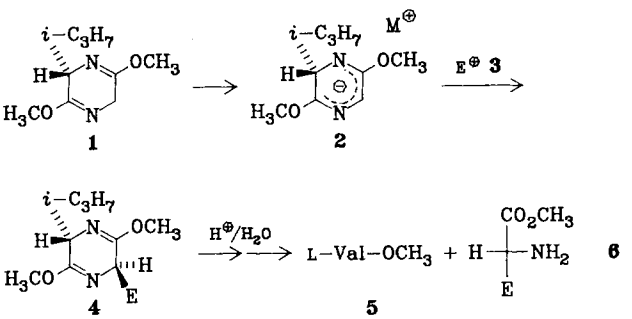
[1] G. Maier, G. Mihm, R. O. W. Baumgärtner, H. P. Reisenauer, *Chem. Ber. 117* (1984) 2337, and references cited therein.
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[7] B. Glaser, H. Nöth, *Angew. Chem. 97* (1985) 424; *Angew. Chem. Int. Ed. Engl. 24* (1985) 416.
[8] First B=C system: H. Klusik, A. Berndt, *Angew. Chem. 95* (1983) 895; *Angew. Chem. Int. Ed. Engl. 22* (1983) 877.—For the structure of *Berndt*'s substance see also: P. H. M. Budzelaar, P. von R. Schleyer, K. Krogh-Jespersen, *ibid. 96* (1984) 809 and *23* (1984) 825; G. Frenking, H. F. Schaefer III, *Chem. Phys. Lett. 109* (1984) 521; P. H. M. Budzelaar, K. Krogh-Jespersen, T. Clark, P. von R. Schleyer, *J. Am. Chem. Soc. 107* (1985) 2773.

Asymmetric Synthesis of (*R*)-β-(Alkoxycarbonyl)aspartic Diesters (Derivatives of (*R*)-Asa) with a Chiral Cationic Amino Acid Synthon**

By *Ulrich Schöllkopf,* Hans-Jürgen Neubauer,* and *Manfred Hauptreif*

Dedicated to Professor Hans Musso on the occasion of his 60th birthday

During the last few years, we have developed an asymmetric synthesis of nonproteogenous amino acids of type **6**, which consists in metalating the bislactim ether **1** of cyclo(L-Val-Gly), reacting the metal derivative **2** with electrophiles **3**, and hydrolyzing the adducts **4**.[1] Upon hydrolysis, the amino acid esters **6** are released (along with L-valine methyl ester **5**). Since the reaction **2** + **3** → **4** usually occurs with very high diastereoselectivity,[1] the amino acid esters **6** are often nearly optically pure.[1]



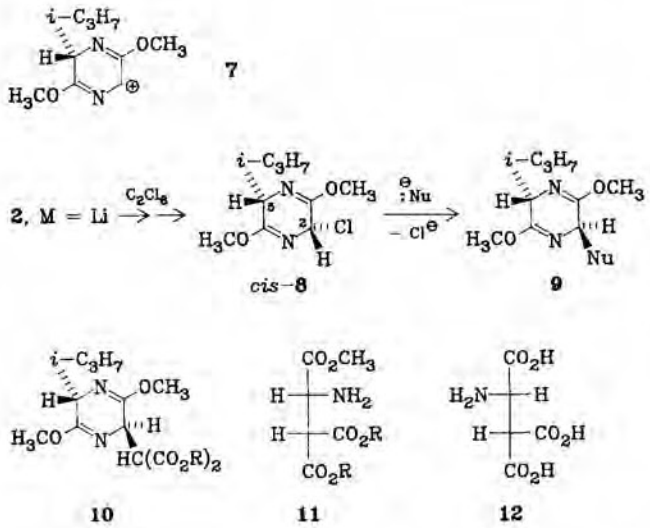
It was therefore of interest to modify the educts **1** in such a way that the ring CH_2 group becomes a cationic acceptor center[2] (see **7**) at which nucleophiles can be introduced diastereoselectively. Since the chloride **8** is a synthetic equivalent for **7**, we attempted its stereospecific synthesis.

When we added a solution of the lithium compound **2** (M = Li)[3] in tetrahydrofuran (THF) at −78 °C to a solution of hexachloroethane, we obtained a 94 : 6 mixture of the *cis/trans* isomeric chlorides **8** in ca. 90% yield, in which, surprisingly, the (2*S*,5*S*)-*cis*-chloride is the predominant diastereomer.[4] Since compound **8** can epimerize and/or undergo elimination of HCl, we carried out the reaction with nucleophiles in situ immediately after its formation.[5] The compound undergoes S_N2 reaction with inversion at C-2 to give the compounds **9**; however, the yield is only satisfactory for "soft" nucleophiles such as thiolates, borohydrides, water, or resonance-stabilized anions of carbon acids.[6]

A typical reaction is, for example, that of **8** with sodium dialkyl malonates (in THF in the presence of 5 mol-% [18]crown-6; 0 °C), which leads to the products **10** with primarily (2*R*) configuration (ca. 65% yields; (2*R*) : (2*S*) = 25 : 1 for **10a**, 32 : 1 for **10b**, and 60 : 1 for **10c**).[7] These were hydrolyzed with two equivalents of 0.25 N hydrochloric acid for **10a**, **b** and with 0.1 N hydrochloric acid for **10c** (at room temperature in ca. 7 d) to **5** and (*R*)-β-(alkoxycarbonyl)aspartic diesters **11**. In the

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[**] Asymmetric Synthesis via Heterocyclic Intermediates. Part 29.—Part 28: R. Gull, U. Schöllkopf, *Synthesis 1985* 1052



a, R = CH_3; **b**, R = i-C_3H_7; **c**, R = t-C_4H_9

case of **11b** and **11c**, we distilled off **5** (kugelrohr distillation at 0.005 torr, room temperature) and isolated **11b** and **11c** by low-pressure chromatography[8] in 63 and 72% yield, respectively, and with *ee* > 95% in each case.[9] In the case of **11a**, after the hydrolysis, we acetylated the mixture of **5**·HCl and **11a**·HCl on nitrogen,[10] separated *N*-acetyl-**5** by chromatography, and obtained (*R*)-*N*-acetyl-**11a**. This compound has already been prepared in racemic form.[11] For (optically pure) (*R*)-*N*-acetyl-**11a**, we found $[\alpha]_D^{20}$ −86.9 (*c* = 2.0, methanol).

β-Carboxyaspartic acid (Asa) is—presumably in the (*S*) form **12**—a constituent of ribosomal bacterial proteins.[11] Syntheses of the racemic triesters of Asa have been described,[11,12] but no asymmetric syntheses are known.

With the bislactim ether of cyclo(D-Val-Gly),[13] the (*S*) enantiomer **11** is obtained.

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[1] Reviews: U. Schöllkopf, *Pure Appl. Chem. 55* (1983) 1799; *Chem. Scr. 25* (1985) 105; H. Prinzbach, G. Schill in K. Streith (Ed.): *Organic Synthesis: An Interdisciplinary Challenge*, Blackwell Scientific Publications, Oxford 1985, p. 101 ff.

[2] For achiral cationic amino acid synthons, see D. Ben-Ishai, S. Hirsch, *Tetrahedron Lett. 24* (1983) 955 and ealier publications of this group: T. Shono, *Tetrahedron 40* (1984) 811; R. Kober, W. Hammes, W. Steglich, *Angew. Chem. 94* (1982) 213; *Angew. Chem. Int. Ed. Engl. 21* (1982) 203; *Angew. Chem. Suppl. 1982*, 542; C. G. Shin, Y. Sato, H. Ohmatsu, J. Yoshimura, *Bull. Soc. Chem. Pharm. Jpn. 54* (1981) 1137; W. D. Bennet, M. J. O'Donell, R. L. Polt, *Tetrahedron Lett. 26* (1985) 695; for chiral cationic amino acid synthons, see R. Kober, K. Papadopoulos, W. Miltz, D. Enders, W. Steglich, H. Reuter, H. Puff, *Tetrahedron 41* (1985) 1693.

[3] U. Schöllkopf, U. Groth, C. Deng, *Angew. Chem. 93* (1981) 793; *Angew. Chem. Int. Ed. Engl. 20* (1981) 798.

[4] In the reaction of **2** with **3**, *trans*-**4** is the main diastereomer formed. Accordingly, the reactions of **2** with electrophiles and the chlorination take place via different mechanisms. For the chlorination, a radical pathway is likely; for the reactions with electrophiles, a polar one [1].

[5] Typical experiment for the in-situ preparation of **8**: **1** (0.92 g, 5.0 mmol) was lithiated according to [3]: the solution of **2** (in THF) was injected at −78 °C under nitrogen into a solution of hexachloroethane (1.42 g, 6.0 mmol). In one experiment, **8** was isolated and characterized [6].

[6] H.-J. Neubauer, *Dissertation*, Universität Göttingen 1984.

[7] Determined by capillary GC (WCOT Chrompack column, 50 m, 210 °C).—The diastereomeric ratio of **10** differs from that of **8** since the sodium dialkyl malonate causes elimination of HCl to a different extent from *trans*-**8** (in competition with the S_N reaction).

[8] Silica gel 60; ether/ethanol = 50 : 1.

[9] Determined by ^{1}H-NMR spectroscopy with Eu(tfc)$_3$ (up to 40 mol-%, shifting but no splitting of the OCH_3 signal). **11b**: oil, ^{1}H-NMR ($CDCl_3$): δ = 1.28 (d, $CH(CH_3)_2$), 1.84 (s, br, NH_2), 3.74 (s, OCH_3), 3.83 (d, OCCHCO), 3.05 (d, HC–N), 5.8 (h, $CH(CH_3)_2$); **11c**: m.p. = 63–64 °C; $[\alpha]_D^{25}$ +0.4 (*c* = 1.0, methanol); ^{1}H-NMR ($CDCl_3$): δ = 1.48 (s, $C(CH_3)_3$), 2.0 (s, br, NH_2), 3.66 (s, OCH_3), 3.75 (d, OCCHCO), 3.99 (d, HC–N). The two amino acid triesters were also isolated as Boc derivatives by allowing the mixture of **5**·HCl and **11**·HCl (obtained by hydrolysis) to react with di(*tert*-butyl) dicarbonate in dimethylformamide and separating the Boc derivatives of **5** and **11** by fractional kugelrohr distillation.

[10] Acetic anhydride, pyridine, a small amount of 4-dimethylaminopyridine, dichloromethane.

[11] M. R. Cristy, R. M. Barkley, T. H. Koch, J. J. van Buskirk, W. M. Kirsch, *J. Am. Chem. Soc. 103* (1981) 3935.

[12] D. H. Rich, M. K. Dhaon, *Tetrahedron Lett. 24* (1983) 1671; E. B. Henson, P. M. Gallop, P. V. Hauschka, *Tetrahedron 37* (1981) 2561.

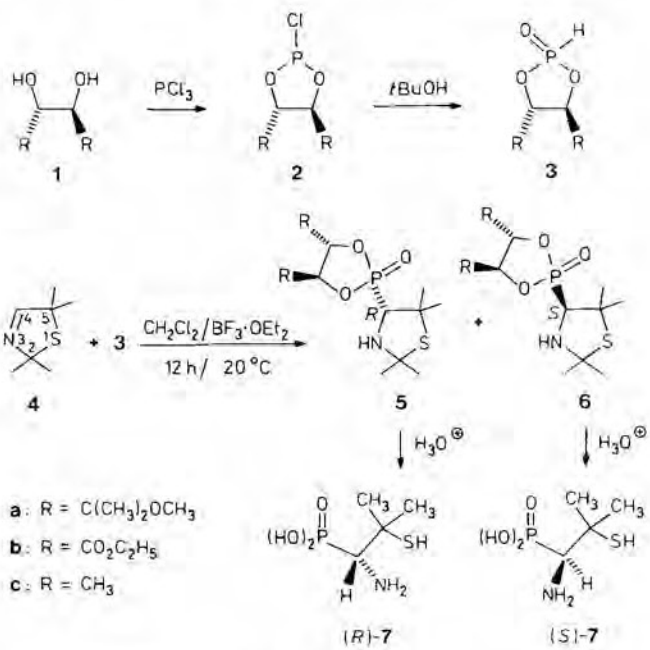
[13] Bislactim ethers of type **1** with L- and D-valine as the inducing centers are obtainable from Merck-Schuchardt.

Asymmetric Addition of a Chiral Cyclic Phosphite to a Cyclic Imine—Synthesis of Phosphonic Acid Analogues of D- and L-Penicillamine**

By *Inga Hoppe,* Ulrich Schöllkopf, Martin Nieger,* and *Ernst Egert**

Dedicated to Professor Hans Musso on the occasion of his 60th birthday

α-Amino phosphonic acids,[1] the phosphonic acid analogues of α-amino carboxylic acids, are of interest owing to their potential biological activity. Only a few asymmetric syntheses for this class of compounds have been reported so far.[2] Thus, for example, only the racemate of the analogue **7** of penicillamine (obtained by addition of



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[**] Asymmetric Synthesis of α-Aminophosphonic Acids, Part 2. This work was supported by the Fonds der Chemischen Industrie. We thank Mrs. *B. Lüer* for dedicated experimental assistance.—Part 1: [2b].

an achiral phosphorous acid derivative to 2,5-dihydro-2,2,5,5-tetramethylthiazole **4**) has been described.[3] We report here a procedure that makes accessible both of the enantiomers, (*R*)-**7** and (*S*)-**7**.

Reaction of the diol[4] **1a** (synthesized from diethyl (*R,R*)-2*O*,3*O*-isopropylidenetartrate) with PCl_3 and *tert*-butanol[5] affords the enantiomerically pure cyclic phosphite (−)-**3a**[6] in 90% yield, which undergoes addition to **4**[7] with BF_3 catalysis. The diastereomers (−)-**5a**[8] and (+)-**6a**[8] are thereby obtained in a ratio of 2 : 1 (yield 82%) and can be easily separated on silica gel.[9] An X-ray structure determination[10] gave the (4*R*) configuration for the diastereomer (−)-**5a**, which is present in excess (Fig. 1).

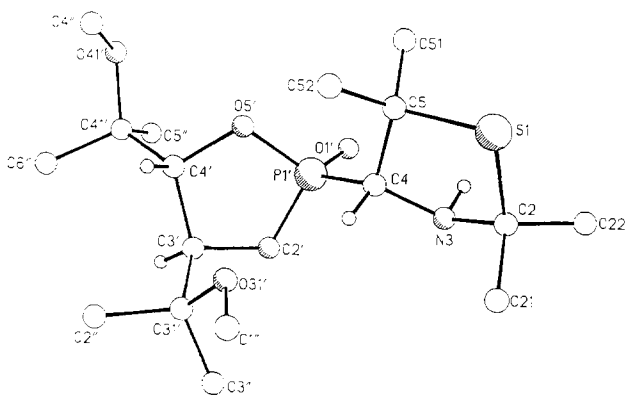


Fig. 1. Crystal structure of (−)-**5a**.

Hydrolysis of (−)-**5a** (48% HBr or conc. HCl, reflux[3b]) gives 52% (*R*)-(−)-**7**,[11] which corresponds to L-penicillamine, while 48% of the enantiomer (*S*)-(+)-**7** is obtained from (+)-**6a**.

With the phosphites **3b** (from diethyl (*R,R*)-tartrate) or **3c** (from (*R,R*)-2,3-butanediol[12]), unsatisfactory results were obtained since the adducts **5b** and **6b** as well as **5c** and **6c** undergo extensive decomposition on chromatographic separation.

The chiral phosphite (−)-**3a** is stable upon storage. It can be added to a variety of prochiral C=N or C=O groups,[13] thus opening up a general route to optically active α-amino and α-hydroxy phosphonic acids.

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[2] a) W. F. Gilmore, H. A. McBride, *J. Am. Chem. Soc. 94* (1972) 4361; A. Kotynski, W. J. Stec, *J. Chem. Res. (S) 1978*, 41; A. Vasella, R. Voeffray, *Helv. Chim. Acta 65* (1982) 1953; b) U. Schöllkopf, I. Hoppe, A. Thiele, *Liebigs Ann. Chem. 1985*, 555.

[3] a) K. J. M. Andrews, Eur. Pat. 33919 (1981), Hoffmann-La Roche; *Chem. Abstr. 96* (1982) 52498r; b) K. Drauz, H. G. Koban, J. Martens, W. Schwarze, *Liebigs Ann. Chem. 1985*, 448.

[4] a) **1a** prepared from diethyl (*R,R*)-2*O*,3*O*-isopropylidenetartrate [4b]: 1) 5 equiv. MeMgBr/Et_2O/reflux, 2 h (98%); 2) NaH/tetrahydrofuran/CH_3I/reflux, 24 h (90%); 3) CH_3OH/8 N H_2SO_4 (2 : 1), RT, 48 h (92%). B.p. = 90°C/0.01 torr, $[\alpha]_{20}^{D}$ −8.5 (*c* = 1.55, $CHCl_3$)); b) J. A. Musich, H. Rapoport, *J. Am. Chem. Soc. 100* (1978) 4865.

[5] A. Zwierzak, *Can. J. Chem. 45* (1967) 2501.

[6] (−)-**3a**: b.p. = 160°C/0.01 torr; m.p. = 51–52°C; $[\alpha]^{D}_{20}$ −50.4 (*c* = 1.48, $CHCl_3$); ^{1}H-NMR ($CDCl_3$): δ = 4.39, 4.25 (each dd, *J*(P,H) = 16 Hz, *J*(4,5) = 2.5 Hz, CH); 3.25, 3.22 (each s, OCH_3), 1.28, 1.27, 1.11 (each s, CH_3); ^{31}P-NMR ($CDCl_3$, standard H_3PO_4): δ = 25.4.

[7] F. Asinger, W. Schäfer, G. Herkelmann, H. Römgens, B. D. Reintges, G. Scharein, A. Wegerhoff, *Justus Liebigs Ann. Chem. 672* (1964) 156.

[8] (−)-**5a**: R_f(Et_2O) = 0.18; m.p. = 126°C; $[\alpha]_{20}^{D}$ −67.4 (*c* = 1.2, $CHCl_3$); ^{1}H-NMR ($CDCl_3$): δ = 4.43, 4.29 (each s, CH), 3.92 (d, *J*(P,H) = 20 Hz, 4-H), 3.26, 3.24 (each s, OCH_3), 3.2 (br., NH), 1.69, 1.64, 1.55, 1.35, 1.31, 1.10 (each s, CH_3); ^{31}P-NMR ($CDCl_3$): δ = 44.7; (+)-**6a**: R_f(Et_2O) = 0.27; m.p. = 118°C; $[\alpha]_{20}^{D}$ +12.2 (*c* = 1.7, $CHCl_3$); ^{1}H-NMR ($CDCl_3$): δ = 4.55–4.15 (m, CH), 3.61 (d, *J*(P,H) = 18 Hz, 4-H), 3.34 (br., NH), 3.23 (s, OCH_3), 1.69, 1.59, 1.55, 1.32, 1.11 (each s, CH_3); ^{31}P-NMR ($CDCl_3$): δ = 45.0.

[9] Eluted with diethyl ether.

[10] (−)-**5a**: $P2_12_12_1$, *a* = 1130.3(1), *b* = 1212.5(1), *c* = 1546.7(1) pm, *V* = 2.120 nm^3, *Z* = 4, μ = 0.24 mm^{-1} ($Mo_{K\alpha}$), 3870 measured intensities (*hkl* and $\bar{h}kl$), $2\theta_{max} = 50°$, 3461 symmetry independent reflections with $|F| 3\sigma_F$ used for structure solution (Patterson and Fourier methods) and refinement. Non-hydrogen atoms refined anisotropically. H atoms localized by difference electron density determination and refined using a "riding" model, $R = 0.036$ ($R_w = 0.038$, $w^{-1} = \sigma_F^2 + 0.0005F^2$), absolute configuration confirmed by η-refinement. Further details of the crystal structure investigation are available on request from the Fachinformationszentrum Energie, Physik, Mathematik GmbH, D-7514 Eggenstein-Leopoldshafen 2, by quoting the depository number CSD 51585, the names of the authors, and the journal citation.

[11] (*R*)-**7**: decomp. point = 221°C; $[\alpha]_{20}^{D}$ −10.8 (*c* = 0.64, 1 N NaOH); ^{1}H-NMR (D_2O): δ = 3.21 (d, *J*(P,H) = 15 Hz, CH), 1.49, 1.43 (each s, CH_3); ^{31}P-NMR ($CF_3CO_2H/CDCl_3$): δ = 14.3; (*S*)-**7**: decomp. point = 219°C; $[\alpha]_{20}^{D}$ +10.0 (*c* = 0.72, 1 N NaOH).

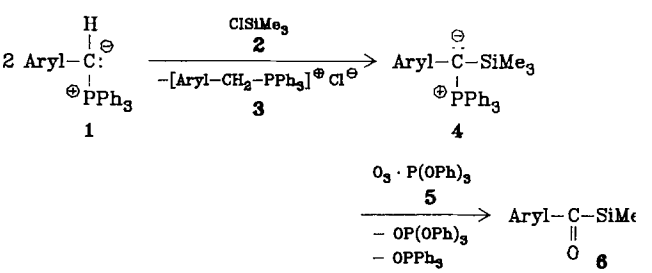
[12] **1c**: R. C. Anderson, M. J. Shapiro, *J. Org. Chem. 49* (1984) 1304.

[13] I. Hoppe, unpublished.

Acylsilanes via Oxidation of Phosphonium Ylides: The First Synthesis of Bis(trimethylsilyl)ketone and Its Use as a $CO^{2\ominus}$ Equivalent

By *Alfredo Ricci,* Mariella Fiorenza, Alessandro Degl'Innocenti, Giancarlo Seconi*, Pasquale Dembech, Konrad Witzgall,* and *Hans Jürgen Bestmann**

Acylsilanes, which are employed as nucleophilic acylation reagents, are a preparatively interesting class of compounds.[1,2] We have found that aromatic acylsilanes **6** can be easily synthesized from phosphonium ylides **1**.



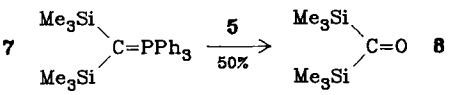
a, Aryl = C_6H_5; **b**, Aryl = *p*–Br–C_6H_4; **c**, Aryl = *p*–CH_3O–C_6

Upon reaction of **1** with chlorotrimethylsilane **2** in a molar ratio of 2 : 1, the silylated ylides **4**,[3] along with the phosphonium salts **3**, are formed by trans-ylidation. Oxidation of **4** with the adduct **5**, formed from ozone and triphenylphosphite (5% less than the stoichiometric amount

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in order to avoid overoxidation) affords the compounds **6**,[4] which are purified by chromatography on silica gel with benzene (**6a**) or with ether/hexane (**6b**, **c**) as eluent and which exhibit a typical absorption for the CO group at 1615 cm^{-1} in the IR spectrum (film) [**6a**:[1] 76%; ^{1}H-NMR ($CDCl_3$): $\delta = 0.37$ (s, 9H); **6b**: 62%; $\delta = 0.37$ (s, 9H); **6c**: 53%; $\delta = 0.33$ (s, 9H), 3.82 (s, 3H)]. The same reaction with **4**, alkyl instead of aryl, leads to a complex mixture of products.

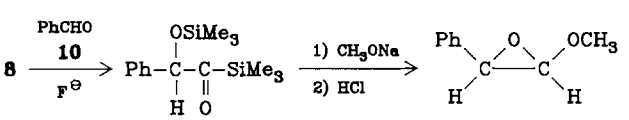
On the other hand, it was possible to prepare the bis(trimethylsilyl)ketone **8** for the first time in pure form via oxidation of the bis-silylated ylide **7**[5] with **5**. Its thio analogue was recently synthesized.[6]



$Me_3Si-CO-O-SiMe_3$ **9**

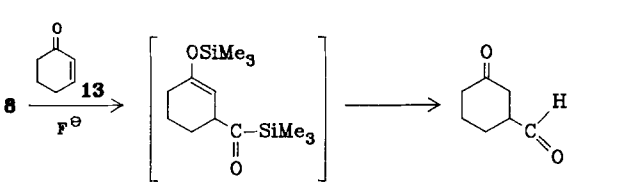
8 is a strawberry-colored oil,[7] which is extraordinarily labile toward autooxidation in air,[8] being converted into the ester **9**.[9] Its structure was established by mass, IR, ^{13}C-NMR, and ^{29}Si-NMR spectroscopy: MS (70 eV): *m/z* 174 (M^+), 159, 147, 146, 133, 131; IR (film): $\nu = 1570$, 1250, 850 cm^{-1}; ^{13}C-NMR (80 MHz, C_6D_6, TMS): $\delta = -2.9$ (CH_3), 318.8 (CO); ^{29}Si-NMR (80 MHz, C_6D_6, TMS): $\delta = -14.4$. Characteristic for a carbonyl group bonded to a silicon atom is the intense IR band at 1570 cm^{-1}. The ^{13}C-NMR and ^{29}Si-NMR signals at exceptionally low and high field, respectively, are in agreement with findings[11,10] for other acylsilanes.

It was expected that **8** would be useful as a synthetic equivalent for the dianion $CO^{2\ominus}$. Preliminary experiments confirm this to be the case. **8** undergoes $F^{\ominus}$-catalyzed (CsF) reaction under very mild conditions with typical carbon electrophiles such as benzaldehyde **10** or 2-cyclohexenone **13** (molar ratio 1 : 1). With **10**, compound



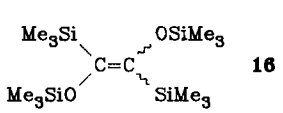
11

12



14

15



16

11 (identified by mass spectroscopy of the reaction mixture) is formed, which, after reaction with sodium methoxide and subsequent addition of acid, affords the desilylated product **12** in good yield (60% yield, b.p. = 65–67 °C/1 torr[11]).

The reaction with **13** leads to **14**, which, in the presence of traces of moisture, immediately undergoes reaction to form regioselectively 3-oxocyclohexanecarbaldehyde **15**[12] (chromatographic purification, polymerizes on attempted distillation, 55% yield, IR: $\nu = 1740$, 1710 cm^{-1} (CO)). These examples demonstrate the synthetic potential of **8** as an exceptionally effective agent for the $F^{\ominus}$-catalyzed formylation under mild conditions with complete control of regioselectivity. The reagent is expected to find a still broader range of applications.

Experimental Procedure:

8: A freshly prepared solution of **5** (4 mmol) in 20 mL of toluene was added to a solution of **7** (1.68 g, 4 mmol) in 20 mL of toluene at −78 °C. After 5 h at −78 °C, the reaction mixture was allowed to warm to room temperature and the solvent was almost completely removed by fractional distillation (30 °C/2 torr). The crude product was purified by flash chromatography on SiO_2 (Merck 60, degassed *n*-pentane, stream of argon). The residue remaining after removal of the solvent was distilled in vacuum. Yield: 0.36 g (50%) **8** as a pink oil (b.p. = 36 °C/1.5 torr); 95% purity.

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[12] In addition to **12** and **15**, a considerable amount of **16** is formed via decomposition of **8**. Analogous dimers were found in the reaction of $PhCOSiMe_3$ with electrophiles catalyzed by $F^{\ominus}$ [1].

Bis(*tert*-butyl)diphosphene as Building Block of a Trichromium Cluster. A Novel Type of Coordination of Diphosphenes

By *Jutta Borm, Gottfried Huttner,** and *Laszlo Zsolnai*

Carbonylchromium complexes, in contrast to the carbonylmetal compounds of Mn, Fe, Co, and Ni, have little tendency to form clusters. Among the numerous carbonylchromium compounds reported to date only three homometallic chromium clusters have been described.[1] We have now found that triangulo-trichromium moieties can be constructed from phosphandiyl (phosphinidene) complexes.[***]

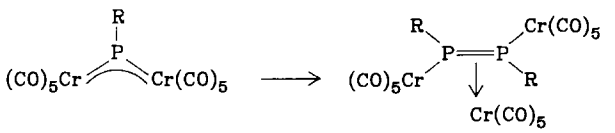
Thermal decomposition of phosphandiyl complexes[2] **1** usually leads via cleavage of a $Cr(CO)_5$ group to formation of diphosphene complexes **2** containing one side-on and two end-on coordinated $Cr(CO)_5$ moieties.[3] However,

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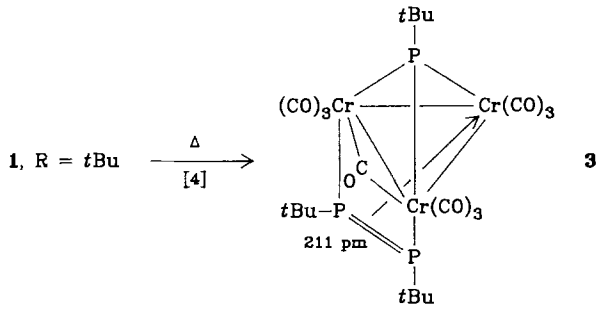
[**] This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.

[***] In accordance with the IUPAC rule D-6.12 the ligands of type RP are referred to here as phosphandiyls.

upon thermolysis of **1**, R = *t*Bu,[2] we were unable to isolate a complex of type **2**. At 100 °C, decarbonylation led to formation of the cluster **3**.[4]



1 **2**



3 is the second example of a triangulo-trichromium cluster[5] whose structure has been confirmed by X-ray analysis.[1] It contains a μ_3-PR bridge, which hitherto has only been observed in clusters containing at least two metals of the eighth subgroup.[6] **3** is the first example of a cluster containing a *Z*-diphosphene moiety $R\ddot{P}{=}\ddot{P}R$ as side-on and end-on coordinated ligand.

Whereas diphosphenes have already been observed as building blocks of complexes with metal-metal bonds in other types of coordination,[7] the type of bonding found for **3** was hitherto unknown. It corresponds to a mode of coordination of *Z*-diazenes in clusters[8] and thus substantiates the analogy between the bonding in $R\ddot{N}{=}\ddot{N}R$ and $P\ddot{P}{=}\ddot{P}R$.

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CAS-Registry-numbers:
1, 90443-62-2; **3**, 99034-13-6; P, 7723-14-0; Cr, 7440-47-3.

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[3] J. Borm, L. Zsolnai, G. Huttner, *Angew. Chem. 95* (1983) 1018; *Angew. Chem. Int. Ed. Engl. 22* (1983) 977; *Angew. Chem. Suppl. 1983*, 1477.

[4] **1** (200 mg, 0.42 mmol), R = *t*Bu [2], was melted at 100 °C. Within 30 min the melt turned brown in color and $Cr(CO)_6$ sublimed off. The brown residue was dissolved in CH_2Cl_2 (5 mL), treated with silica gel (1 g), and evaporated to dryness. Chromatography on silica gel (30 °C; 15 × 2.5 cm) with *n*-pentane/CH_2Cl_2 (1:1) furnished an orange-brown zone from which **3** was separated from a yellow, still unidentified byproduct by fractional crystallization in the form of brown crystals. **3** is also slowly formed from crystalline **1** upon storage at 20 °C for several months. Yield: 20 mg of **3** (20% based on **1**); correct elemental analysis. IR (*n*-pentane): ν = 2034 (w), 1983 (vs), 1968 (s), 1955 (m), 1946 (w), 1836 (w). ^{1}H NMR ($CDCl_3$): δ = 1.74 (pseudotriplet, $^3J(PH)$ = 10 Hz, 18 H); 2.46 (d, $^3J(PH)$ = 19 Hz, 9 H). $^{31}P\{^1H\}$ NMR (CH_2Cl_2): δ = 352 (s, 2 P); 659 (s, 1 P). MS: *m/z* 700 (5%), 672 (1), 644 (3), 616 (1), 588 (3), 560 (7), 532 (3), 504 (10), 476 (5), 448 (5), 420 (5), 392 (2), 364 (6), 336 (1), 308 (20), 251 (M^+ − 10 CO − Bu, 32), 137 (M^+ − 10 CO − 3 Bu, 3), 57 (Bu^+, 60), 52 (Cr^+, 10), 41 ($C_3H_5^+$, 100), 39 ($C_3H_3^+$, 51). **3** is stable up to 250 °C in the solid state.

[5] $P2_1/c$, Z = 4, $\rho_{calc.}$ = 1.62 g cm^{-3}, a = 1648.5(7), b = 924.8(3), c = 1888.9(7) pm; V = 2879 × 10^6 pm^3, $\mu(Mo_{K\alpha})$ = 13.8 cm^{-1}, T = 20 °C, 2856 independent reflections ($I > 2\sigma(I)$), R_1 = 0.051, R_2 = 0.054. Important bond lengths [pm]: Cr-Cr 281.4(2)-285.1(2), Cr-μ_3-P 224.0(2)-230.1(2), P-P 211.2(3), Cr-P(diphosphene) 228.7(2)-232.4(2). Further details of the crystal structure investigation are available on request from the Fachinformationszentrum Energie, Physik, Mathematik GmbH, D-7514 Eggenstein-Leopoldshafen 2, on quoting the depository number CSD-51546, the names of the authors, and the full citation of the journal.

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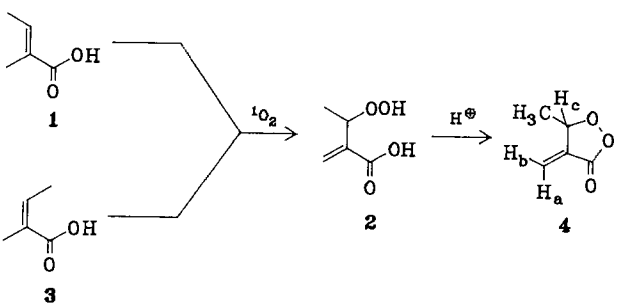
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Synthesis of the First α-Methylene-β-peroxylactone—Regiospecific Ene Reaction of $^1O_2$ with α,β-Unsaturated Carboxylic Acids**

By *Waldemar Adam** and *Axel Griesbeck*

Alkyl-substituted β-peroxylactones have long been known,[1-3] and their behavior upon thermolysis and upon direct or triplet-sensitized photolysis has been investigated in detail.[4] We report here on an entry to 5-methyl-4-methylene 1,2-dioxolan-3-one **4**, the first α-methylene-β-peroxylactone. The key step of the synthesis is the regiospecific photooxygenation of an α,β-unsaturated carboxylic acid (Scheme 1).



Scheme 1.

Irradiation (λ: 150-W sodium lamp, unfiltered) of a solution of tiglic acid **1** in CCl_4 (concentration: 0.25 mol/L) in the presence of traces of tetraphenylporphine at 10 °C affords the allylic hydroperoxide **2** (yield: 92%). The isomeric ene product is not formed. **2** can also be synthesized by photooxygenation of angelic acid **3**, but three- to fourfold longer reaction times are required.

This $^1O_2$-reaction is remarkable, for two reasons: a) as shown by competition experiments,[5] the addition of a carboxyl group in 2-butene does not lead to appreciable diminution in the reactivity, i.e. *trans*-2-butene reacts only ca. twice as fast as tiglic acid **1** with $^1O_2$; b) both the ene reaction of **1** as well as that of **3** proceed regiospecifically to give the β-hydroperoxy-α-methylenecarboxylic acid **2**.

Acid-catalyzed dehydration with H_2SO_4 in $CHCl_3$ at 0 °C affords the α-methylene-β-peroxylactone **4**, which can

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be isolated in 61% yield by short-path distillation at 32–36°C/0.08 torr as a colorless oil having an unpleasant odor. **4** gives with potssium iodide a distinct peroxide spot on the thin-layer chromatogram ($R_f = 0.70$; SiO_2, CH_2Cl_2). The titrimetrically determined peroxide content amounted to 27.65% (calc. 28.04%), corresponding to a purity of 98.6%.

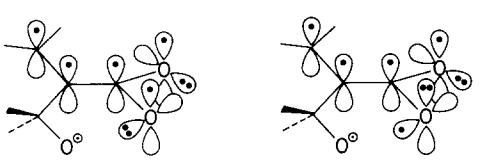
Table 1. ^{1}H- and ^{13}C-NMR data and selected IR data of **2** and **4**.

	2 [c]	**4** [c, d]
^{1}H-NMR (δ values) [a]	1.35 (d, 3H, J=6.2 Hz) 4.95 (q, 1H, J=6.2 Hz) 6.02 (s, 1H) 6.48 (s, 1H) 9.67 (br. s, 2H)	1.53 (d, 3H, J=6 Hz) 5.42 (ddd, H_c, ^3J=6 Hz, $J_{b,c}$=2.5 Hz, $J_{a,c}$=3.0 Hz) 5.77 (dd, H_b, $J_{b,a}$=0.75 Hz, $J_{b,c}$=2.5 Hz) 6.30 (dd, H_a, $J_{a,b}$=0.75 Hz, $J_{a,c}$=3.0 Hz)
^{13}C-NMR (δ values) [a]	18.34 (q) 79.13 (d) 128.32 (t) 139.91 (s) 171.90 (s)	17.76 (q) 81.27 (d) 122.11 (t) 138.66 (s) 168.48 (s)
IR [cm^{-1}] [b]	3300 (s), 2990 (m), 1700 (s), 1628 (m), 1272 (m), 1178 (m)	2990 (w), 1790 (s), 1672 (w), 1410 (s), 1246 (s), 1132 (s)

[a] 400 MHz, $CDCl_3$, δ values referred to TMS. [b] Film (NaCl plates). [c] Correct elemental analyses. [d] Molecular weight: experimental, 116 (osmometric); theoretical, 114.

A comparison of the IR and of the ^{1}H- and ^{13}C-NMR data of **2** and **4** (Table 1) lends support to the proposed structures. A striking feature of the ^{1}H-NMR spectrum of **4** is the additional $^4J_{HH}$-coupling between H_a and H_c and between H_b and H_c, which do not occur in the open-chain compound **2**. **4** can be stored without deterioration at −20°C, but on heating to 70–80°C it undergoes complete polymerization.

4 proves to be exceptionally stable upon flash photolysis: Even on passage through a quartz tube (60-cm long, 14-mm diameter, unpacked) heated to 1000°C at 0.08 torr only 15% of the substance polymerizes; 85% thereof can be recovered in the cold trap. This finding can be explained in terms of the diradical state **5**,[6] which is proposed as intermediate.



π-**5** σ-**5**

Since the relative energies of π-**5** and σ-**5** are unknown, it is impossible to make any definite statement about the electronic nature of the diradical. Decarboxylation of π-**5** should lead to a n,π*-excited CO_2-molecule—an energetically very expensive fragmentation path. The cleavage of CO_2 from σ-**5** would lead to a vinyl radical or, at least, require a concomitant 1,2-methyl shift to an olefinic C-atom, both of which are unfavorable for stereoelectronic reasons.

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Sensitized UV/Laser Photolysis of Azoalkanes: Conformational Influences on Intersystem-Crossing and Lifetimes of Triplet Diradicals**

By *Waldemar Adam,* Klaus Hannemann,* and *R. Marshall Wilson*

Dedicated to Professor Rolf Huisgen on the occasion of his 65th birthday

The importance of diradicals in chemical reactions is reflected in the large number of studies devoted to the detection and determination of the lifetime of these short-lived intermediates.[1] Although their behavior is qualitatively well understood,[2] experimental data essential for testing theoretical models are still greatly lacking. For example, the law of conservation of total angular momentum for triplet-singlet intersystem-crossing requires a conformational arrangement of the radical orbitals in which the radical orbital axes are oriented orthogonally to one another and also to the axis about which the orbital angular momentum is generated (Fig. 1a). In contrast, a parallel arrangement (Fig. 1b) of the radical orbitals proves to be unfavorable for spin-orbital coupling.[2] To our knowledge no experimental evidence has hitherto been put forward in support of this theoretical prediction. Either the geometrical prerequisites are not given or the diradical is so strongly perturbed by substituents that no influences of the conformation on intersystem-crossing and, thus, on the lifetime of the triplet diradical, can be recognized.[1]

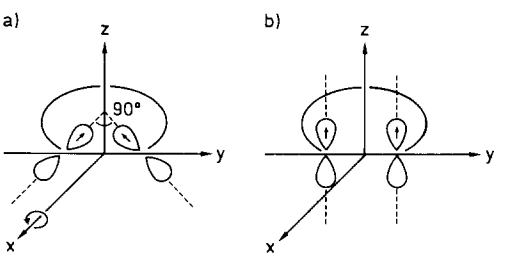


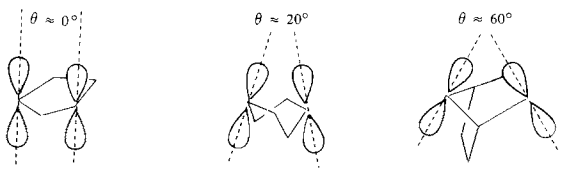
Fig. 1. Optimal orthogonal (a) and unfavorable parallel (b) arrangements of the radical orbital axes for intersystem-crossing in triplet diradicals.

Using the localized diradicals 1,3-cyclopentadiyl **1a**, 1,4-cyclohexadiyl **1b**, and 2,7-bicyclo[2.2.1]heptadiyl **1c**, which are not perturbed by substituents, as examples, we show that the arrangement of the radical orbitals considerably influences the lifetimes of these transient species—they differ by more than four orders of magnitude. The di-

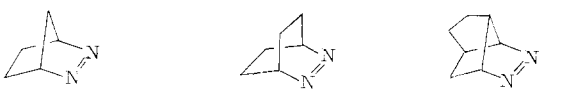
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radicals **1a**–**1c** were generated by photochemical benzophenone-sensitized N_2-cleavage from the corresponding azo compounds **2a**–**2c**. The laser photolyses (Coherent supergraphite CR18 argon ion laser) were carried out in inert solvents (CCl_4, $CFCl_3$) under oxygen (10 bar) in order to trap and detect the short-lived diradicals **1a**–**1c** as peroxides. The lifetimes could be determined from the O_2-pressure-dependent product distribution between trapping product (peroxides) and cyclization product (hydrocarbon) with the aid of a Stern-Volmer plot.[3]



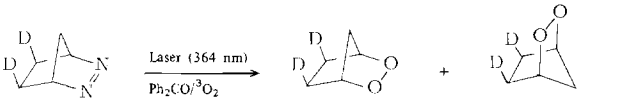
1a **1b** **1c**



2a **2b** **2c**

1,3-Cyclopentadiyl **1a** can readily be trapped with oxygen[4] and a quantitative evaluation of the reaction in CCl_4 at 8 °C yields a lifetime of $\tau_T = 900 \pm 40$ ns,[3] whereas 1,4-cyclohexadiyl **1b** can merely be detected by trapping with oxygen.[5] The amounts of peroxides are too small for a reliable determination of the oxygen-dependent product distribution. It can be concluded from this finding that the triplet lifetime of **1b** is very short (an estimated 0.1–1.0 ns).[5] All attempts to detect even traces of peroxides by trapping with oxygen met without success in the case of 2,7-bicyclo[2.2.1]heptadiyl **1c**. Even the very sensitive KI/HOAc test (limit of detection ca. 0.01%) gave no indication of the presence of peroxide in the concentrated photolyzate. The triplet diradical **1c** is apparently too short-lived to be intercepted by bimolecular reactions such as trapping with oxygen. Accordingly, the lifetime of this triplet diradical must be shorter than 0.1 ns.

The sequence of the lifetimes (τ_T(**1a**) > τ_T(**1b**) > τ_T(**1c**)) and their large differences (a factor of 10^4) cannot be explained in terms of steric or energy factors. This is only possible if the arrangement of the radical orbitals are taken into consideration. Consistent with this explanation is the result of the photolysis of the deuterated compound *exo*-[D_2]-**2a**, yielding the isomeric peroxides **3a** in a 1:1 ratio (D-NMR).[6] The 1,3-cyclopentadiyl triplet **1a** must therefore be planar on the average during the time of the oxygen trapping reaction, thus requiring the parallel arrangement of the radical orbitals ($\theta \approx 0°$); hence the long lifetime of **1a** becomes understandable on the basis of the



exo-[D_2]-**2a** *exo*-[D_2]-**3a** *endo*-[D_2]-**3a**

unfavorable intersystem crossing (Fig. 1). In contrast, the arrangement of the radical orbitals in the triplet diradical **1c** ($\theta \approx 60°$) is almost optimal for rapid intersystem-crossing as a result of the rigid bicyclo[2.2.1]heptane skeleton (Fig. 1a). A twist-boat conformation is assumed for the 1,4-cyclohexadiyl **1b**,[5] in which the radical orbital axes make an angle of 20° to each other. As expected, the lifetime of the triplet diradical **1b** lies between those of the two extreme cases **1a** and **1c**, as demonstrated by the successful trapping with oxygen; unfortunately the oxygen trapping cannot be quantified in this case.

All these results indicate that the very different lifetimes (factor of 10^4) of the triplet diradicals **1a**–**c** can be ascribed to conformational influences on the intersystem-crossing rates. Thus, the above theoretical predictions[2] have, for the first time, been confirmed experimentally.[7]

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[7] N. J. Turro, W. R. Cherry, M. F. Mirbach (*J. Am. Chem. Soc. 99* (1977) 7388) explains the very rapid intersystem-crossing in tricyclo[2.2.1.$0^{2,6}$]heptadiyl in the triplet-sensitized photocycloaddition of norbornadiene to quadricyclane in terms of the Salem rule [2].

Chemistry and Technology of Water-Soluble Polymers. Edited by *C. A. Finch*. Plenum Press, New York 1984. xvi, 358 pp., bound $ 55.00.—ISBN 0-306-41251-9

According to the editor the aim of this book is to provide insight into the relationship between theoretical investigations into water-soluble polymers and the industrial application of these products and to close the gap between empirical knowledge and theoretical background. It is based on the manuscripts of the speakers at a seminar, which took place in Cambridge in 1981.

Some defects in the external form are a consequence of this. Diagrams, tables and formulas are heterogeneous in execution. A range of printing errors has crept into the text. Nor are the formulas free from errors. However, these formal defects are not so extensive that they impede the comprehension of the contents.

This book provides a diversified account in 19 chapters of the state of knowledge in the field of water-soluble polymers, whereby natural polymers are only treated peripherally. Alongside two review articles covering the chemistry and application and the preparation of the polymers, there are four contributions concerned with individual areas of application—medicine, flocculating agents, crude oil production, stabilization of dispersions. Contributions concerned with theoretical aspects are in the majority. The main emphasis is on the description of the polymers in solution, with contributions concerned with thermodynamics, rheology, interactions with solvents, with small molecules (salts, surfactants) and with polymers. A large amount of space is given to cross-linked systems which are no longer water-soluble in the true sense of the word, being merely able to swell in water. A separate chapter is devoted to their preparation by the cross-linking of soluble starting compounds, whereas unfortunately the other polymer-analogous reactions are practically ignored. There is a detailed treatment of the behavior of water-soluble polymers at the interface between water and dispersed solids and as protective colloids in emulsion and suspension polymerization.

With its copious literature citations this book stimulates to an enriching occupation with the primary literature and opens up a rapid access to the chemistry and technology of water-soluble polymers even for the non-specialist. All in all a volume worth recommending.

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Solid State Chemistry and its Applications. By *A. R. West*. Wiley, Chichester 1984, 734 pp., hardback, £ 37.00.—ISBN 0-471-90377-9 (U. S.)

The author attempts to cover in around 700 pages that which is currently embraced by the concept of solid state chemistry. To define those aspects of the interdisciplinary field of solid state research which are of interest to chemists and principally dealt with by them is not an easy undertaking. In this the author succeeds remarkably well. In 21 chapters varying in length between 11 and 72 pages the following subjects are dealt with: preparative methods of solid state chemistry (reactions in the solid state, chemical transport, the use of pressure, hydrothermal synthesis, crystal growth), physical methods for characterizing materials (divided into the subsections: diffraction techniques, microscopic techniques and spectroscopic techniques—separate chapters are devoted to thermal analysis and X-ray diffraction), principles of crystallography and crystal chemistry, the defect structure of crystalline solids, state diagrams, phase transformations and, finally, selected solid state properties that are of interest for practical application. This book is indeed the first that deserves the description "Textbook of Solid State Chemistry". The textbook character is emphasized not only by the selection of material but also by the manner of its presentation. Patterns of regular behavior, methods of investigation and general perspectives of solid state chemistry are handled to a large extent by means of examples in a clear form which is also comprehensible to non-specialists. The necessary simplifications are justifiable apart from some exceptions. One such exception, for example, is the treatment of phase transformations. Even at the qualitative level, a discussion which does not take account of the concept of "other parameters" as introduced by *Landau* seems inadequate. The contents overlap considerably with monographs already available. This is inevitable, given the aims and layout of the book, but by no means problematic since the sources of information complement one another due to their different degrees of detail. At the end of each section is a compilation of carefully selected references to further literature which make it easier for the reader to investigate particular areas in more depth.

There are only a few printing errors. In some cases, however, they distort the meaning and could mislead the beginner. The typeface is clear and the diagrams are comprehensible without being used to excess.

The book may be recommended without reservation as a text for university teaching, though its high price may stand in the way of a larger readership.

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Amorphe und glasartige Festkörper. By *A. Feltz*. Akademie-Verlag, Berlin 1983. xix, 460 pp., bound, ca. DM 85.00.—Order No. 763 0341 (6654).

This book is a very important contribution to a field much neglected in the minds of chemists; namely the study of amorphous and glass-like substances. This can be explained by the fact that the field lies between those of molecules and crystalline solids but does not fit into either. However, the technical implications of this class of materials are most important. This book will play a key role because the author has succeeded in summarizing and critically representing the present state of practical and theoretical knowledge concerning amorphous and glass-like inorganic materials. The four main sections (the amorphous and glass-like state, material systems, properties, applications) provide a wealth of information and are clearly arranged. The lucidly formulated text is a witness to the personal experience of the author in this field. This experience has evidently provided the author with the capability of dealing with the wealth of material and the completely

different theoretical treatments without losing his way. The first section deals with the preparation, then with the thermodynamics of glasses and the kinetics of glass formation. A detailed discussion of structure and bonding then follows, which does not omit the treatment of new developments in electronic structure. The long section on material systems deals in a very detailed manner with the behavior of elements, binary systems and finally complex systems from the fields of metallic glasses, semiconductors and insulators. The relationships to crystalline structure pointed out in this section are worthy of note. The electrical and optical properties are dealt with in detail as the principal physical properties, before the final chapter on contemporary applications. The importance of structural disorders and defects for the understanding of these properties is very clearly presented. All in all a book that is worth reading, both for rapid information and also for a detailed study of amorphous materials and glasses.

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Allenes in Organic Synthesis. By *H. E. Schuster* and *G. M. Coppola*. Wiley, New York 1984. 358 pp., hardcover, $ 54.95.—ISBN 0-471-87284-9

Amongst the hydrocarbons, allenes were regarded for a long time as curiosities. Their stereochemical properties, correctly predicted by *van't Hoff*, were indeed dealt with in most textbooks but not so their reactions nor even their systematic application in organic synthesis. This monograph—the fifth comprehensive treatment of this class of compounds to appear recently—shows how fundamentally this situation has changed in the course of the last decade.

Above all, three properties of allenes make them useful to the preparative chemist as educts and intermediates: (i) their readiness to take part in additions of all kinds (amongst others ionic additions, [2+2]-, [2+4]-, 1,3-dipolar cycloadditions), (ii) their tendency to isomerize to noncumulated dienes and acetylenes, a reaction which can be brought about thermally, photochemically, catalytically or ionically, and, finally, (iii) their C–H acidity, which is particularly important for the functionalization of allenes.

Of course, the wholesale exploitation of a class of compounds in synthesis requires reliable methods for their preparation. This condition is met for allenes and, consequently, the book begins with a description of the most important syntheses of allenes, with particular reference to the parent compounds (alkyl, aryl, and cycloallenes). This is followed by extensive chapters on allene alcohols, aldehydes, ketones and carboxylic acids and their derivatives as well as their application to the synthesis of natural products and complex organic compounds. Two further chapters are allotted to heterosubstituted allenes (oxygen, sulfur, selenium, nitrogen, phosphorus, silicon and boron containing functional groups) and to halogenoallenes. Amongst the latter are found the remarkable bromoallenes which have recently been isolated as secondary metabolites of certain types of algae. The reactions of allenes are presented in three chapters. The first is concerned with addition reactions of all kinds except cycloadditions (amongst others, hydrogenation, electro- and nucleophilic additions). It makes sense to describe cycloadditions in a chapter of their own, simply on account of the amount of material to be covered. Most mechanistic investigations in allene chemistry have been concerned with this class of reactions, which is also extraordinarily useful in synthesis (4 ring syntheses by allene dimerization, allene/ketene and allene/olefin co-dimerization, allene/enone photoadditions). In a concluding "mixed" chapter, organometallic derivatives and rearrangements—mostly Claisen type—are dealt with. Even if certain individual aspects of allene chemistry are perhaps handled patchily (for example, more is known about the photochemistry, thermal isomerization reactions and organometallic complexes than would be thought after reading this book), the book offers a comprehensive survey of modern allene chemistry and complements the other recent publications particularly in the area of synthetic applications. Although the clear print and unfussy formula diagrams are pleasing, it is regrettable that this book has no author index. Since certain groups of compounds are associated chiefly with the names of those working on and with them, the absence of such an index makes literature searching unnecessarily laborious—a simple matter that is often overlooked these days, particularly in American texts.

It isn't so long ago that chemists working in this field greeted one another with the question, "are you working allene, too?" (*allene* = Berlin slang for alone!). "No longer", is the answer after the rapid and diverse development of recent years and after reading *Schuster* and *Coppola*'s book.

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